Front Matter

Pharmaceutical and Biotech Patent Law (2024)
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Author(s): Arnold & Porter Kaye Scholer LLP (Arnold & Porter Kaye Scholer LLP)
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Pharmaceutical and Biotech Patent Law

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Pharmaceutical and Biotech Patent Law

Edited by
David K. Barr and Daniel L. Reisner

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About the Author. About the Authors

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Preface

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Preface

Patents are a focal point in the development, manufacture, and marketing of pharmaceutical and biotechnological products. The scope of patent protection for these products has profound effects upon pharmaceutical and biotech research, and the development of new therapeutic products.

For over twenty-five years, we and our colleagues have advised pharmaceutical and biotechnology companies on patent issues and represented them in patent litigations involving major drugs, diagnostic products, and medical devices. From our work with these companies, we saw the need for a practical guide to help both lawyers and non-lawyers navigate through these complex issues. To this end, our group has produced *Pharmaceutical and Biotech Patent Law*.

Traditional patent law treatises cover patent law as a general topic without focusing on the law's impact on specific areas of technology. Over the past several decades, however, the courts and the U.S. Congress have made many significant changes to U.S. patent law that uniquely affect the pharmaceutical and biotech industries. Both political and technological forces have driven these changes. Specific provisions of the Patent Statute, such as the Hatch-Waxman Act, have been enacted to adjust the balance between pioneering and generic drug companies. An entire chapter of the book has been devoted to this topic, which is often overlooked in other patent treatises and relegated to non-patent books on FDA regulation. Congress also amended the U.S. Patent Statute to harmonize United States law with foreign patent law. The book discusses these changes in the context of pharmaceutical and biotech issues. There has also been a tremendous growth in patent litigation involving the pharmaceutical sciences. New and developing areas of technology, such as molecular biology, have generated an ever-growing body of case law specific to these areas. This body of pharmaceutical and biotech law, we believe, deserves separate treatment apart from the general discussion of patent law.

We organized the book to present patent law issues that arise from the earliest stages of drug discovery through final regulatory approval, marketing, and enforcement, and arranged the chapters in that order. To make this book accessible to the non-lawyer, we have kept lengthy discussions of case law to a minimum. Instead, we emphasize fundamental holdings and principles organized by substantive topics, rather than by individual cases. Where necessary, we provide a more

expansive treatment for the most important decisions. However, to provide rapid access to relevant cases for practitioners, we have made an effort to provide citations to significant decisions in footnotes.

One particularly unique feature of the book is a chapter on different types of pharmaceutical patents. Rather than limiting the book's organization to general topics such as anticipation and obviousness, we created individual sections organized based on the types of pharmaceutical and biotech patents, much as the industry informally categorizes its patents. Thus we have sections that focus on the case law and issues surrounding chemical compound patents, pharmaceutical formulations, methods of treatment, and numerous other categories. Although the book remains a text on the law, not science, of pharmaceutical and biotech patents, we included general discussions of the science throughout the text when needed to provide context. We also provided an appendix that gives an overview of relevant scientific concepts, and a glossary that gives definitions for scientific terminology taken from court decisions to provide the reader with an understanding of how the courts view and apply these concepts. We included a chapter on antitrust and unfair competition issues which have arisen with increasing regularity in pharmaceutical and biotech patent litigations, and therefore have an impact on all aspects of patent procurement, licensing, and enforcement.

Although it is not the purpose of this volume to replace the many fine general treatises on patent law, a concise background on general patent law principles is also provided to give context to the issues that relate more specifically to the pharmaceutical and biotech industries.

We hope our book proves to be a valuable guide to this important and fascinating area of law.

David K. Barr
Daniel L. Reisner
Editors

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Chapter 1. A Brief Introduction to the United States Patent System

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Chapter 1

A Brief Introduction to the United States Patent System

David K. Barr

§ 1:1 Constitutional Basis of the Patent System and Sources of Governing Authority

§ 1:1.1 Constitutional Basis

The U.S. Constitution provides Congress with the power to "promote the [p]rogress of . . . useful arts by securing for limited [t]imes to . . . [i]nventors the exclusive . . . [r]ight to their . . . [d]iscoveries."[1] To this end, Congress established the U.S. Patent and Trademark Office (PTO) within the Department of Commerce with the authority to grant patents.[2]

§ 1:1.2 Sources of Governing Authority

A U.S. patent gives its owner the "right to exclude others" from practicing the patented invention in the United States.[3]

There are several sources of authority that govern the granting and enforcement of U.S. patents:

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1. U.S. CONST. art. I, § 8, cl. 8.
2. 35 U.S.C. §§ 1, 2. The PTO also has responsibility for trademarks, a subject not covered by this treatise.
3. 35 U.S.C. § 154(a) provides that a U.S. patent gives its owner

> the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States, and, if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States, or importing into the United States, products made by that process, referring to the specification for particulars.

(1) The patent laws enacted by Congress, codified in title 35 of the United States Code, govern, among other things, the requirements for patentability, the examination of patent applications, the issuance of patents, and the enforcement of patents against infringement. The first U.S. patent laws were enacted in 1790 and have undergone numerous revisions in the over 200 succeeding years.

(2) The decisions of the U.S. federal courts, which have exclusive jurisdiction over causes of action arising under the patent laws,[4] have created a body of case law interpreting the patent laws. These federal courts include the federal district courts in which patent actions are initially filed, the Court of Federal Claims (and its predecessors), which hears patent infringement actions brought against the U.S. government,[5] the Circuit Courts of Appeals, and the U.S. Supreme Court. Of particular note are the decisions of the Court of Appeals for the Federal Circuit (the "Federal Circuit"), created by Congress in 1982 and given exclusive jurisdiction to hear all appeals in patent cases, including appeals from the federal district courts, the Court of Federal Claims, and from the PTO's Board of Patent Appeals and Interferences.[6]

(3) The rules of practice promulgated by the PTO that are codified in title 37 of the Code of Federal Regulations.

(4) Decisions of the PTO's Board of Patent Appeals and Interferences, which hears appeals of final rejections of applications by patent examiners and decides "interferences," which involve competing claims to priority of invention.

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4. 28 U.S.C. § 1338(a) provides that "[t]he district courts shall have original jurisdiction of any civil action arising under any Act of Congress relating to patents, plant variety protection, copyrights, and trademarks. Such jurisdiction shall be exclusive of the courts of the states in patent, plant variety protection and copyright cases."
5. 28 U.S.C. § 1498.
6. 28 U.S.C. § 1295. The Federal Circuit was created from two predecessor courts, the Court of Customs and Patent Appeals and the U.S. Court of Claims. Prior to the creation of the Federal Circuit, appeals from district court cases were heard by the Circuit Court of Appeals for the geographic region in which the district court was located. The Federal Circuit was intended to unify patent law, in view of perceived splits among the regional circuits on patent law issues. In its first decision, the Federal Circuit stated that the decisions of its predecessor courts would be binding precedent. S. Corp. v. United States, 690 F.2d 1368, 1369 (Fed. Cir. 1982).

(5) The Manual of Patent Examining Procedure (M.P.E.P.) published by the PTO. While the M.P.E.P. is not law, it provides guidance on PTO procedure to patent examiners and patent practitioners. The PTO also issues guidelines relating to patentability.

§ 1:1.3 The America Invents Act

On September 16, 2011, the America Invents Act (AIA) was signed into law.[7] The AIA created a number of important substantive and procedural changes to the U.S. patent laws. Among the AIA's significant changes are:

- Replacing a "first-to-invent" system with a "first-to-file" system and concomitant changes in the scope of prior art.[8]
- Eventual elimination of interference proceedings (to determine priority of inventorship) and the institution of "derivation" proceedings (to determine whether a first-filing applicant derived his or her invention from a later-filing applicant).[9]
- Replacing inter partes reexamination proceedings with "inter partes review," an adjudicative proceeding before a three-judge panel of the new Patent Trial and Appeal Board (PTAB).[10]
- Instituting "post-grant review" proceedings to be heard by the PTAB, which permit a non–patent owner to challenge a patent within nine months of issuance on any ground that can be raised in a patent infringement litigation.[11]
- Instituting "supplemental examination proceedings," permitting patent owners to disclose and have the PTO consider additional information, thereby potentially shielding such information from serving as a basis for an inequitable conduct allegation.[12]
- Eliminating "best mode" as a basis for patent invalidity or unenforceability.[13]

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7. Leahy-Smith America Invents Act, Pub. L. No. 112-29 (2011).
8. *See* sections 1:6, 5:2.1[C].
9. *See* sections 1:6, 1:7.
10. *See* section 1:5.3.
11. *See* section 1:5.4.
12. *See* section 1:5.5.
13. *See* section 5:6.1[B].

- Expanding the scope of the "prior commercial use" defense to a charge of patent infringement.[14]
- Amending the provision for false patent marking to, among other things, eliminate civil penalty "qui tam" actions that formerly could be brought by anyone who alleged that a product was falsely marked with a patent with the intent of deceiving the public.[15]

§ 1:2 Patentable Subject Matter

The PTO grants three general types of patents:

(a) utility patents, which relate to a "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof";[16]

(b) plant patents, which relate to "any distinct and new variety of plant";[17] and

(c) design patents, which relate to "any new, original and ornamental design for an article of manufacture."[18]

This book focuses on utility patents relating to pharmaceutical and biotechnological inventions, including patents relating to active pharmaceutical ingredients, pharmaceutical formulations, and methods of treatment.[19]

Inventions relating to biotechnology and biological materials, including living organisms and DNA sequences and diagnostic methods and methods of treatment, have raised unique issues concerning the scope of patentable subject matter. The district courts, the Federal Circuit, and the Supreme Court have addressed the limitations of patent coverage for such inventions in decisions discussed in this volume.[20]

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14. *See* section 10:5.12.
15. *See* section 1:9.
16. 35 U.S.C. § 101.
17. 35 U.S.C. § 161.
18. 35 U.S.C. § 171.
19. *See* chapter 7.
20. These issues are addressed in detail in section 7:6.2.

§ 1:3 The Patent Application

In the United States, patents are issued after a substantive examination of an application for patent by the PTO to determine whether the invention meets the statutory requirements that the invention be useful, novel, and non-obvious.[21] In addition to the payment of the required filing fee, a patent application also requires an oath or declaration by the inventor that he considers himself to be the original and first inventor of the claimed subject matter.[22] Under section 112, an application for a patent is required to have a specification that (a) contains a written description of the invention that will enable any person skilled in the applicable art to make and use the invention; and (b) sets forth the best mode contemplated by the inventor for carrying out the invention.[23] The specification is required to conclude with one or more claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[24] The claims define the invention and determine the patent owner's right to exclude others from practicing the invention.[25] A patent application must also avoid both statutory and non-statutory double-patenting that can result from an attempt to seek two identical or similar patents for the same or similar inventions.[26] A patent applicant must comply with the duty of disclosure in dealing with the PTO, which requires the disclosure of material information during the examination of the application.[27]

The following table summarizes the major requirements for obtaining a patent, with cross-references to chapters that specifically discuss those requirements:

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21. 35 U.S.C. §§ 101, 102, 103.
22. 35 U.S.C. §§ 111(a)(2), (3), 115.
23. 35 U.S.C. § 112.
24. *Id*.
25. "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Innoval Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004).
26. *See, e.g.*, 35 U.S.C. § 101.
27. 37 C.F.R. § 1.56.

Table 1-1

Summary of Major Requirements for Obtaining a Patent

Requirement	Authority	Treatise Reference
utility	35 U.S.C. § 101	chapter 3
inventorship	35 U.S.C. §§ 102(f), 111(a)(2), (3), 115	chapter 4
novelty	35 U.S.C. § 102	§ 5:2
non-obviousness	35 U.S.C. § 103	§ 5:3
written description	35 U.S.C. § 112, ¶ 1	§ 5:4
enablement	35 U.S.C. § 112, ¶ 1	§ 5:5
best mode	35 U.S.C. § 112, ¶ 1	§ 5:6
definite claims	35 U.S.C. § 112, ¶ 2	§ 5:7
avoid double-patenting	35 U.S.C. § 101 and case law	§ 5:8
duty of disclosure	37 C.F.R. § 1.56	§ 5:9

The Patent Act also provides for the filing of a "provisional" application, which requires a specification meeting the requirements of section 112 (as specified in Table 1-1) and the payment of a filing fee, but does not require a claim.[28] A provisional application is not examined,[29] but provides the application with a filing date. A provisional application can be converted into a non-provisional application, which will be examined, within twelve months of its filing.[30] If the provisional application is not converted to a non-provisional application within twelve months of filing, it is regarded as abandoned.[31]

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28. 35 U.S.C. § 111(b).
29. 35 U.S.C. §§ 111(b)(8), 131.
30. 35 U.S.C. § 111(b).
31. *Id.*

§ 1:3.1 Examination of Patent Applications

[A] General

After a patent application is filed with the PTO, it is assigned to an examining group based on the technology to which the application relates. The application is examined for compliance with the statutory requirements of novelty, non-obviousness, and utility, and to determine whether the specification satisfies the written description, enablement, and best mode requirements. The examination of a patent application involves responsive written communications between the patent examiner and the applicant. The applicant, or his representative, may also interview the examiner, either in person or by telephone, in order to facilitate examination. Such interviews are summarized in writing by the examiner or the applicant. The overall process of obtaining a patent is called "prosecution" and the written PTO record of the prosecution of an application is called the "prosecution history."

Novelty and non-obviousness of the claimed invention are determined with reference to publications and events that generally occur either prior to the date of invention or more than one year before the filing of the application for the patent.[32] Such events and publications constitute evidence of the "prior art," and include issued patents (both United States and foreign), printed publications, public uses and the placing of things "on sale," and prior inventions that have not been abandoned, suppressed, or concealed.[33] Prior art usually comes to the attention of the PTO either by citation by the applicant or through searches conducted by the patent examiner. An applicant for patent has a duty of candor to bring to the PTO's attention any information, including prior art of which the applicant is aware and that is material to the examination of the application.[34]

[B] PTO Office Actions

If the patent examiner concludes that any requirement for patentability is not met, the examiner rejects the claims in an Office Action, which explains the basis for the rejection. The applicant may respond to an Office Action by arguing against the rejection and/or amending the claims in an effort to overcome the rejection. The applicant's response may be accompanied by declarations, which may be submitted to establish a prior date of invention to antedate a reference

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32. See 35 U.S.C. § 102, providing the scope of prior art.
33. *See infra* section 5:2.3.
34. 37 C.F.R. § 1.56.

relied upon by the PTO[35] or to offer evidence supporting patentability, such as experimental data.[36] If the examiner is satisfied that the requirements for patentability have been met, a Notice of Allowance is issued. After payment of an issue fee, the PTO will issue a patent.

If the examiner is not satisfied that the requirements for patentability have been met, the examiner will issue a second Office Action that may contain a "final" rejection of the claims.[37] The applicant can respond to a final rejection by either

(a) appealing to the Board of Patent Appeals and Interferences,[38]

(b) filing a request for continuing examination (RCE) to present additional evidence and/or argument in support of patentability,[39]

(c) filing a "continuation" application to continue prosecution of rejected claims when an RCE cannot be filed,[40] or

(d) abandoning the application.[41]

Prior to the patenting or abandonment of an application, an applicant may also file a continuation application to continue prosecution in order to introduce a new set of claims into the application.[42] An adverse decision of the Board of Appeals can be appealed to the Court of Appeals for the Federal Circuit,[43] or the applicant can initiate a civil action against the PTO in the U.S. District Court for the District of Columbia.[44]

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35. 37 C.F.R. § 1.131.
36. 37 C.F.R. § 1.132.
37. 37 C.F.R. § 1.113.
38. 35 U.S.C. § 134(a).
39. 37 C.F.R. § 1.114.
40. *See* M.P.E.P. § 201.07.
41. An application can be abandoned expressly. 37 C.F.R. § 1.138. An application can also be abandoned by failing to respond to a PTO action within the required time period. 37 C.F.R. § 1.135. The PTO rules provide for revival if an abandonment was unavoidable or unintentional if certain conditions are met. 37 C.F.R. § 1.137.
42. *See* M.P.E.P. § 201.07. A continuation application may claim priority from a prior application as long as it is filed while the prior application is still pending. 35 U.S.C. § 120. Another reason for filing a continuation application is if the PTO finds some, but not all, of the pending claims allowable. A continuation application can be filed to prosecute the non-allowed claims so that the allowable claims can issue.
43. 35 U.S.C. § 141.
44. 35 U.S.C. § 145. However, under 37 C.F.R. § 1.303(b), by appealing to the Court of Appeals for the Federal Circuit, the applicant waives his or her right to initiate a civil action under 35 U.S.C. § 145.

The AIA amended 35 U.S.C. § 122 to provide that for applications filed before, on, or after the effective date of September 16, 2012, third parties may submit for inclusion in the record of a patent application any patent, published patent application, or other printed publication, if the submission is made before the earlier of (1) the date of a notice of allowance or (2) the later of (a) six months after the application is first published, or (b) the date of the first rejection of any claim. The submission is required to include a concise description of the relevance of each submitted document.[45]

[C] Satisfaction of Requirements As of Filing Date

A patent application must satisfy the requirements for patentability as of its filing date. There is a prohibition against amending the disclosure of an application to introduce "new matter," which is information not contained in the application as originally filed.[46] An applicant may file a "continuation-in-part" or "CIP" application that contains information not in the original application. Information in a CIP application, which is the same as the prior application, is accorded the filing date of the earlier application, while new information is accorded the filing date of the CIP application.[47] Claims issuing from a CIP application may be entitled to claim priority to the original (or "parent") application if the claims are supported by the original application in accordance with section 112 of the Patent Act.[48]

[D] One Invention per Patent

If, in the PTO's view, an application claims "two or more independent and distinct inventions," the PTO may require that the application be restricted to one of the inventions.[49] Unless the applicant succeeds in arguing that the requirement for restriction should be

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45. 35 U.S.C. § 122(e).
46. 35 U.S.C. § 132; 37 C.F.R. § 1.121(f).
47. *See* Transco Prods., Inc. v. Performance Contracting, Inc., 38 F.3d 551, 555-56 (Fed. Cir. 1994).
48. *See* 35 U.S.C. § 120; *Transco Prods.*, 38 F.3d at 557 n.6 ("Any claim in a continuation-in-part application which is directed *solely* to subject matter adequately disclosed under 35 U.S.C. § 112 in the parent application is entitled to the benefit of the filing date of the parent application. However, if a claim in a continuation-in-part application recites a feature which was not disclosed or adequately supported by a proper disclosure under section 112 in the parent application, but which was first introduced or adequately supported in the continuation-in-part application, such a claim is entitled only to the filing date of the continuation-in-part application.") (citing to M.P.E.P. § 201.11) (emphasis in original).
49. 35 U.S.C. § 121.

withdrawn, the applicant is required to elect one of the inventions for initial prosecution. The other non-elected inventions may be prosecuted in separate applications known as "divisional" applications.[50] A divisional application must be filed prior to the issuance or abandonment of the prior application.[51]

[E] One Patent per Invention

By statute, an inventor is entitled to obtain only one patent for an invention.[52] This has been interpreted as an absolute prohibition against the issuance of a second patent for the same invention and is called "Statutory Double Patenting."[53] In addition, there is a judicially created doctrine called "Obviousness-Type Double Patenting," which addresses the issuance to the same inventor or assignee of a second patent, the claims of which are merely obvious in view of the claims of the first issued patent. In contrast to Statutory Double Patenting, the second patent may be issued on the conditions that the patentee disclaim any additional term beyond the expiration of the first patent (so that the two patents expire simultaneously) and that the two patents remain commonly owned.[54]

§ 1:3.2 Claims to Priority

A U.S. application can claim priority to an earlier-filed foreign or U.S. application if certain conditions are met. Under section 119 of the Patent Act, a U.S. application can claim priority to a foreign-filed application if the U.S. application is filed within twelve months from the earliest date on which the foreign application was filed and if the foreign application satisfies the disclosure requirements of section 112, so long as the foreign country provides similar privileges to U.S. applicants filing in that country.[55] However, the foreign filing

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50. A divisional application is a type of continuation application that is "carved out of an earlier application which disclosed and claimed more than one independent invention, the result being that the divisional application claims only one or more, but not all, of the independent inventions of the earlier application." *Transco Prods.*, 38 F.3d at 555. *See also* M.P.E.P. § 201.06.
51. 35 U.S.C. § 120.
52. 35 U.S.C. § 101 (providing for the grant of "*a* patent").
53. *See* Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 364 F. Supp. 2d 820, 909 (S.D. Ind. 2005) ("same-invention or 'statutory' double patenting prevents a second patent from issuing on an identical invention"), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).
54. *In re* Longi, 759 F.2d 887, 892–94 (Fed. Cir. 1985). Double patenting is discussed in detail in section 5:8.
55. *In re* Gosteli, 872 F.2d 1008, 1010 (Fed. Cir. 1989).

date is not effective if the invention was patented or described in a printed publication in any country or was in public use or on sale in the United States more than one year before the actual filing in the United States.[56]

Under section 120, a U.S. application can claim priority to an earlier-filed U.S. application that describes the invention in the manner required by section 112 if the later-filed application (a) was filed before the abandonment of the earlier application, and (b) contains a specific reference to the earlier application as long as there is at least one common inventor.

§ 1:3.3 Publication of Patent Applications

In the United States, patent applications filed on or after November 29, 2000, are published eighteen months after the earliest filing date for which a claim to priority is sought.[57] Previously, U.S. patent applications were maintained in secret by the PTO until a patent was granted.[58] Publication of U.S. patent applications was implemented pursuant to the General Agreements on Tariffs and Trade (GATT).[59] An applicant can prevent publication by abandoning the application prior to the expiration of the eighteen-month period or by certifying at the time of filing that the application will not be filed in another country that requires publication of applications.[60]

§ 1:4 Patent Term

For patent applications filed on or after June 8, 1995, the term of a U.S. utility patent begins on the date of grant by the PTO and ends twenty years from the date of filing of the application in the United States. If the application contains a reference to an earlier-filed application under section 120, 121, or 365(c) of the Patent Act (that is, claims priority to an earlier-filed application), the twenty-year term is measured from the filing date of that earlier application.[61]

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56. 35 U.S.C. § 119(a).
57. 35 U.S.C. § 122(b).
58. Patents, Pub. L. No. 593, § 122, 66 Stat. 792, 801 (1952) (amended 1999).
59. Uruguay Round Agreements Act, Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4983 (1994) (implementing legislation pursuant to GATT).
60. 35 U.S.C. § 122(b). In addition, an application will not be published if it is classified for national security purposes or subject to a secrecy order under 35 U.S.C. § 181. *See* 37 C.F.R. § 1.211(a)(2).
61. 35 U.S.C. § 154(a)(2). The term for plant patents is the same as for utility patents. The term of a design patent is fourteen years from the date of grant. 35 U.S.C. § 173.

The twenty-year term was enacted in 1994 and became effective for applications filed on or after June 8, 1995. The prior law provided for a term of seventeen years from the date of issuance of the patent. The law was changed pursuant to GATT to harmonize the U.S. patent term with the terms in most countries, including Europe and Japan.[62] For patents that were in force on or which issued from applications filed before June 8, 1995, the patent is entitled to the longer of twenty years from the date of filing or seventeen years from the date of issue.[63]

Pursuant to section 154, the term of a patent can be extended for delays in examination by the PTO. Section 154 provides for a "guarantee of prompt patent and trademark office responses."[64] If patent issuance is delayed due to one of the enumerated PTO actions[65] and takes longer than the statute provides, "the term of the patent shall be extended for 1 day for each day" that the action took longer than specified.[66] Section 154(b) also provides a "[g]uarantee of no more than 3-year application pendency"[67] and provides, with certain exceptions, for an extension of term due to PTO delay of "1 day for each day after the end of that 3-year period until the patent issued."[68] Lastly, the statute provides similar relief for delays due to an interference proceeding, secrecy order, or an appeal of an adverse determination of patentability.[69] An extension under section 154 is called a patent term adjustment or PTA.

These three extensions for PTO delay, however, are each subject to the following limitations:

> *First*, "[t]o the extent that periods of delay . . . overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed."[70]

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62. Uruguay Round Agreements Act, Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4983 (1994) (implementing legislation pursuant to GATT).
63. 35 U.S.C. § 154(c)(1).
64. 35 U.S.C. § 154(b)(1)(A).
65. 35 U.S.C. § 154(b)(1)(A)(i)–(iv).
66. 35 U.S.C. § 154(b)(1)(A).
67. 35 U.S.C. § 154(b)(1)(B).
68. *Id*.
69. 35 U.S.C. § 154(b)(1)(C) ("[I]f the issue of an original patent is delayed due to [an interference, a secrecy order pursuant to § 181 or an] appellate review by the Board of Patent Appeals and Interferences or by a Federal court in a case in which the patent was issued under a decision in the review reversing an adverse determination of patentability, the term of the patent shall be extended 1 day for each day of the pendency of the proceeding, order, or review, as the case may be.").
70. 35 U.S.C. § 154(b)(2)(A).

> *Second*, "[n]o patent the term of which has been disclaimed beyond a specified date may be adjusted under this section beyond the expiration date specified in the disclaimer."[71]
>
> *Third*, each of the above extensions "shall be reduced by a period equal to the period of time during which the applicant failed to engage in reasonable efforts to conclude prosecution of the application."[72]

The term of a patent can also be extended because of delays due to the regulatory review process by the U.S. Food and Drug Administration pursuant to 35 U.S.C. § 156.[73] An extension under section 156 is called a patent term extension or PTE.

The relationship between PTA, PTE, and the doctrine of double patenting is discussed in section 5:8.[74]

§ 1:5 Post-Grant Actions

§ 1:5.1 Reissue (35 U.S.C. § 251)

An issued U.S. patent may be reissued, upon surrender of the original patent, if it is "through error without any deceptive intention, deemed wholly or partly inoperative or invalid."[75] Bases for filing a reissue application include narrowing or broadening the claims, correcting inventorship, and making or correcting a claim to priority. The scope of the claims cannot be broadened unless the reissue application is filed within two years from the grant of the original patent.[76] The statute prohibits the introduction of new matter into the reissue application.[77] In addition, during reissue a patentee cannot recapture subject matter that was surrendered in an application to obtain the original patent.[78] An applicant's recourse from an adverse decision in

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71. 35 U.S.C. § 154(b)(2)(B).
72. 35 U.S.C. § 154(b)(2)(C)(i).
73. The determination of such extension is discussed in section 8:4.
74. See, in particular, discussion regarding *In re* Cellect, LLC, 81 F.4th 1216 (Fed. Cir. 2023) (holding that obviousness-type double patenting is determined based on a patent's expiration date, including any patent term adjustment under section 154), and Novartis AG v. Ezra Ventures LLC, 909 F.3d 1367 (Fed. Cir. 2018) (holding that obviousness-type double patenting is determined based on a patent's expiration date without considering any patent term extension under section 156).
75. 35 U.S.C. § 251.
76. *Id*.
77. *Id*.
78. M.P.E.P. § 1412.02, citing, among other cases, Pannu v. Storz Instruments Inc., 258 F.3d 1366 (Fed. Cir. 2001).

a reissue application is the same as for a non-provisional application, discussed above.[79]

The grant of a reissued patent may be subject to the "intervening rights" of a party whose activities fall within the scope of the reissued claims, but which were not covered by the original claims.[80] "Intervening rights" is an affirmative defense to an action for patent infringement brought under a reissued patent.

§ 1:5.2 Reexamination (35 U.S.C. §§ 302–307)

Any person, including a patent owner, may file a request that an issued U.S. patent be reexamined by the PTO to consider the effect on patentability of prior art patents or printed publications.[81] In addition, the PTO can reexamine a patent on its own initiative.[82] The ground for proceeding with a reexamination is a finding by the PTO of a "substantial new question of patentability affecting any claim of the patent," which can be based on patents or printed publications that are newly raised or that were cited to or considered by the PTO during the original examination.[83] If a substantial new question of patentability is found, the patent is reexamined. During reexamination, the patent owner may amend the claims and/or add new claims to distinguish over the cited prior art, but no amended or new claim that enlarges the scope of the claims will be permitted.[84]

Reexaminations proceed *ex parte*, which limits the participation of a third-party requestor in regard to responding to any statement filed by the patent owner to an order for reexamination made by the PTO.[85] The AIA replaced inter partes reexamination, which permitted participation by the requester, with "inter partes review," an adjudicative proceeding between a petitioner and the patent owner, discussed below.[86]

The PTO's decision on a reexamination is subject to appeal to the Board of Patent Appeals and Interferences.[87] In an *ex parte* reexamination filed on or after November 29, 1999, a patent owner dissatisfied with the Board's decision can appeal to the Court of Appeals

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79. *See supra* section 1:3.1.
80. 35 U.S.C. § 252.
81. 35 U.S.C. §§ 301, 302.
82. 35 U.S.C. § 303(a).
83. *Id*.
84. 35 U.S.C. § 305.
85. 35 U.S.C. § 304.
86. Pub. L. No. 112-29, § 6 (2011).
87. 35 U.S.C. §§ 134, 306, 315.

for the Federal Circuit, but may not initiate a civil action in the U.S. District Court for the District of Columbia.[88]

In *ex parte* reexamination, at the expiration of any time to appeal or at the termination of any appeal proceeding, the PTO will issue a certificate canceling any claim determined to be unpatentable, confirming any claim found to be patentable, and incorporating into the patent any amended or new claim determined to be patentable.[89] Any amended or new claim determined to be patentable is subject to the same "intervening rights" discussed earlier with respect to reissued patents.[90]

§ 1:5.3 *Inter Partes Review (35 U.S.C. §§ 311–318)*

Pursuant to the AIA, commencing September 16, 2012, "inter partes review" replaced inter partes reexamination.[91] "Inter partes review" is an adjudicative proceeding before the new PTAB, which sits in three-judge panels.[92] Any person who is not a patent owner

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88. 35 U.S.C. §§ 141–145, 306; 37 C.F.R. § 1.303. For *ex parte* reexaminations filed before November 29, 1999, the patent owner had the option to initiate a civil action in the U.S. District Court for the District of Columbia. 37 C.F.R. § 1.303(a). However, by appealing to the Court of Appeals for the Federal Circuit, the patent owner waived the right to initiate a civil action under 35 U.S.C. § 145. *See* 37 C.F.R. § 1.303(b).

89. 35 U.S.C. § 307(a).

90. *See supra* section 1:5.1. *See also* 35 U.S.C. §§ 307(b), 316(b).

91. The statutory provisions for inter partes reexamination were codified at former 35 U.S.C. §§ 311–318. Inter partes reexamination permitted third-party requesters to file written comments addressing issues raised in Office Actions and patent owners' responses. A third party could appeal an adverse decision of the Board of Appeals only to the Federal Circuit. 35 U.S.C. §§ 141–44, 315. In addition, after inter partes reexamination, a third-party requester was estopped from asserting in a later civil action for patent infringement that involves a claim already determined in the reexamination to be valid and patentable, any ground that was raised or could have been raised during the reexamination. 35 U.S.C. § 315(c). However, the third-party requester was not prevented from asserting invalidity based on newly discovered prior art that was not available at the time of the inter partes reexamination. *Id*.

92. The U.S. Supreme Court addressed the constitutionality of inter partes review in Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC, 138 S. Ct. 1365 (2018). The Court considered whether the ability of the PTAB to decide inter partes reviews violates the separation of powers requirement of Article III or the right to a jury trial of the Seventh Amendment to the U.S. Constitution. The Court held that the granting of a patent is a public right, resulting in the grant of a public franchise, and Congress was permitted to reserve the authority for the Patent and Trademark Office and the PTAB to reconsider the granting

may file a petition for inter partes review seeking to cancel one or more claims of an issued patent as unpatentable, but only for reasons under 35 U.S.C. § 102 or 103 based on prior art consisting of patents or printed publications.[93] The petition must identify all real parties in interest.[94] The petition for inter partes review can only be filed nine months after patent issuance or at the termination of any post-grant review proceeding. The PTAB is required to issue a determination within one year, which can be extended up to six months for good cause.[95]

The standard for initiating inter partes review is a determination by the PTAB that "there is a reasonable likelihood that the petitioner would prevail on at least one claim."[96] Under 35 U.S.C. § 314(d), the

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of an already-issued patent without violating Article III. As a result of this holding, the Court also held that inter partes review did not violate the Seventh Amendment, as it does not apply where Congress properly assigns a matter for adjudication by a non–Article III tribunal such as inter partes reviews before the PTAB.

93. 35 U.S.C. § 311(a), (b).

94. 35 U.S.C. § 312(a)(2).

95. 35 U.S.C. § 316(a)(11).

96. 35 U.S.C. § 314. The PTAB has laid out a six-factor test for determining whether to institute an IPR proceeding when there is parallel district court litigation. *See* Apple Inc. v. Fintiv, Inc., IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020). The six factors are:

    1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
    2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
    3. investment in the parallel proceeding by the court and the parties;
    4. overlap between issues raised in the petition and in the parallel proceeding;
    5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
    6. other circumstances that impact the Board's exercise of discretion, including the merits.

    On June 22, 2022, the USPTO issued interim guidance for discretionary denials, clarifying that institution will not be denied under *Fintiv* when (1) "a petition presents compelling evidence of unpatentability"; (2) "a request for denial under *Fintiv* is based on a parallel ITC proceeding"; or (3) "a petitioner stipulates not to pursue in a parallel district court proceeding the same grounds as in the petition or any grounds that could have reasonably been raised in the petition." Memorandum from USPTO Director Katherine K. Vidal to Members of the PTAB regarding Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation at 9 (June 21, 2022). The guidance also

"determination by the Director whether to institute an inter partes review under this section shall be final and non-appealable."[97] The petitioner bears the burden of proving unpatentability by a preponderance of the evidence. During the proceedings, a patent owner may file one motion to cancel challenged claims or propose substitute claims,[98] although with the same intervening rights consequences of a reissue patent.[99] If the PTAB issues a final written decision on an inter partes review, and the time for appeal had expired or any appeal has terminated, the PTO issues a certificate canceling any claim of the patent determined to be unpatentable, confirming any claim determined to be patentable, and incorporating in the patent by operation of the certificate any new or amended claim determined to be patentable.[100]

Under section 315, inter partes review carries with it certain procedural and estoppel consequences:

- A prior declaratory judgment suit by the petitioner challenging patent validity (but not the filing of a counterclaim) bars a petition for inter partes review and vice versa.[101]
- A civil action filed by the petitioner challenging the validity of a claim of the patent on or after the date the petitioner files a petition for inter partes review will be stayed until the patent

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provides that, "where other relevant factors weigh against exercising discretion to deny institution or are neutral, the proximity to trial should not alone outweigh all of those other factors." *Id*. at 8.

97. The U.S. Supreme Court upheld the constitutionality of section 314(d) in Cuozzo Speed Techs., LLC v. Lee, 136 S. Ct. 2131 (2016). In *Cuozzo*, the Supreme Court also concluded that 35 U.S.C. § 316(a)(4) permitted the Patent Office to establish a rule providing that claims should be construed in IPR proceedings under their "broadest reasonable construction." In 2018, the USPTO issued a new rule that patent claims in PTAB proceedings would be construed consistent with the federal court claim construction standard that is used to construe a claim in a civil action under 35 U.S.C. § 282(b), which is the standard set forth in Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) (en banc). *See* 37 C.F.R. § 42.100(b).

98. 35 U.S.C. § 316(d).

99. 35 U.S.C. § 318(c).

100. 35 U.S.C. § 318(b).

101. The Federal Circuit clarified the standard for determining estoppel effects on non-petitioned inter partes review grounds and held that a petitioner is estopped from raising in a subsequent district court or ITC proceeding "any [invalidity] ground that the petitioner raised or reasonably could have raised during that inter partes review." Ironburg Inventions Ltd. v. Valve Corp., 64 F.4th 1274 (Fed. Cir. 2023).

owner moves to lift the stay or files a civil action or counterclaim that the petitioner has infringed the patent.

- Inter partes review may not be instituted more than one year after an infringement suit is brought against the petitioner.
- A final decision of the PTAB is appealable to the Federal Circuit.[102] Parties to a PTAB inter partes review proceeding may also request review of a PTAB final decision by a rehearing by the Director of the USPTO. The Director also has the authority to initiate a *sua sponte* review of these final decisions.[103]
- Estoppel effects of a final decision on post-grant review are:
  - The petitioner is precluded from proceeding in the PTO on any ground that was raised or which could have been raised with respect to the claim(s).
  - The petitioner is precluded from asserting in a district court or International Trade Commission (ITC) proceeding that a claim is invalid on any ground that was raised or could have been raised during inter partes review.

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102. The right to appeal the PTAB's decision in an IPR proceeding is not guaranteed, however. To appeal, a party must have "Article III" standing, which may require a showing that the appealing party "is engaging in, or has nonspeculative plans to engage in, conduct even arguably covered by the upheld claims of the" patent. Allgenesis Biotherapeutics Inc. v. Cloudbreak Therapeutics, LLC, 2023 U.S. App. LEXIS 29594 (Fed. Cir. Nov. 7, 2023); *see also* AVX Corp. v. Presidio Components Inc., 923 F.3d 1357, 1365 (Fed. Cir. 2019).

103. The process of requesting or *sua sponte* Director review of PTAB inter partes review final decisions is a recent development following the U.S. Supreme Court's decision in United States v. Arthrex, 141 S. Ct. 1970 (2021). In *Arthrex*, the Court addressed whether the appointment of administrative patent judges under the PTAB regime violated the Appointments Clause of the Constitution. Under the Appointments Clause, "principal officers" can be appointed by the President only with the advice and consent of the Senate. The Court determined that the existing PTAB inter partes review procedure was unconstitutional because administrative patent judges who served on the PTAB panels do not have the authority to act as "principal officers" capable of rendering unreviewable final decisions because they have not been appointed by the President and confirmed by the Senate. The Court severed the unconstitutional portion of the statute at issue, preserving the rest of the PTAB procedure but allowing the opportunity for discretionary Director review of the panel final decisions.

Under section 317, an inter partes review can be settled prior to decision on the merits without estoppel effect. The settlement must be filed with the PTO, but it can be maintained confidential.

§ 1:5.4 Post-Grant Review (35 U.S.C. §§ 321–329)

For patents issuing with a claim having an effective filing date of March 16, 2013, or later, the AIA provides a post-grant review proceeding by which by a person who is not a patent owner can petition to cancel an issued claim as unpatentable on any ground that could be raised in an invalidity challenge in district court. The petition must identify all real parties in interest.[104] Post-grant review is an adjudicative proceeding before the new PTAB, which sits in three-judge panels. A petition for post-grant review can be filed up to nine months after a patent is granted.[105] The PTAB is required to issue a determination within one year, which can be extended up to six months for good cause.[106]

The PTO is required to make a determination to institute post-grant review proceedings within three months of patentee's preliminary response to the petition.[107] To proceed with a petition, the PTO must conclude that "it is more likely than not that one or more claims of challenged claims is unpatentable" or that "the petition raises a novel or unsettled legal question."[108] The PTO's determination to proceed is not appealable.[109]

The petitioner bears the burden of proving unpatentability by preponderance of the evidence.[110] The patent owner can file one motion to cancel challenged claims or propose substitute claims,[111] although with the same intervening rights consequences of reissue.[112] If the PTAB issues a final written decision on a post-grant review, and the time for appeal had expired or any appeal has terminated, the PTO issues a certificate canceling any claim of the patent determined to be unpatentable, confirming any claim determined to be patentable, and incorporating in the patent by operation of the certificate any new or amended claim determined to be patentable.[113]

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104. 35 U.S.C. § 322(a)(1)(2).
105. 35 U.S.C. § 321(c).
106. 35 U.S.C. § 326(a)(11).
107. 35 U.S.C. § 324(c).
108. 35 U.S.C. § 324(a), (b).
109. 35 U.S.C. § 324(e).
110. 35 U.S.C. § 326(e).
111. 35 U.S.C. § 326(d).
112. 35 U.S.C. § 328.
113. 35 U.S.C. § 328(b).

Under section 325, post-grant review carries with it certain procedural and estoppel consequences:

- A prior declaratory judgment suit by the petitioner challenging patent validity (but not the filing of a counterclaim) bars a petition for post-grant review.
- A civil action filed by the petitioner challenging the validity of a claim of the patent on or after the date the petitioner files a petition for post-grant review will be stayed until the patent owner moves to lift the stay or files a civil action or counterclaim that the petitioner has infringed the patent.
- If a civil action alleging infringement is filed within three months of patent issuance, a court cannot stay consideration of a preliminary injunction motion based on the institution of post-grant review proceedings.
- The final decision of the PTAB on a petition for post-grant review is appealable to the Federal Circuit.
- Estoppel effects of final decision in post-grant review are:
    - A petitioner is precluded from proceeding in the PTO on any ground that was raised or which could have been raised with respect to the claim(s) during post-grant review.
    - A petitioner is precluded from asserting in a district court or ITC proceeding that the claim is invalid on any ground that was raised or could have been raised during post-grant review.

The claims of a reissue patent that are identical to or narrower than the original claims cannot be the subject of post-grant review if more than nine months have passed since issuance of the original patent.[114]

Under section 327(f), post-grant reviews can be settled prior to a decision on the merits by the PTAB without estoppel effect. Written settlement agreements are to be filed with the PTO, but may be accorded confidential treatment.

§ 1:5.5 Supplemental Examinations (35 U.S.C. § 257)

Effective September 16, 2012, under new section 257, "[a] patent owner may request supplemental examination of a patent in the

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114. 35 U.S.C. § 325(f).

Office . . . [t]o consider information believed to be relevant to the patent."[115] If the PTO determines that a "substantial new question of patentability" has been raised, the patent enters ex parte reexamination on any issue, and is not limited to patentability over printed publications and patents.

Section 257 further provides, with certain limitations, that information submitted by patent owners during supplemental examination cannot be subsequently used to assert that the patent is unenforceable due to inequitable conduct: "A patent shall not be held unenforceable on the basis of conduct relating to information that had not been considered, was inadequately considered, or was incorrect in a prior examination of the patent if the information was considered, reconsidered, or corrected during a supplemental examination of the patent."[116] However, under section 257(c)(2), this protection does not apply with respect to:

- "an allegation pled with particularity in a civil action" or in a Hatch-Waxman notice letter "before the date of a supplemental examination request" to consider the relevant information, or
- "any defense raised" in a patent infringement or ITC action based on information submitted in a supplemental examination unless the supplemental examination and any reexamination ordered pursuant to the request are "concluded before the date on which the action is brought."

§ 1:5.6 Certificates of Correction

The PTO may issue Certificates of Correction to correct printing errors in a patent without payment of a fee for errors caused by the PTO.[117] The PTO may also issue such certificates to correct clerical and typographical errors or errors of a minor character made by the applicant in good faith upon payment of a fee, as long as the changes do not constitute new matter or require reexamination.[118]

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115. 35 U.S.C. § 257(a).
116. 35 U.S.C. § 257(c)(1).
117. 35 U.S.C. § 254.
118. 35 U.S.C. § 255.

§ 1:5.7 Disclaimers

Under section 253 of the Patent Act, a patent owner may disclaim any complete claim of a patent or may dedicate to the public the entire term, or any terminal part of a patent granted, or to be granted.[119]

§ 1:6 Interferences and Interfering Patents; Transition from "First to Invent" to "First to File"

Prior to the enactment of the AIA, in the United States, the first to invent[120] the claimed subject matter is entitled to a patent, as opposed to the first to file a patent application. Under the AIA, patent applications and patents containing at any time a claim having an effective filing date of March 16, 2013, or later will be governed under a new "first-to-file" system, which awards a patent to the first inventor to file a patent application, rather than the first to invent. However, patent applications and patents for which all claims have an effective filing date prior to March 16, 2013, will still be governed under the first-to-invent system. Under the first-to-invent system, if two or more applications claim the same subject matter, the PTO can declare an "interference" between them in order to determine which applicant was the first to invent, and therefore has the right to a patent.[121] An interference can also be declared between a pending patent application and an issued U.S. patent.[122] An interference in the PTO is an inter partes action decided by the Board of Patent Appeals and Interferences that involves the taking of testimony regarding priority of invention. The interference can also decide issues of patentability.[123] Decisions of the Board of Patent Appeals and Interferences are appealable to the Federal Circuit.[124] Alternatively, a dissatisfied

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119. The use of terminal disclaimers to obviate obviousness-type double patenting rejections is discussed in section 5:8.5[E].
120. The issue of inventorship is discussed in section 4:1.
121. 35 U.S.C. § 135. *See* Capon v. Eshhar, 418 F.3d 1349, 1351 (Fed. Cir. 2005) ("A patent interference is an administrative proceeding pursuant to 35 U.S.C. §§ 102(g) and 135(a), conducted for the purpose of determining which of competing applicants is the first inventor of common subject matter.").
122. A patent applicant can "copy" the claim of published U.S. patent application or an issued U.S. patent to provoke an interference so long as the claim is copied within one year of the publication of the application or granting of the patent where the claim first appears. 35 U.S.C. § 135(b)(1) and (2).
123. 35 U.S.C. § 135(a).
124. 35 U.S.C. § 141.

party to an interference can commence a civil action in federal district court.[125]

Under the first-to-invent system, if two or more issued U.S. patents claim the same subject matter, an owner of one of the patents can bring a civil action in federal district court to determine the issues of priority of invention and validity of any of the interfering patents.[126] If the owners of the patents reside in a plurality of districts not within the same state, or a party resides in a foreign country, the U.S. District Court for the District of Columbia has jurisdiction over the interfering patents action.[127]

As explained below, the AIA eliminates PTO interferences and district court interfering-patent actions and replaces them with derivation proceedings and derived-patent actions.

§ 1:7 Derivation Proceedings and Derived Patents

Under the AIA, for patent applications and patents having at least one claim with an effective filing date of March 16, 2013, or later, "derivation proceedings" will replace interferences. Derivation proceedings will be governed by amended section 135 and will be determined by the PTAB. A derivation proceeding may be instituted by a patent applicant who files a petition asserting that an inventor named on an earlier-filed patent application derived the claimed invention from an inventor named in the petitioner's application. A petition to institute a derivation proceeding must be filed "within the one year period beginning on the date of the first publication of a claim to an invention that is the same or substantially the same as the earlier applicant's claim to the invention."[128]

The PTAB determines "whether an inventor named in the earlier application derived the claimed invention from an inventor named in the petitioner's application and, without authorization, the earlier application claiming such invention was filed."[129] The PTAB "may correct the naming of the inventor in any application or patent at issue."[130] The AIA also amended 35 U.S.C. § 291 to create a "derived patents" action by which the "owner of a patent can bring a civil action against the owner of another patent that claims the same invention and which has an earlier effective filing date alleging that the other

125. 35 U.S.C. § 146.
126. 35 U.S.C. § 291.
127. 35 U.S.C. §§ 291, 146.
128. 35 U.S.C. § 135(a).
129. 35 U.S.C. § 135(b).
130. *Id.*

patent was derived from the inventor of the invention claimed in the patent owner by the party seeking relief." A derived patents action must be filed "before the end of the one year period beginning on the date of the issuance of the first patent containing a claim to the allegedly derived invention and naming an individual alleged to have derived such invention."[131]

§ 1:8 Enforcement of Patents

§ 1:8.1 Actions for Infringement

A U.S. patent provides its owner with the right, during the patent's term, to exclude others from practicing the invention defined by the claims of the patent.[132] The right to exclude is granted in exchange for the disclosure of a new, non-obvious, and useful invention, which becomes available to the public upon the expiration of the patent.[133] A U.S. patent is infringed by the unauthorized activities of making, using, offering to sell, selling, or importing into the United States the claimed invention.[134]

Those who induce or contribute to infringement by others are liable as infringers.[135]

A U.S. patent claiming a product is subject to infringement by the supply from the United States of all or a substantial portion of the components of a patented invention in such a manner as to induce the making of the claimed invention outside the United States, or by

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131. 35 U.S.C. § 291(b).
132. 35 U.S.C. § 154(a)(1).
133. *See* Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 480–81 (1974) ("To insure adequate and full disclosure so that upon the expiration of the 17-year period 'the knowledge of the invention enures to the people, who are thus enabled without restriction to practice it and profit by its use,' . . . the patent laws require that the patent application shall include a full and clear description of the invention and 'of the manner and process of making and using it' so that any person skilled in the art may make and use the invention. 35 U.S.C. § 112.") (citations omitted); Aronson v. Quick Point Pencil Co., 440 U.S. 257, 262 (1979) ("patent law . . . promotes disclosure of inventions, to stimulate further innovation and to permit the public to practice the invention once the patent expires"). However, there are circumstances in which an invention described in a patent may be subject to the claims of another, later expiring patent. *E.g.*, *In re* Kaplan, 789 F.2d 1574 (Fed. Cir. 1986) (second, later expiring patent could issue to joint inventors even though that joint invention is also described in a patent issued to only one of the investors, which will expire earlier).
134. 35 U.S.C. § 271(a).
135. 35 U.S.C. § 271(b) & (c).

the supply from the United States of a component especially made or adapted for use in the invention with the knowledge that the component is so made or adapted, and with the intent that the component will be combined outside the United States so as to infringe the patent if the combination occurred in the United States.[136]

A U.S. patent claiming a process for making a product may be infringed by the importation into the United States of a product made by the claimed process.[137]

§ 1:8.2 Remedies for Infringement

[A] Injunctive Relief: Permanent and Preliminary Injunctions

A court may grant a permanent injunction to prevent infringement of a patent as long as the traditional test for obtaining such equitable relief is met by showing:

(1) irreparable injury,

(2) inadequacy of remedies at law (that is, monetary damages) to compensate for the infringement,

(3) that the balance of hardships between the parties weighs in favor of equitable relief, and

(4) that the public interest would not be disserved by an injunction.[138]

A patent owner may also obtain a preliminary injunction to prevent further infringement pending a trial on the merits. The four factors relevant to determining whether to grant or deny a preliminary injunction are:

(1) the likelihood of the patentee's success on the merits;

(2) irreparable harm if the injunction is not granted;

(3) the balance of hardships between the parties; and

(4) the public interest.[139]

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136. 35 U.S.C. § 271(f).

137. 35 U.S.C. § 271(g). A detailed discussion of patent infringement is covered in chapter 10.

138. 35 U.S.C. § 283; eBay, Inc. v. MercExch., LLC, 547 U.S. 388, 391 (2006) (holding that there is no rule that a permanent injunction should necessarily issue after an adjudication of patent infringement, but rather that traditional rules of equity apply).

139. Abbott Labs. v. Andrx Pharm., Inc., No. 06-1101, 2007 U.S. App. LEXIS 171, at *9–10 (Fed. Cir. Jan. 5, 2007).

On the likelihood of success factor, the patent owner must show that it will likely prove infringement of at least one valid and enforceable patent claim.[140] In order to defeat a preliminary injunction on invalidity and unenforceability grounds, the accused infringer, "as the party bearing the burden of proof on the issue at trial, must establish a substantial question of invalidity or unenforceability, that is, that it is likely to succeed in proving invalidity or unenforceability of the asserted patents."[141] The Federal Circuit has held that "[i]rreparable harm is presumed when a clear showing of patent validity and infringement has been made."[142] The issuance of a preliminary injunction requires the giving of security, usually by posting a bond, in an amount to be determined by the court for the payment of costs and damages to the enjoined party in the event it is determined that the preliminary injunction was wrongfully granted.[143]

[B] Damages: Lost Profits and Reasonable Royalty

Upon a determination of infringement, a patent owner is entitled to obtain damages "adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer, together with interest and costs as fixed by the court."[144] The Patent Act provides that "[e]xcept as otherwise provided by law, no recovery shall be had for any infringement committed more than six years prior to the filing of the complaint or counterclaim for infringement in the action."[145]

If the patent owner can prove that it lost sales due to the infringement, the patent owner may be able to recover its lost profits. In general, in order to recover lost profits, the patent owner is required to prove the existence of sales it would have made "but for" the infringement, which includes proof of demand for the patented product, absence of acceptable non-infringing substitutes, manufacturing and marketing capacity to make the infringer's sales and proof of the

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140. *Id*. at *10.
141. *Id*. (citing Gonzales v. O. Centro Espirita Beneficente Uniao Do Vegetal, 126 S. Ct. 1211, 1219–20 (2006) ("[T]he burdens at the preliminary injunction stage track the burdens at trial.")); Ashcroft v. ACLU, 542 U.S. 656, 666 (2004).
142. Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1350 (Fed. Cir. 2001).
143. FED. R. CIV. P. 65(c).
144. 35 U.S.C. § 284. Interest can include both pre- and post-judgment interest.
145. 35 U.S.C. § 286.

amount of its lost profits.[146] If a patent owner is not entitled to lost profits (either because it cannot prove the necessary elements or it does not make any product as to which sales could have been lost due to the infringement), the patent owner is nevertheless entitled, as a statutory minimum, to a "reasonable royalty." A reasonable royalty is based on a hypothetical negotiation between a "willing" licensor and a "willing" licensee at the time infringement began.[147] A number of factors may be considered in determining a reasonable royalty, including:

1. The royalties received by the patentee for the licensing of the patent in suit, proving or tending to prove an established royalty.
2. The rates paid by the licensee for the use of other patents comparable to the patent in suit.
3. The nature and scope of the license, as exclusive or non-exclusive; or as restricted or non-restricted in terms of territory or with respect to whom the manufactured product may be sold.
4. The licensor's established policy and marketing program to maintain his patent monopoly by not licensing others to use the invention or by granting licenses under special conditions designed to preserve that monopoly.
5. The commercial relationship between the licensor and licensee, such as whether they are competitors in the same territory in the same line of business; or whether they are inventor and promoter.
6. The effect of selling the patented specialty in promoting sales of other products of the licensee; the existing value of the invention to the licensor as a generator of sales of his non-patented items; and the extent of such derivative or convoyed sales.
7. The duration of the patent and the term of the license.
8. The established profitability of the product made under the patent; its commercial success; and its current popularity.

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146. Golden Blount, Inc. v. Robert H. Peterson Co. (*Golden Blount II*), 438 F.3d 1354, 1371–72 (Fed. Cir. 2006).
147. *See, e.g.*, Catalina Lighting, Inc. v. Lamps Plus, Inc., 295 F.3d 1277, 1289 (Fed. Cir. 2002).

9. The utility and advantages of the patent property over the old modes or devices, if any, that had been used for working out similar results.

10. The nature of the patented invention; the character of the commercial embodiment of it as owned and produced by the licensor; and the benefits to those who have used the invention.

11. The extent to which the infringer has made use of the invention; and any evidence probative of the value of that use.

12. The portion of the profit or of the selling price that may be customary in the particular business or in comparable businesses to allow for the use of the invention or analogous inventions.

13. The portion of the realizable profit that should be credited to the invention as distinguished from non-patented elements, the manufacturing process, business risks, or significant features or improvements added by the infringer.

14. The opinion testimony of qualified experts.

15. The amount that a licensor (such as the patentee) and a licensee (such as the infringer) would have agreed upon (at the time the infringement began) if both had been reasonably and voluntarily trying to reach an agreement; that is, the amount which a prudent licensee—who desired, as a business proposition, to obtain a license to manufacture and sell a particular article embodying the patented invention—would have been willing to pay as a royalty and yet be able to make a reasonable profit and which amount would have been acceptable by a prudent patentee who was willing to grant a license.[148]

In addition to the above remedies, a granted U.S. patent includes the right to recover a reasonable royalty from any person who, beginning on the date of publication of a patent application through the date of issuance, made, used, offered for sale, or sold the invention as claimed in the published application if (a) that person had actual notice of the published application, and (b) the claims in the patent

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148. These factors were discussed in Ga.-Pac. Corp. v. U.S. Plywood Corp., 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970), *modified and aff'd*, 446 F.2d 295, 302 (2d Cir. 1971), and are known as the "*Georgia-Pacific* factors." The Federal Circuit has cited the use of the *Georgia-Pacific* factors with approval in the determination of a reasonable royalty. *See, e.g.*, Gargoyles, Inc. v. United States, 113 F.3d 1572, 1580 (Fed. Cir. 1997).

issued are substantially identical to the claims in the published application.[149]

Attorney fees may also be recovered by the prevailing party if the court finds the case to be "exceptional." Examples of exceptional cases include those where there is a finding of willful infringement,[150] or a finding that the patent is unenforceable due to inequitable conduct.[151]

Patentees and those making, offering for sale, or selling within the United States any patented article may give notice to the public that the article is patented by marking the article with the word "patent" or the abbreviation "pat.", together with the number of the patent.[152] If, because of the nature of the article, this cannot be done, the patent information may be placed on packaging or on a label.[153] Effective with the September 16, 2011, enactment of the AIA, a product can be "virtually marked" by marking it with the word "patent" (or "pat.") together with an Internet address that associates the patented article with the number of the patent.[154] Failure to mark may result in a limitation in the ability to recover damages:

> In the event of failure to so mark, no damages shall be recovered by the patentee in any action for infringement, except on proof that the infringer was notified of the infringement and continued to sell thereafter, in which event damages may be recovered only for infringement occurring after such notice. Filing of an action for infringement shall constitute such notice.[155]

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149. 35 U.S.C. § 154(d).

150. *See, e.g.*, Golight, Inc. v. Wal-Mart Stores, Inc., 355 F.3d 1327, 1339–40 (Fed. Cir. 2004).

151. *See, e.g.*, Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp., 267 F.3d 1370, 1380–81 (Fed. Cir. 2001).

152. 35 U.S.C. § 287(a).

153. *Id*. In Am. Med. Sys., Inc. v. Med. Eng'g Corp., 6 F.3d 1523, 1538–39 (Fed. Cir. 1999), the Federal Circuit stated that "[t]he law is clear that the notice provisions of section 287 do not apply where the patent is directed to a process or a method." The court further stated:

> The purpose behind the marking statute is to encourage the patentee to give notice to the public of the patent. The reason that the marking statute does not apply to method claims is that, ordinarily, where the patent claims are directed to only a method or process there is nothing to mark. Where the patent contains both apparatus and method claims, however, to the extent that there is a tangible item to mark by which notice of the asserted method claims can be given, a party is obliged to do so if it intends to avail itself of the constructive notice provisions of section 287(a).

154. 35 U.S.C. § 287(a), as amended.

155. 35 U.S.C. § 287(a).

[C] Enhanced Damages for Willful Infringement

In awarding damages for patent infringement, courts under 35 U.S.C. § 284 "may increase the damages up to three times the amount found or assessed." The U.S. Supreme Court in *Halo Electronics, Inc. v. Pulse Electronics, Inc.*[156] held that section 284 "gives the district courts the discretion to award enhanced damages," in "egregious cases of misconduct beyond typical infringement."[157] In reviewing the history of enhanced damages awards under the Patent Act, the Supreme Court stated that enhanced damages "are not to be meted out in a typical infringement case, but are instead designed as a 'punitive' or 'vindictive' sanction for egregious infringement behavior. The sort of conduct warranting enhanced damages has been variously described in our cases as willful, wanton, malicious, bad faith, deliberate, consciously wrongful, flagrant, or—indeed—characteristic of a pirate."[158]

In *Halo*, the Supreme Court rejected the Federal Circuit's standard for determining enhanced damages as set forth in *In re Seagate Technology, LLC*,[159] which had required showings by clear and convincing evidence that first, "the infringer acted despite an objectively high likelihood that its actions constituted infringement of a valid patent," and second, that the risk of infringement "was either known or so obvious that it should have been known to the accused infringer."[160] The *Halo* Court also rejected *Seagate*'s holding that an infringer's ability to "muster a reasonable (even though unsuccessful) defense at an infringement trial" would insulate the infringer from enhanced damages: "Under that standard, someone who plunders a patent—infringing it without any reason to suppose his conduct is arguably defensible—can nevertheless escape any comeuppance under § 284 solely on the strength of his attorney's ingenuity."[161] Thus, the Court in *Halo* concluded that "culpability is generally measured against the knowledge of the actor at the time of the challenged conduct,"[162] not at the time it is litigating its defenses in court. *Halo* also rejected the Federal Circuit's application of a heightened clear and convincing evidence standard for enhanced damages and held that the preponderance of the evidence standard should be applied. Finally, the *Halo* Court held that appellate review of awards of

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156. Halo Elecs., Inc. v. Pulse Elecs., Inc., 136 S. Ct. 1923 (2016).
157. *Id*. at 1935.
158. *Id*. at 1932.
159. *In re* Seagate Tech., LLC, 497 F.3d 1360 (Fed. Cir. 2007) (en banc).
160. *Id*. at 1371.
161. *Halo Elecs.*, 136 S. Ct. at 1933.
162. *Id*.

enhanced damages for willful infringement are reviewed under an abuse of discretion standard.[163]

[D] Award of Attorney Fees in Exceptional Cases to the Prevailing Party

Under 35 U.S.C. § 285, a "court in exceptional cases may award reasonable attorney fees to the prevailing party." In *Octane Fitness, LLC v. Icon Health & Fitness, Inc.*,[164] the Supreme Court held that

> an "exceptional" case is simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated. District courts may determine whether a case is "exceptional" in the case-by-case exercise of their discretion, considering the totality of the circumstances.[165]

Whether a case is "exceptional" is decided under a preponderance of the evidence standard.[166]

In *Octane Fitness*, the Supreme Court expressly rejected the Federal Circuit's test for the award of attorney fees as set forth in *Brooks Furniture Manufacturing, Inc. v. Dutailer International, Inc.*,[167] as "overly rigid"[168] because it restricted a finding of "exceptional case" to instances in which "a district court either finds litigation-related misconduct of an independently sanctionable magnitude or determines that the litigation was both 'brought in subjective bad faith' and 'objectively baseless.'"[169] The Supreme Court found that these categories were either based on "independently sanctionable conduct" or "too restrictive"[170] and that the standard in *Brooks Furniture* was "so demanding that it would appear to render § 285 largely superfluous."[171]

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163. *Id*. at 12–13. In SRI Int'l, Inc. v. Cisco Sys., Inc., 930 F.3d 1295, 1309 (Fed. Cir. 2019), the Federal Circuit, applying *Halo*, concluded that there was no willfulness when "the record is insufficient to establish that Cisco's conduct rose to the level of wanton, malicious, and bad-faith behavior required for willful infringement."
164. Octane Fitness, LLC v. Icon Health & Fitness, Inc., 572 U.S. 545 (2014).
165. *Id*. at 554.
166. *Id*. at 557–58.
167. Brooks Furniture Mfg., Inc. v. Dutailer Int'l, Inc., 393 F.3d 1378 (Fed. Cir. 2005).
168. *Octane Fitness*, 134 S. Ct. at 1756.
169. *Id*.
170. *Id*. at 1756–57.
171. *Id*. at 1758.

Accordingly, under *Octane Fitness*, district courts will have broader discretion to find a patent case "exceptional" in deciding whether to award attorney fees to the prevailing party, whether the patent owner or the accused infringer.

§ 1:8.3 Defenses to a Charge of Patent Infringement

A party accused of patent infringement can raise a number of defenses, including:[172]

(1) the accused product or process does not infringe because it does not satisfy the requirements of every limitation of the asserted patent claim, either literally or under the doctrine of equivalents;

(2) the asserted claim is invalid for failing to meet the requirements for patentability;[173]

(3) the accused activity was carried out for the purposes of developing data to obtain regulatory approval by the FDA and is subject to the safe harbor of section 271(e)(1) of the Patent Act;

(4) the accused activity is subject to "intervening rights" where the claims of a reissued or reexamined patent have been amended;

(5) the patent is unenforceable against anyone based on, for example, inequitable conduct in obtaining the patent, patent misuse, or prosecution history laches;

(6) the doctrine of patent exhaustion precludes assertion of the patent against an item which has been the subject of an initial authorized sale;

(7) the patent cannot be enforced against the particular defendant due to an express or implied license;

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172. See 35 U.S.C. § 282, which lists "defenses in any action involving the validity or infringement of a patent" that "shall be pleaded."

173. As discussed in section 10:5.1, *infra*, the doctrine of licensee estoppel, which precluded licensees from challenging the licensed patent's validity, was abrogated in Lear v. Adkins, 395 U.S. 653, 671 (1969). The doctrine of assignor estoppel, which precludes assignors of patents from challenging the assigned patent's validity, was confirmed but limited by the U.S. Supreme Court in Minerva Surgical, Inc. v. Hologic, Inc., 141 S. Ct. 2298, 2298 (2021), and applies only where the "assignor's claim of invalidity contradicts explicit or implicit representations he made in assigning the patent."

(8) the patent cannot be enforced against the particular defendant due to equitable estoppel based on a misleading statement or conduct by the patentee, reasonable reliance by the accused infringer, and prejudice to the accused infringer;[174]

(9) with respect to a method patent, the accused infringer may have a defense under section 273 if he can prove by clear and convincing evidence that he "had, acting in good faith, actually reduced the subject matter to practice at least 1 year before the filing date of such patent, and commercially used the subject matter before the effective filing date of such patent." This defense is subject to the limitations set forth in section 273;

(10) under section 287(c)(1), a medical practitioner may not be subject to the remedies for patent infringement (that is, monetary damages, injunctive relief, and attorney fees) for infringing a patent in the performance of a medical or surgical procedure that does not include the use of patented machine, composition of matter, or a process covered by a biotechnology patent; and

(11) the use was experimental in nature because it was "for amusement, to satisfy curiosity, or for strictly philosophical inquiry."[175]

A more detailed discussion of these defenses is covered in chapter 10.

§ 1:9 "False Marking" Actions

Under 35 U.S.C. § 292, "false marking" is the (a) marking upon, affixing to, or use in advertising, without a patentee's consent, in connection with anything made, used, offered for sale, sold, or imported into the United States, of the patentee's name or patent number with the intent of counterfeiting or imitating the patentee's mark, or of deceiving the public into believing that the thing was made, offered for sale, sold, or imported into the United States with the patentee's

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174. In SCA Hygiene Prods. AB v. First Quality Baby Prods. LLC, 137 S. Ct. 954 (2017), the Supreme Court abrogated the related defense of laches, which had previously served as a basis for precluding a claim for past damages for patent infringement due to a patentee's undue delay in asserting the claim and prejudice to the accused infringer. *See* section 10:5.5, *infra*.

175. *See* chapter 11.

consent; (b) marking upon, affixing to, or the use in advertising, of a patent number or the word "patented" on an unpatented article with the intent to deceive the public; or (c) marking upon, affixing the words to, or the use in advertising, of the words "patent applied for" or "patent pending" when a patent application has not been filed with the intent to deceive the public. The penalty for false marking is a fine of "not more than $500 for every such offense."

Prior to the September 16, 2011, enactment of the AIA, section 292 provided that "any person" could file an action alleging false marking and if successful, would share the total amount of the fine with the United States. Under amended section 292(a), actions for civil penalties for false marking can be brought only by the United States. However, amended section 292(b) creates a new civil action for compensatory damages that can be brought by a person who has suffered a competitive injury due to false marking. In addition, the AIA added section 292(c), which eliminates false marking claims based on the marking of a patent that covered the product but has expired.

Chapter 2. An Overview of Research & Development, Product Launch, and Patent Enforcement

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Chapter 2

An Overview of Research & Development, Product Launch, and Patent Enforcement

Gerald Sobel & Daniel L. Reisner

§ 2:1 General

The basic principles of the patent law apply equally across all types of technology.[1] Basic patent law principles may be general in the abstract, but when applied to pharmaceutical and biotech patents, they present recurring issues that are often unique to this field. The present chapter provides an overview of the research and development process, launching new products, and patent enforcement.

Research and development (R&D) can be broken up into several phases, as illustrated in Fig. 2-1. The steps of pharmaceutical R&D, however, are not usually performed in a simple linear sequence as depicted in Fig. 2-1.[2] Often different phases of R&D overlap and even circle back to prior phases because active compounds may, after further evaluation, turn out to be unsuitable as drug candidates. Furthermore, pharmaceutical R&D takes many other forms not depicted here. Figure 2-1 nevertheless provides a framework for the pharmaceutical and biotech patent issues discussed in this treatise.

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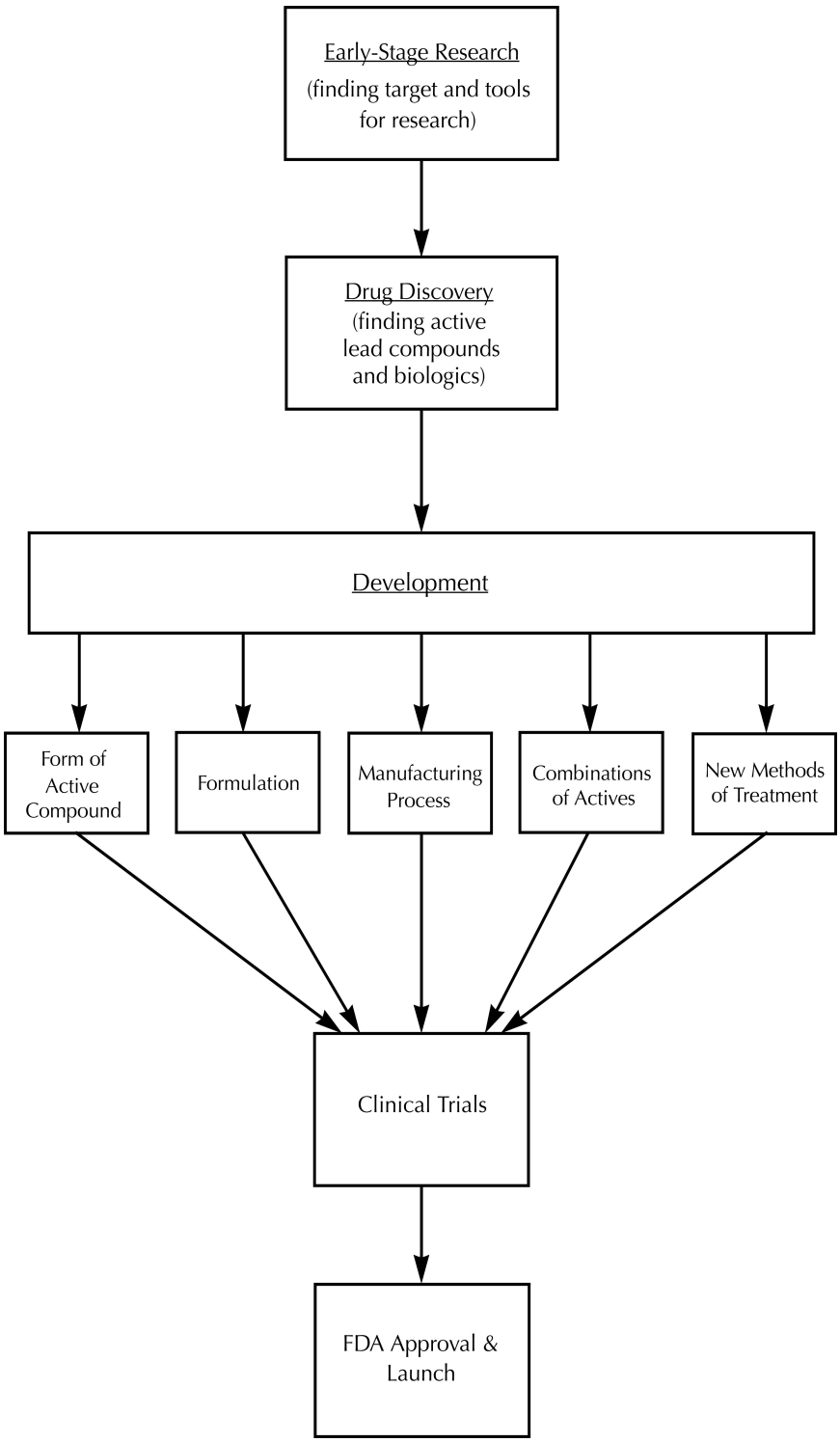
1. Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1325–26 (Fed. Cir. 2003) (referring to "the technology-neutral language of the Patent Act").
2. The term "drug" or "pharmaceutical" refers both to traditional small molecules such as acetylsalicylic acid (aspirin) and biologics such as erythropoietin (EPO). This book also covers non-drug-based therapies and medical procedures such as use of medical devices, performance of medical procedures, and the use of diagnostics.

Fig. 2-1
Examples of Phases of
Research and Development



The research phase in pharmaceutical R&D often includes early-stage research, which involves identifying relevant biological targets and developing tools to test the activity of potential drug candidates against those targets.[3] Early stage research serves as the foundation for further drug discovery that involves making new compounds and evaluating them for the desired biological activities. Universities and startup companies as well as major pharmaceutical companies engage in early-stage research.

Development of a drug candidate, however, requires greater resources because it involves continued preclinical testing, devising reliable and efficient methods for manufacturing bulk quantities of the drug, formulating it in an appropriate manner to deliver the right quantities of the drug to the patient over the optimum period of time, and testing the drug in a series of human clinical trials.

The research and development needed to create a new medical treatment can span decades, involve hundreds of scientists, technicians, and managers from one or several institutions, cost tens or hundreds of millions of dollars, and, at the last moment, end in commercial failure. Yet, even partial success against major diseases can provide life-changing benefits to millions. New treatments, if protected by patent rights, can also yield substantial profits. Only the prospect of this reward can economically justify the expense and the risk of research and development.

The reward of commercially valuable patents rights, however, does not flow automatically from successful and original research. Patent rights, like the drugs they protect, usually come from execution of a carefully planned strategy. Patent planning should begin at the earliest stage and evolve with the drug discovery and development process that, with enough skill and luck, will produce a new and useful treatment.

§ 2:2 Research Teams

Increasingly, modern research and development requires teams of scientists. The chemical structure and biological characteristics of the next anti-cancer agent will likely require the sweat and brains of many. Likewise, the patent law has evolved to accommodate the existence of team-based innovation.

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3. RICHARD B. SILVERMAN, THE ORGANIC CHEMISTRY OF DRUG DESIGN AND DRUG ACTION (Academic Press, 1992); ANDREJUS KOROLKOVAS, ESSENTIALS OF MOLECULAR PHARMACOLOGY (John Wiley & Sons, 1970).

§ 2:2.1 Patent Issues Related to Research Teams

The team-based approach to drug discovery and development raises many legal questions including the following, which are addressed in later chapters:

- When does the invention occur?[4]
- Who are the actual inventors?[5]
- When does one entity's own prior work hamper the ability to obtain new patent rights?[6]
- When there are multiple inventors to a single patent, who owns the invention?[7]
- What happens to inventorship when one team uses technology or innovations made by another team?[8]
- What happens to patent ownership when an institution uses government-funded research to make its invention?[9]
- How does one safely collaborate to avoid unexpected loss of patent rights or joint ownership of resulting patents?[10]
- How does one define ordinary skill in the art in a field involving teams of researchers when determining obviousness?[11]

§ 2:2.2 Government-Funded Research: The Bayh-Dole Act

Prior to the 1980 Bayh-Dole Act,[12] government policy required that the federal government retain ownership in any resulting inventions for most federally funded research directed towards public health.[13] The Bayh-Dole Act made it possible for private institutions,

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4. *See infra* section 4:1 (inventorship).
5. *See infra* section 4:1.
6. *See infra* sections 5:2.1 and 5:2.3 (concerning statutory bars that prevent applicant from obtaining a patent based on categories of prior art existing a year prior to the filing date even if it is the inventor's own work); section 5:3.1[C] (co-ownership/joint venture exception to prior art: section 103(c)); section 5:8 (double patenting).
7. *See infra* sections 4:5 (inventorship and ownership) and 4:6 (anticipating and resolving joint inventorship issues).
8. *See infra* section 4:2 (joint inventorship); section 4:5 (inventorship and ownership); and section 12:5 (ownership of private party-government employee co-inventions).
9. *See infra* chapter 12 (government funded research and the Bayh-Dole Act).
10. *See infra* section 4:6.
11. *See infra* section 5:3.6.
12. 35 U.S.C. § 200; 37 C.F.R. § 401.
13. *See infra* section 12:1.1.

such as universities, to own patent rights in inventions arising out of government-funded research. Obtaining rights under Bayh-Dole requires compliance with a series of regulations.[14] Any patent applicant who wants to obtain ownership of a patent arising out of government-funded research, or any party who wants to obtain a license under such a patent, must exercise care to make certain that the applicant has complied with applicable requirements under the Bayh-Dole Act, the corresponding regulations, and the government funding agreement.

Parties should also be aware that ownership rights in inventions obtained under the Bayh-Dole Act are not unlimited.[15] The government retains a non-exclusive license to make the invention or have the invention made, and certain "march-in" rights permitting the government to require the patent owner to grant a license to a responsible third party. Although these government rights, if exercised, could have a great impact on the rights to any patent subject to Bayh-Dole, so far the government has rarely, if ever, exercised its Bayh-Dole rights.[16]

§ 2:2.3 Joint Inventions Made by Federal Employees and Private Parties

Sometimes during the course of government-funded research, a government employee and private employee become co-inventors. Under these circumstances a federal agency may jointly own the invention along with the private party. Alternatively the government agency may license or assign its rights to the private party or acquire the private party's rights in the invention.[17]

§ 2:3 Research

§ 2:3.1 Early-Stage Research

Some drugs are discovered accidentally, without any prior understanding of the biological mechanism responsible for the drug's activity. Nevertheless, modern drug discovery efforts are increasingly predicated on some prior discovery that provides both tools for identifying potential drug candidates and a theoretical basis for understanding the drug's mechanism of action. Early-stage research often involves the identification of a relevant biological target. It can involve identification of a new gene, receptor, or enzyme, and its biological function. It can also involve a new methodology for testing

14. *See infra* section 12:2.
15. *See infra* section 12:3.
16. *See infra* section 12:3.
17. *See infra* section 12:5.

compounds for potential biological activity. This early-stage research often precedes the drug discovery process, but it can continue in parallel with ongoing drug discovery efforts.

Not all early-stage research, however, results directly in patentable inventions. A discovery must yield something useful to be patentable. A new compound, gene, protein, antibody or fragment without any known pharmacological activity or other practical utility, will not normally be patentable. This safeguard prevents would-be inventors who fail to provide some practical benefit to the public from blocking promising avenues of research by others. For a pharmaceutical invention to be patentable, research must progress to the point of some pharmacological activity or other identifiable utility, even if it has not been conclusively demonstrated in humans.[18] On the other hand, when a discovery has practical utility and satisfies the other requirements of patentability, a patent may be obtained.[19]

Patents based on early-stage research are sometimes directed to materials and methods used in drug research and development. These patents are sometimes referred to as "research tool" patents and often affect the ability of others to pursue further research in that area.[20] Research tool patents provide a way for the inventors to derive profit from their work without taking on the heavy burden of developing new treatments. On the other hand, research tool patents can present obstacles to others trying to develop new drugs that can only be overcome by licensing, designing around, conducting research outside the United States, or obtaining the benefit of the statutory safe harbor provision covering collection of data for FDA submissions.[21]

Even if some discoveries merit award of patent rights, the rights granted must be commensurate with the scope of the discovery. Identifying the mechanism by which some compounds achieve their pharmacological activity and the tools to identify such activity in test compounds may support claims to that research tool. It may not, however, support claims to the method of treating patients with compounds found by that research tool—particularly if no such compounds were known by the time of the invention.[22]

§ 2:3.2 Drug Discovery

The drug discovery process often begins with searching for a small organic molecule (in the case of traditional pharmaceuticals), or a

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18. *See infra* chapter 3 (utility).
19. *See generally* chapter 5 (Patentability).
20. *See infra* section 7:1 (research tool patents).
21. *See infra* section 7:1.
22. *See infra* section 7:4.6[B] (Field of Use Claim); *see also infra* section 5:5.5.

larger organic molecule (in the case of biologics) such as a nucleic acid or antibody that has some desired activity against a particular target in the body. Searching for such molecules usually requires an assay to conveniently test for the desired activity and a source of potentially active compounds. Once compounds are identified that have the desired activity and potency, they are often tested in a series of other assays to assess whether that activity might translate into therapeutically meaningful results and whether the compound will have all of the other properties, such as acceptable duration of action in the body and side effect profile, necessary to make it into a clinically useful treatment. Patent applications can and usually are filed on the active compounds and methods of treatment using these compounds in the discovery phase prior to development.[23]

Although the goal of drug discovery is to develop new treatments through extensive testing, one must be mindful that the path to such discovery may be covered by other patents that can block or impede progress. The compounds being tested, and the testing methods themselves, may be covered by patents. Congress provided some relief by exempting from infringement certain activities directed to developing data for the Food and Drug Administration to obtain certain drug approvals.[24] Nevertheless, not all activities are exempt from infringement so awareness of patent issues must begin with the inception of a research program. To illustrate the development process, we focus in the next section on development of small molecule drugs.

§ 2:4 Development

§ 2:4.1 Preclinical Development

Preclinical development begins at some point after identification of an active compound and development continues through human clinical trials. The problems tackled during preclinical development continue during the clinical trials. During preclinical development, researchers evaluate candidates for such parameters as efficacy, side effects, pharmacokinetics (for example, absorption, distribution, metabolism, elimination and duration of action), and stability. Sometimes various pharmacokinetic properties and drug stability (for example, shelf life) can be modified by experimenting with changes to the form of the active compound or formulating it with specific

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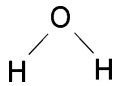
23. *See infra* section 7:2 (compounds); section 7:4 (Method of Treatment); section 7:6 (nucleic acids); section 7:7 (Antibodies); *see also supra* section 1:3 for a discussion of the requirements for obtaining a patent.
24. *See infra* section 8:1.8 (exemption from infringement related to FDA submission); *see also* chapter 11 (experimental use defense to infringement).

inactive ingredients known as excipients. Researchers must also usually develop methods for making large quantities of the active compound that are commercially practical and result in the desired level of purity. Preclinical development and clinical trials may also result in identification of new methods of treatment not identified during drug discovery and identification of therapies based on combining two active compounds in one formulation.

[A] Form of the Active Compound

Active compounds, small molecules in particular, are generally claimed by specifying the compound's molecular formula (for example, H_2O) and its structure (for example):



An active compound's properties, however, do not depend solely on its atomic composition. The form in which the compound is administered to a patient, such as its particle size, can also affect its properties.

Active compounds can be placed into a variety of different forms to modify various properties such as pharmacokinetics and stability, as well as its biological properties such as efficacy and side effects. Modifying the forms of the active compound often produces unpredictable changes in its properties. Researchers, therefore, can potentially obtain patents on particular forms of the active compound even if the compound itself is known to the person of ordinary skill.

Figure 2-2 (below) illustrates the following ways in which the form of an active compound can be modified to change the compound's properties: preparing specific stereoisomers of the compound, preparing specific polymorphs of the compounds, putting the compound into a salt form, modifying the particle size of the compound, and selecting compounds that are converted in the body into other compounds with pharmaceutically desirable properties.[25]

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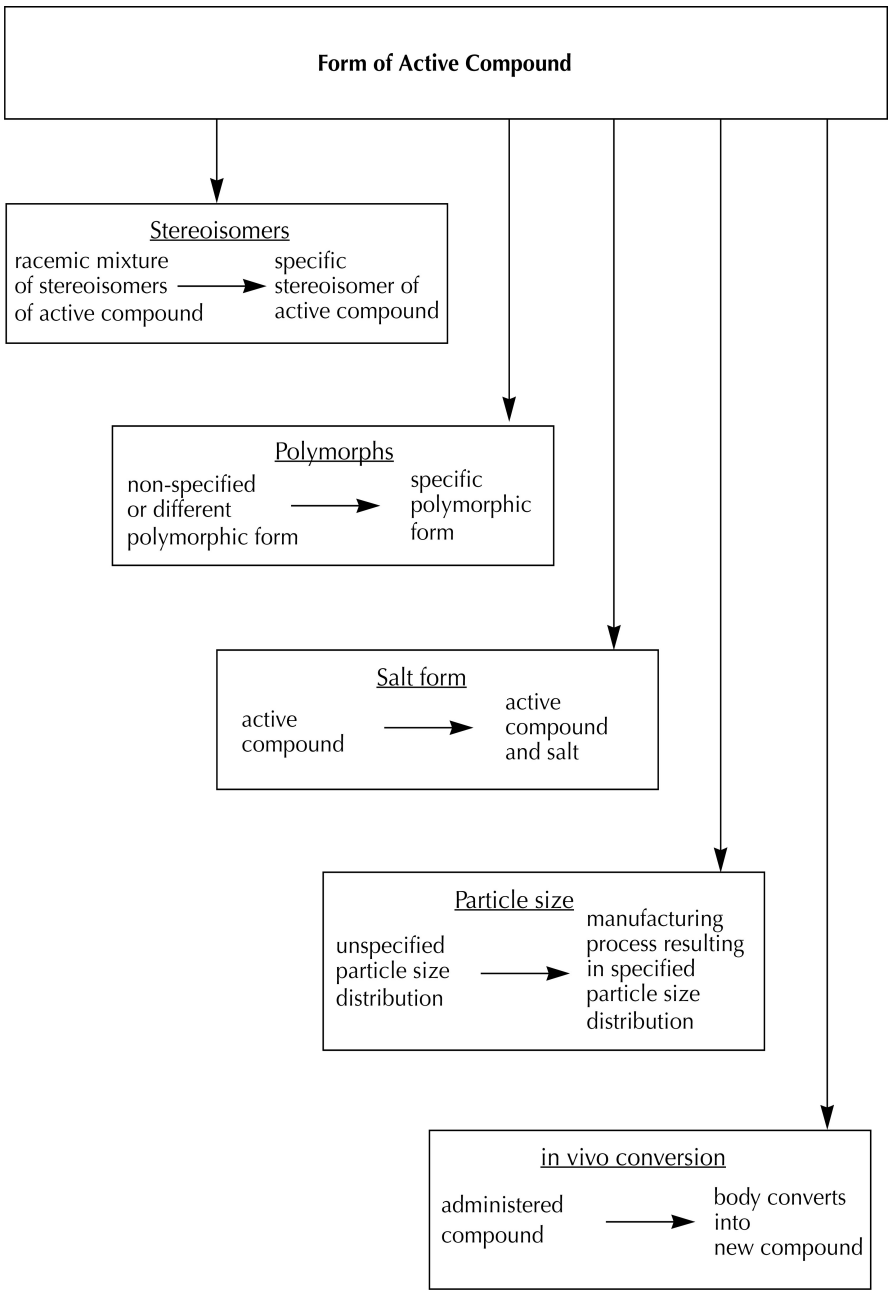
25. The foregoing ways in which the form of a compound can be modified are not exclusive. For example, a compound could be micronized to a desired particle size *and* put into a specified salt form if that results in an optimal mix of properties.

Fig. 2-2
Modifying Form of Active Compound



[A][1] Stereoisomers

Certain compounds exist as stereoisomers, which means that the compounds are composed of the same constituent atoms but are arranged in space in different ways resulting in enantiomers (compounds that are mirror images of each other) and diastereomers (compounds with the same atoms, connected in the same way without being mirror images). Enantiomers and diastereomers are two types of stereoisomers. Such compounds can exist in mixtures of multiple isomeric forms or can be resolved into purer forms consisting of a single isomeric form with resulting differences in its properties.[26]

[A][2] Polymorphs

Compounds may also exist in different crystalline forms known as polymorphs. Polymorphs, like stereoisomers, are compounds that have the same chemical formula (type and quantity of atoms) but a different structural form. Polymorphism refers to the way in which the individual molecules stack upon each other to form crystals. Different polymorphic forms of a compound can impart different properties, serving as a basis for drug design and providing potential grounds for patent protection.[27]

[A][3] Salt Forms

Another way to modify the properties of a compound is to create a salt form of the compound. Different salt forms can affect various properties such as solubility, stability, and processability (ease of handling during the manufacturing process). A large number of potential salt forms exist, often with unpredictable properties, providing a basis for innovation and patentability.[28]

[A][4] Particle Size

Changing the particle size of an active compound can also change its properties. Micronizing particles of a compound, for example, increases a particle's surface area and thereby changes properties such as solubility and processability. This affords researchers yet another way to develop drug candidates and can provide a basis for obtaining patents.[29]

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26. *See infra* section 7:2.4.
27. *See infra* section 7:2.5.
28. *See infra* section 7:2.6.
29. *See infra* section 7:2.8.

[A][5] In Vivo *Conversion*

The body provides a final way to modify the form of an active compound. After administration of a drug, the body usually metabolizes (converts) the active compound into another compound as part of the body's natural process for ridding itself of foreign chemicals. The converted form of the administered compound, known as a metabolite, can have different properties from the original compound including retained or even enhanced pharmacological activity.[30]

[B] Formulation

Active compounds are usually mixed with inactive compounds to make a pharmaceutical formulation that permits administration in a convenient form. For many drugs, the most convenient form is a tablet or capsule. Other drugs, however, must be formulated in solution to permit injection for administration directly into the bloodstream or injection into a particular muscle, nerve, or other local site, or formulated as creams, pastes, inhalables, or other forms for a wide variety of reasons. The formulation design process must take into account the resulting composition's biological properties, as well as manufacturing issues and the end product's shelf life.

Formulation design presents a host of problems as well as opportunities to improve a drug's properties. For example, a drug with half life that is too short can sometimes be extended by developing an extended release formulation. Formulations are important to drug design and numerous patents have been awarded for pharmaceutical formulation. Many cases address issues concerning these patents.[31]

[C] Manufacturing Process

All active compounds are inevitably the end product of a manufacturing process. Most pharmaceuticals are made synthetically. Even natural extracts must be extracted.

The process for making the first small batch of test compound during drug discovery to identify potential drug candidates is often insufficient for large scale commercial production. New methods of manufacture, in a process known as "scale-up," must often be devised. The manufacturing design process can result in important innovations that should be protected by patents.[32] Furthermore, in some cases, the end product can only be described by the manner in which it

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30. See *infra* section 7:2.7, for a discussion of the variety of patent issues raised by *in vivo* conversion.
31. *See infra* section 7:3.
32. *See infra* section 7:5.

is made. These compounds are often patented by product-by-process claims that link the description of the compound to its manufacturing process.[33]

[D] Combination Therapies

Researchers have found numerous instances where administration of two drugs to treat a single problem provides a superior therapy. Co-administration of two active compounds or administration of a single formulation that combines two active compounds into a single form such as a tablet can, in appropriate circumstances, be covered by a patent—even in cases where both active compounds were previously known.[34]

[E] Methods of Treatment

During drug discovery researchers often have an idea about potential treatments available for compounds that show some activity in the initial assays. It is this hoped-for activity that has likely motivated the drug discovery effort in the first place. When such compounds are identified in the research phase of a drug R&D program, it is often prudent to file patent applications on the compounds and the methods of treatment identified by this research. Identification of new methods of treatment, however, does not end with the drug discovery or even with the entire preclinical phase. A better understanding of the compound's mechanism of action, further animal studies, or human clinical trials may yield new therapies for the drug candidates. Researchers and their patent attorneys must therefore be alert to opportunities for patenting new methods of treatment.[35]

§ 2:4.2 Clinical Trials

If preclinical development results in identification of a drug candidate with sufficient promise, it must be subjected to rigorous testing in a series of human clinical trials. This process is highly regulated by the FDA. This process also affects the drug developer's intellectual property rights in a wide variety of ways. For example, the FDA approval process affects the commercial value of any patent rights associated with the drug therapy, and can affect the length of the patent term and provide non-patent based data exclusivity that prevents generics from relying on the innovator's clinical data for a certain period of time.

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33. *See infra* section 7:5.2.
34. *See infra* section 7:3.4[A][2].
35. *See infra* section 7:4.

[A] The FDA Approval Process

The FDA approval process is a topic unto itself deserving extensive treatment beyond the scope of this book. Nevertheless, it has become sufficiently entwined with patent law to merit discussion here.

[A][1] Clinical Studies and Trials

Human clinical trials must be preceded by pre-clinical studies described above to test safety and efficacy using available models.[36] FDA review generally begins with human clinical trials as illustrated in Fig. 2-3. Regulatory review can be broken up into a "testing" process and an "approval" process. Testing of human drug candidates, including biologics, is usually conducted pursuant to an Investigational New Drug Application (IND). The approval process begins when a New Drug Application (NDA), or in the case of a biologic, a Biologic License Application (BLA) contains enough information to permit FDA review.

The pre-approval testing process is itself broken up into three phases of clinical trials. Phase I testing involves safety testing with a small number of healthy volunteers who take the drug candidate in increasing doses. Phase II involves testing larger groups for both safety and efficacy. Phase III involves the largest groups, often hundreds or thousands of patients, placed into randomized, controlled clinical trials resulting in the most definitive measurement of efficacy and safety. Depending on the circumstances, testing during human clinical trials presents a potential risk of public use of an invention that can result in loss of patent rights if patent applications were not filed within a year of the clinical trials.[37]

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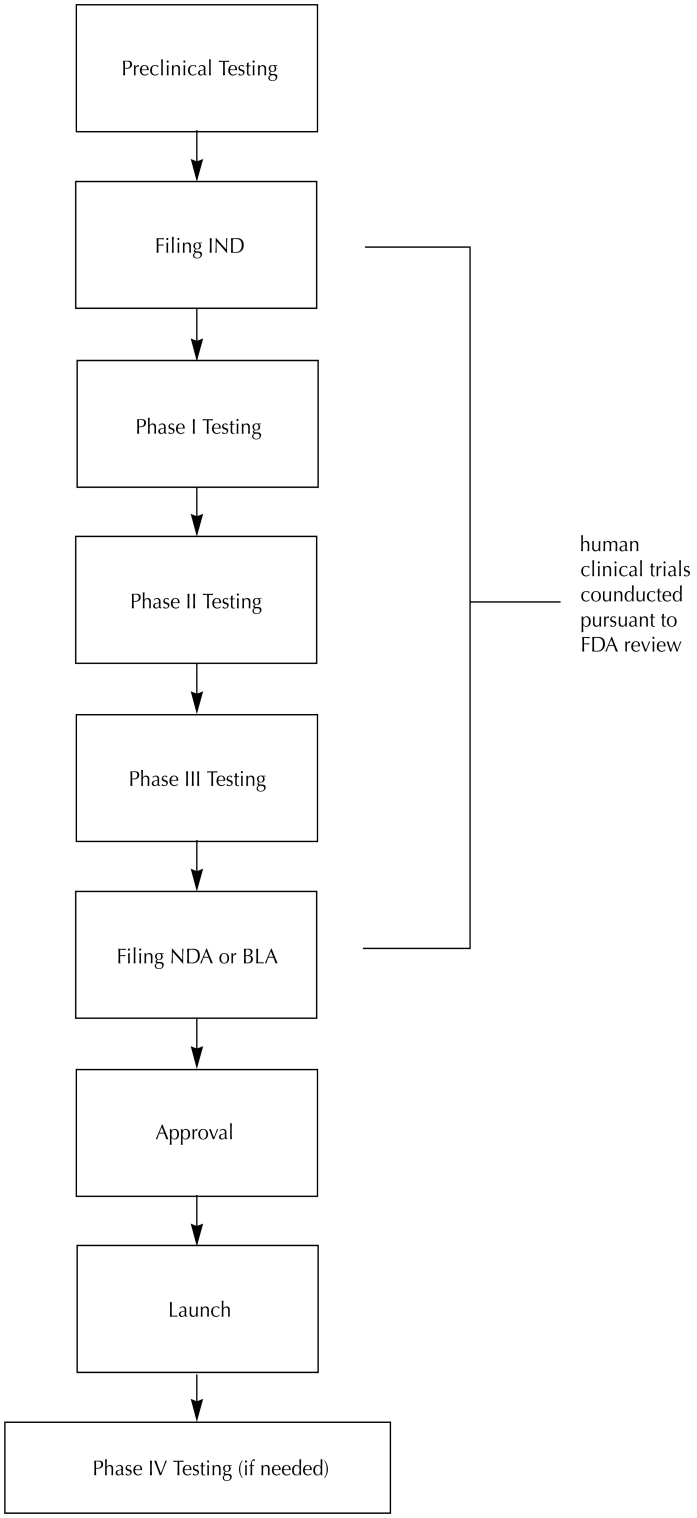
36. See *infra* section 3:6.3, for a discussion on whether human clinical data is needed to demonstrate patentability.
37. *See infra* section 5:2.3[B][2][d].

Fig. 2-3
Phases of FDA Regulatory Process



Post-approval testing, whether voluntary or required by the FDA, is known as Phase IV. Such testing can result in obtaining approvals for new indications but can also uncover new safety concerns that result in losing existing FDA approval. Clinical trials can also be conducted on children for pediatric indications and may result in an extension of existing patent or FDA based exclusivities known as pediatric exclusivity.[38]

[A][2] Patent Term Restoration for FDA Delay

Congress provided a remedy to restore the effective loss of patent term due to delays in the regulatory approval process for pharmaceutical and other products, such as certain types of medical devices, subject to pre-market review.[39]

Accordingly, a patentee who complies with the appropriate regulations, which include filing an application for extension with the PTO (which the PTO in turn provides to the FDA), may be able to extend the term of an eligible patent with respect to a particular product.[40]

[B] The Hatch-Waxman Act: Generic Competition

[B][1] ANDA Litigation

The Hatch-Waxman Act allows generic drug makers to file abbreviated new drug applications (ANDAs) without having to undertake the clinical trials described above that are required for approval of an innovator drug.[41] Presently, ANDAs can be filed for drugs approved pursuant to an NDA but not for biologic drugs approved pursuant to a BLA. An ANDA applicant only needs to show that the generic version and the previously approved innovator drug are "bioequivalent."[42] To facilitate the research needed to file ANDAs, Congress immunized from patent infringement conduct that is reasonably related to drug development and the submission of applications for marketing approval.[43] On the other hand, Congress created a mechanism for innovators to litigate their patent infringement claims before FDA approval of the generic products, and barred the FDA from approving

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38. *See infra* section 8:3.5.
39. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669–70 (1990).
40. *See infra* section 8:4.
41. *See infra* section 8:1.1[C] (requirements for filing an ANDA).
42. *See infra* section 8:1.1[C][4] (bioequivalence).
43. Although the exemption from infringement for certain FDA related activity was intended to facilitate the filing of ANDAs, the exemption is not limited to ANDA filings. *See infra* section 8:1.8.

the generic products for up to thirty months when such a patent infringement suit is brought.[44]

[B][2] Data Exclusivity

Congress gave certain rights to NDA holders, apart from patent rights, to compensate them for performing clinical studies and obtaining data to support the approval of new therapies. These grant rights, known as data exclusivity, generally take the form of various exclusivity periods, mostly independent of patent rights, during which the FDA may not approve competing products.

The following types of data exclusivity are available from the FDA for specific periods of time upon satisfaction of the appropriate conditions:

- New Chemical Entity (NCE) Exclusivity (five years data exclusivity)[45]
- Other Significant Changes (OSC) Exclusivity (three years data exclusivity)[46]
- Orphan Drug Exclusivity (seven years marketing exclusivity)[47]
- Pediatric Exclusivity (six-month extension to patent or data exclusivities)[48]

§ 2:5 Patent Protection for Pharmaceutical and Biotech Inventions

The Patent Act permits patenting of many types of subject matter, so long as the patentability requirements are satisfied. An inventor may obtain a patent, according to the statute, for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" upon satisfying the requirements for patentability.[49] Beyond this statutory definition of patentable subject matter, the statute does not generally define different types or categories of patents for any area of technology, including pharmaceuticals. Practitioners, however, find it useful to categorize pharmaceutical and biotech patents such as research tools, compounds, formulations, methods of treatment, methods of manufacture, nucleic acids, proteins, and antibodies. The categories are by no means exclusive. Many patent claims can easily fall within multiple categories. For example, a

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44. *See infra* section 8:1.4 (ANDA filing as an artificial act of infringement).
45. *See infra* section 8:3.2.
46. *See infra* section 8:3.3.
47. *See infra* section 8:3.4.
48. *See infra* section 8:3.5.
49. 35 U.S.C. § 101.

screening assay employing a nucleic acid sequence-based probe could be a research tool, medical diagnostic/method of treatment, and a nucleic acid sequence patent.

A discussion of research tool patents, including what these patents cover, how they can affect other parties' research efforts, the interface between research tool patents and the exemption from infringement for research directed towards generating data to submit for FDA approval, and efforts to conduct research efforts outside the United States to avoid the reach of research tool patents is provided in section 7:1. A discussion of chemical compound patents is provided in section 7:2. A discussion of pharmaceutical formulations and the issues unique to these types of patents, including an explanation of what formulation claims can cover, claim construction issues of certain terms that arise in pharmaceutical formulation patents, and examples of infringement and validity issues is provided in section 7:3. A discussion of method of treatment claims, including when conception of a method of treatment claim occurs, certain recurring claim construction issues such as when preambles (common to method of treatment claims) limit the scope of the claim, and proving infringement (often based on theories of indirect infringement) of method of treatment claims is provided in section 7:4. A discussion of pharmaceutical manufacturing, including manufacturing intermediates, product-by-process claims, and the patentability of process claims is provided in section 7:5. A discussion of nucleic acids and antibodies, and the growing body of case law and issues specific to these types of inventions is provided in sections 7:6 and 7:7.

Chapter 3. Utility and Patentable Subject Matter Requirements

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Chapter 3

Utility and Patentable Subject Matter Requirements

Daniel L. Reisner

§ 3:1 General

Not all scientific research, even if groundbreaking, results directly in patentable inventions. Einstein's theory of relativity, though it profoundly changed our understanding of the universe, did not entitle that former patent office employee to a patent. A discovery must be directed to patent eligible subject matter and must also yield something useful to be patentable. And the usefulness, or utility, must be practical and specific, not merely of scientific interest. From the perspective of pharmaceutical research, that means a new compound, gene, or antibody, without any known pharmacological activity or other practical utility, will not normally be patentable. Without this safeguard, patents could block promising research by others before a patentee is able to provide the public with a new treatment. Research must progress to the point of some pharmacological activity or other identifiable utility, even if it has not been conclusively demonstrated in humans, for a pharmaceutical invention to be patentable.

§ 3:2 Statutory Provision: Section 101

Section 101 of the Patent Act sets forth the requirement that an invention be useful in order to be patentable:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and useful improvement therefor, may obtain a patent therefor, subject to the conditions and requirements of this title.[1]

The utility requirement of section 101 is also closely related to the enablement requirement of section 112, paragraph 1.[1.1]

Section 101 has also been interpreted to impose a requirement of patent-eligible subject matter. This excludes subject matter such as laws of nature.

§ 3:3 Test for Utility: *Brenner v. Manson*

The U.S. Supreme Court set the bar for the utility requirement many years ago:

> The basic *quid pro quo* . . . for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.[2]

The Supreme Court in *Brenner v. Manson* held a process for making a steroid compound without disclosing a use for the steroid failed to satisfy the utility requirement. The Court rejected the argument that the utility requirement for the claimed process was satisfied merely "because it works—that is, produces the intended product."[3] In addition, it rejected the argument that utility was satisfied "because the compound yielded belongs to a class of compounds now the subject of serious scientific investigation."[4] Lastly, because of the recognized

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1. 35 U.S.C. § 101 (emphasis added).
1.1. *In re* '318 Patent Infringement Litig., 583 F.3d 1317, 1323 (Fed. Cir. 2009) ("Enablement is closely related to the requirement for utility."); Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1358 (Fed. Cir. 1999) ("If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement.").
2. Brenner v. Manson, 383 U.S. 519, 534 (1966); *In re* Fisher, 421 F.3d 1365, 1371 (Fed. Cir. 2005) ("The Supreme Court has not defined what the terms 'specific' and 'substantial' mean per se. Nevertheless . . . we have offered guidance as to the uses which would meet the utility standard of § 101.").
3. *Brenner*, 383 U.S. at 532.
4. *Id*.

unpredictability in the steroid field, the Court found unpersuasive evidence that a homologous compound had utility.[5]

Although the claim at issue in *Brenner* was to a process, the Court stated that its reasoning with respect to the utility requirement "would apply equally to the patenting of the product produced by the process."[6] *Brenner* thus laid the foundation for the utility requirement as applied to pharmaceutical inventions.

§ 3:4 Policy Behind Utility Requirement

The fundamental purpose of the utility requirement is to prevent the patenting of mere ideas.[6.1] The Supreme Court explained that until an idea is reduced to something shown to be useful, granting a patent may impede scientific development.

> [A] process patent in the chemical field, which has not been developed and pointed to the degree of *specific utility*, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, without compensating benefit to the public.[7]

The Supreme Court also explained that without disclosing to, and conferring on the public a specific and substantial utility, there is no reason to grant a patent.

> The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with *substantial utility*. Unless and until a process is refined and developed to this point—where *specific benefit* exists in currently available form—there

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5. *Id*. ("Indeed, respondent himself recognized that the presumption that adjacent homologues have the same utility has been challenged in the steroid field because of a 'greater known unpredictability of compounds in that field.'").
6. *Id*. at 535.
6.1. *In re '*318 Patent Infringement Litig., 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("The utility requirement prevents mere ideas from being patented."); *In re* Fisher, 421 F.3d 1365, 1373 (Fed. Cir. 2005) (when "asserted uses represent merely hypothetical possibilities, objectives which the claimed [inventions] . . . could possibly achieve, but none for which they have been used in the real world," they fail to satisfy the utility requirement).
7. *Brenner*, 383 U.S. at 534 (emphasis added).

> is insufficient justification for permitting an applicant to engross what may prove to be a broad field.[8]

The *Brenner* Court concluded with the often-quoted aphorism: "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."[9]

§ 3:5 Threshold for Satisfying Utility Is Not High

Although, as stated in *Brenner*, the utility requirement places a limitation on the patentability of pharmaceutical inventions, the requirement is not difficult to satisfy. The Federal Circuit has stated that "[t]he threshold of utility is not high: [a]n invention is 'useful' under section 101 if it is capable of providing some identifiable benefit."[10] "When a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown."[11] Moreover, "[t]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility."[12] Although the

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8. *Id*. at 534–35 (emphasis added).
9. *Id*. at 536; Fujikawa v. Wattanasin, 93 F.3d 1559, 1563 (Fed. Cir. 1996) ("For over 200 years, the concept of utility has occupied a central role in our patent system."). See *infra* section 3:6.3 for a further discussion of policy considerations.
10. Juicy Whip, Inc. v. Orange Bang, Inc., 185 F.3d 1364, 1366 (Fed. Cir. 1999) (rejecting argument that claimed invention lacked utility because it deceived consumers into believing that a beverage was dispensed from a bowl filled with fluid simulating the appearance of the beverage); *see also* Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result. . . .").
11. Raytheon Co. v. Roper Corp., 724 F.2d 951, 958 (Fed. Cir. 1983); *see also* Tol-O-matic, Inc. v. Proma Produkt-Und Mktg. Gesellschaft, m.b.H., 945 F.2d 1546, 1553 (Fed. Cir. 1991) ("It is not required that a particular characteristic set forth in the prosecution history be achieved in order to satisfy § 101."), *overruled on other grounds by* Laitram Corp. v. NEC Corp., 32 U.S.P.Q.2d (BNA) 1602 (E.D. La. 1994), *and* Read Corp. v. Protec, Inc., 970 F.2d 816 (Fed. Cir. 1992); Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762 (Fed. Cir. 1984) ("the defense of non-utility cannot be sustained without proof of total incapacity"). As stated in the PTO's response to comments accompanying the 2001 Utility Guidelines, "[t]he patentee is required to disclose only one utility, that is, teach others how to use the invention in at least one way." Utility Examination Guidelines, 66 Fed. Reg. 1092, 1094 (Jan. 5, 2001). The PTO also stated that "[t]he courts interpret the statutory term 'useful' to require disclosure of at least one available potential benefit to the public." *Id*.
12. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762 (Fed. Cir. 1984); *see also In re* Malachowski, 530 F.2d 1402, 1405 (C.C.P.A. 1976) ("even if proof of utility of the claimed inventions as an anti-arthritic agent for

threshold of utility is not high, it still must be demonstrated by more than an unsupported hypothesis.[12.1]

If, however, multiple asserted utilities are actually claimed, as in a method of treatment claim using a compound to treat several diseases, the demonstrated utility must be commensurate with the scope of the claims.[13]

§ 3:5.1 Satisfying Threshold in the PTO

The PTO must accept an assertion of a utility as true "unless there is reason to doubt the objective truth of the statements in the specification.[14] "From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure."[15] If the PTO satisfies this initial burden, the burden shifts "to the applicant to provide rebuttal evidence sufficient to convince [the skilled artisan] of the invention's asserted utility."[16] Thus, evaluation of utility depends in part on the examiner's expertise and general familiarity with the relevant field.[17] If the burden is shifted to the

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human beings is lacking, there remains the proven utility . . . for lower animals"); Chiron Corp. v. Genentech, Inc., 268 F. Supp. 2d 1148, 1168 (E.D. Cal. 2002) ("[i]f *some* monoclonal antibodies of the invention are useful as immunotoxins, that is sufficient" to meet the utility requirement) (emphasis added).

12.1. *In re* '318 Patent Infringement Litig., 583 F.3d 1317, 1327 (Fed. Cir. 2009) ("the specification, even read in the light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis," therefore it does not satisfy the utility requirement).

13. *In re* Buting, 418 F.2d 540, 544 (C.C.P.A. 1969) ("We do not find such evidence limited to one compound and two types of cancer, to be commensurate with the broad scope of utility asserted and claimed, viz. that of treating seven types of cancer with several compounds."); *In re* Surrey, 370 F.2d 349, 356 (C.C.P.A. 1966) (no utility for genus claim because specification lacked "unequivocal statement . . . that compounds other than those actually tested are anticonvulsants or psychomotor stimulants"); *In re* Cavallito, 282 F.2d 357, 361 (C.C.P.A. 1960) ("An applicant is not entitled to a claim for a large group of compounds merely on the basis of a showing that a selected few are useful and a general suggestion of a similar utility in the others.").

14. *In re* Marzocchi, 439 F.2d 220, 223 (C.C.P.A. 1971).

15. *Brana*, 51 F.3d at 1566 (citing *Marzocchi*, 439 F.2d at 223).

16. *Id.*; *In re* Bundy, 642 F.2d 430, 433 (C.C.P.A. 1981) ("The PTO must have adequate support for its challenge to the credibility of applicant's statements as to utility. Only then does the burden shift to appellant to provide rebuttal evidence.").

17. *See, e.g.*, *In re* Chilowsky, 229 F.2d 457, 462 (C.C.P.A. 1956) ("[W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is

applicant, the applicant can respond with rebuttal evidence including declarations and test results.[18] Although utility is determined as of the application's filing date, a subsequently filed declaration can be used to substantiate the accuracy of an assertion of utility "already in the specification."[19]

"Whether an application discloses a utility for a claimed invention is a question of fact."[20] Patent Office determinations that an application "failed to satisfy the utility requirement of section 101" are reviewed for substantial evidence.[21]

§ 3:5.2 Satisfying Threshold in Litigation

Utility, as a requirement for patentability, has historically been relegated to practice before the PTO. Once obtained, invalidating a patent based on lack of utility is rare. The Federal Circuit stated that a "correct finding of infringement of otherwise valid claims" during infringement litigation "mandates as a matter of law a finding of utility under § 101."[22] Thus, "[i]f a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established. People rarely, if ever, appropriate useless inventions."[23]

More recently, however, the Federal Circuit found an issued patent invalid for failure to provide a sufficient basis for concluding the claimed invention would work for its intended purpose even though there was no dispute that the invention did in fact work as the inventor intended.[23.1]

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required."). *But see In re* Marzocchi, 439 F.2d at 223 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles."). *See also Brana*, 51 F.3d at 1560 n.17.

18. *Brana*, 51 F.3d at 1567 n.19; *cf. In re* '318 Patent Infringement Litig., 583 F.3d 1317, 1324 n.8 (Fed. Cir. 2009) (distinguishing *Brana* because "unlike the present case" involving an issued patent, "the testing was submitted to the PTO during prosecution").
19. *Brana*, 51 F.3d at 1567 n.19.
20. *In re* Fisher, 421 F.3d 1365, 1369 (Fed. Cir. 2005) (citing *In re* Ziegler, 992 F.2d 1197, 1200 (Fed. Cir. 1993)).
21. *Fisher*, 421 F.3d at 1369 (citing *In re* Gartside, 203 F.3d 1305, 1315 (Fed. Cir. 2000)).
22. *Raytheon*, 724 F.2d at 959; *Tol-o-matic*, 945 F.2d at 1553 (reversing a jury finding of invalidity based on lack of utility because jury could not have found the "total incapacity" required to prevail on a section 101 defense).
23. *Raytheon*, 724 F.2d at 959.
23.1. *In re* '318 Patent Infringement Litig., 583 F.3d 1317 (Fed. Cir. 2009).

§ 3:6 Utility for Pharmaceutical Inventions

The utility requirement has often been raised during Patent Office examination of applications directed to drug therapies because of the often-speculative nature of early-stage pharmaceutical research. Early-stage research uncovers potential medicants of uncertain value. The desire to patent these findings immediately has led to a body of case law delineating the boundary between the unduly speculative and therefore unpatentable, and that which is of sufficiently promising utility to be worthy of patent rights.[24] For example, early-stage research has uncovered gene fragments of unknown function that do not necessarily satisfy the utility requirement.[25]

§ 3:6.1 Pharmacological Activity Must Be Specified

As stated by the Supreme Court in *Brenner*, a would-be inventor of a pharmaceutical invention cannot obtain a patent without disclosure of a "specific utility."[26] This is a "threshold requirement[ ]."[27] Merely disclosing the fact that the compound is one of many currently "the subject of serious scientific study" is not sufficient.[28] An assertion of utility based on treating a disease generally requires some degree of specificity in identifying the disease to be treated or the nature of the pharmacological activity.[29] The assertion of utility can be based

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24. *Brana*, 51 F.3d at 1564 ("The question is with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention."). *See* M.P.E.P. § 2107.03 (Special Considerations for Asserted Therapeutic or Pharmacological Utilities). See *infra* section 5:5.6[B][1] for a discussion of the relationship between utility and enablement.
25. See *infra* section 7:6.3[C] for a further discussion of the utility requirements application to expressed sequence tags (ESTs) and single nucleotide polymorphs.
26. *Brenner*, 383 U.S. at 536.
27. Cross v. Iizuka, 753 F.2d 1040, 1048 (Fed. Cir. 1985) (stated utility "has been delimited with sufficient specificity to satisfy the threshold requirements of *Kawai* and *Kirk*").
28. *Brenner*, 383 U.S. at 532; *Fisher*, 421 F.3d at 1374 ("claiming five particular ESTs which are capable of hybridizing with underlying genes of unknown function found in the maize genome" fail to satisfy utility requirement).
29. *See, e.g.*, *In re* Kirk, 376 F.2d 936, 941 (C.C.P.A. 1967) ("biological activity" too "nebulous" to satisfy utility requirement); *In re* Diedrich, 318 F.2d 946, 949 (C.C.P.A. 1963) (disclosure that "the claimed compounds are useful for 'technical and pharmaceutical purposes'" not sufficient despite later-developed evidence of their use as X-ray contrast agents); *but see Brana*, 51 F.3d at 1565 (specification "alleges a sufficiently specific use" based on evidence that claimed compounds worked in tumor models

on pharmacological activity[30] for the actual compound claimed, or produced from a claimed process,[31] or, in the case of intermediates, for the final compound.[32]

Disclosing a specific utility does not require disclosure of a therapeutic use for a claimed compound. One court held that the disclosure of specific pharmacological activities satisfies the utility requirement although no specific therapeutic use is disclosed.[33] There, the application of one of the parties in an interference stated two utilities for the chemical compound: the ability to influence blood pressure in rats *in vivo* and the ability to relax smooth muscle cells of gerbils *in vitro*. The court reversed the Patent Office Board's finding of a lack of practical utility, stating that "the board erred in not recognizing that tests evidencing pharmacological activity may manifest a *practical* utility even though they may not establish a *specific* therapeutic use."[34] Thus, "*specific* pharmacological activities, that is, smooth muscle stimulation and blood pressure modulation, were recognized as *practical* utilities" because "a correlation between test results and pharmacological activities has been established."[35]

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that "represent actual specific lymphocytic tumors"); *Cross*, 753 F.2d at 1048 ("the inhibition of thromboxane synthetase *in vitro*" states a utility "delimited with sufficient specificity").

30. *E.g., compare* Brenner v. Manson, 383 U.S. 519 (1966), *with* Cross v. Iizuka, 753 F.2d 1040, 1051–52 (Fed. Cir. 1985). See discussion of *Brenner* and *Cross* in the next sections.

31. *In re* Moore, 444 F.2d 572, 576 (C.C.P.A. 1971) ("a chemical process is not 'useful' . . . unless the product of that process has a specific practical utility").

32. *See, e.g., In re* Kirk, 376 F.2d 936, 945 (C.C.P.A. 1967) ("if a process for producing a product of only conjectural use is not itself 'useful' within § 101, it cannot be said that the starting materials for such a process—*i.e.*, the presently claimed intermediates are 'useful'"); *In re* Joly, 376 F.2d 906 (C.C.P.A. 1967) (claims to intermediates for making steroids of unknown utility do not satisfy the utility requirement). Judges Rich and Smith filed vigorous dissents in *Kirk* and *Joly*. Their dissents distinguished *Brenner* and argued that new and unobvious chemical compounds have utility in the conduct of further research. *Kirk*, 376 F.2d at 947, 966; *Joly*, 376 F.2d at 909–10. *See also Fisher*, 421 F.3d at 1375 ("Just as the claimed compounds in *Kirk* and *Joly* were useful only as intermediates in the synthesis of other compounds of unknown use, the claimed ESTs can only be used as research intermediates in the identification of underlying protein-encoding genes of unknown function.").

33. Nelson v. Bowler, 626 F.2d 853 (C.C.P.A. 1980).

34. *Id*. at 856 (emphasis added).

35. *Id*. at 857–58 (emphasis added). The requirement for "practical utility" is sometimes referred to as "substantial utility." *Brenner*, 383 U.S. at 534 ("The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by

An applicant may rely on the assertion of utility in a prior application from which applicant claims priority.[36] The fact that the prior application asserts a different utility from that of the pending application does not defeat the claim of priority.[37]

§ 3:6.2 PTO's Initial Burden

As explained earlier,[38] once the patent application asserts a specific practical utility, the PTO has the initial burden of challenging the application's assertion. Thus, for pharmaceutical inventions involving "a drug, medicant, and the like in human therapy," the patent office examiner may "ask for substantiating evidence" of utility unless the skilled artisan "would accept the allegations as obviously correct."[39] Several cases illustrate satisfaction of this threshold requirement.[40]

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the public from an invention with substantial utility."); *see also* Cross v. Iizuka, 753 F.2d 1040, 1046 n.13 (Fed. Cir. 1985) ("For purposes of the present opinion, we consider the *phrase* 'substantial utility,' as enunciated by *Brenner*, to be synonymous with the phrase 'practical utility' as used in subsequent opinions of the C.C.P.A."); *Fisher*, 421 F.3d at 1372 ("Courts have used the labels 'practical utility' and 'real world' utility interchangeably in determining whether an invention offers a 'substantial' utility."); *Nelson*, 626 F.2d at 858 ("'[p]ractical utility' is a shorthand way of attributing 'real-world' value to claimed subject matter . . . [*i.e.*,] provides some immediate benefit to the public").

36. *In re* Kirchner, 305 F.2d 897 (C.C.P.A. 1962).

37. *Kirchner*, 305 F.2d at 900 (upholding claim of priority from application claiming compounds per se disclosed as possessing anticholinesterase activity to parent application claiming same compounds disclosed as possessing curarimimetic activity).

38. *See supra* section 3:5.1.

39. Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1323 (Fed. Cir. 2005); *Brana*, 51 F.3d at 1566 (specification's teaching of "making and using the invention" must be accepted as in compliance with the enablement requirement "unless there is reason to doubt the objective truth of the statements").

40. *See, e.g.*, *Brana*, 51 F.3d at 1566 ("The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking. . . . Modern science [and prior art for structurally similar compounds] has previously identified numerous successful chemotherapeutic agents."); *In re* Cortright, 165 F.3d 1353, 1357 (Fed. Cir. 1999) (reversing PTO rejection of method for treating baldness based on finding that "the asserted statements of utility were incredible" in absence of clinical data because, although "[t]reating baldness was once considered an inherently unbelievable undertaking . . . , treatments for baldness have gained acceptance."); *In re* Sichert, 566 F.2d 1154, 1159 (C.C.P.A. 1977) (reversing rejection assertion of utility treating lymphatic congestion was "incredible"). *But see In re* Novak, 306 F.2d 924, 928 (C.C.P.A. 1962) ("we find no indication that one skilled in this art would accept without

§ 3:6.3 *Rebutting PTO with* In Vitro *and* In Vivo *Data and Relation to FDA Approval Process*

As explained earlier,[41] an applicant can respond to a rejection for lack of utility with rebuttal evidence including declarations and data. For pharmaceutical inventions, the Federal Circuit has held that *in vitro* testing in validated models predictive of *in vivo* activity "may establish a practical utility" for a compound claim.[42] Likewise, "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility" even though *in vivo* animal testing does not necessarily mean that compound will have the same properties when used in humans.[43] Thus, *in vitro* testing and *in vivo* animal testing, in

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question statements that carboxymethyl dextran has the alleged effects on the functioning of *any* base, physiologically active or not, and no evidence has been presented to demonstrate that the claimed products do have those effects") (emphasis added); *In re* Citron, 325 F.2d 248, 253 (C.C.P.A. 1963) (assertion of utility amounting to reversing the effects of aging rejected as incredible even without evidence from the examiner).

41. *See supra* section 3:5.1.

42. Cross v. Iizuka, 753 F.2d 1040, 1051 (Fed. Cir. 1985) ("where the disclosed *in vitro* utility is supplemented by the similar *in vitro* and *in vivo* pharmacological activity of structurally similar compounds, *i.e.*, the parent imidazole and 1-methylimidazole compounds, we agree with the Board that this *in vitro* utility is sufficient to comply with the practical utility requirement of § 101"); M.P.E.P. §§ 2107.03, 2100–43 (8th ed. Aug. 2001) ("The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such utility is asserted."); *but see Fisher*, 421 F.3d at 1377 ("Fisher disclosed a variety of asserted uses for the claimed ESTs, but failed to present any evidence—test data, declaration, deposition testimony, or otherwise—to support those uses as presently beneficial and hence practical."); *Ex parte* Balzarini, 21 U.S.P.Q.2d (BNA) 1892, 1897 (B.P.A.I. 1991) ("There is no evidence of record that experimental animal models have been developed in this area which would be predictive of human efficacy.").

43. *In re* Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995); *see also Fujikawa*, 93 F.3d at 1564 ("In the pharmaceutical arts, . . . practical utility may be shown by adequate evidence of pharmacological activity."); Nelson v. Bowler, 626 F.2d 853, 856 (C.C.P.A. 1980) ("adequate proof" of pharmacological activity "constitutes a showing of practical utility"); *In re* Krimmel, 292 F.2d 948, 953 (C.C.P.A. 1961) ("[W]hen an applicant for a patent has alleged in his patent application that a new and unobvious chemical compound exhibits some useful pharmaceutical property and when this property has been established by statistically significant tests with 'standard experimental animals,' sufficient statutory utility for the compound has been presented.").

appropriate models, can also provide evidence of a practical utility for pharmaceutical inventions.[44]

For *in vitro* or animal *in vivo* data of pharmacological activity to prove a utility in humans, there must be a reasonable correlation between that type of data and human *in vivo* results.[45] A "'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices."[46] *In vivo* human data may be relied upon without necessarily requiring double blind placebo-controlled tests.[47]

Mere deduction of a potential new treatment, even if the drug, treatment regimen, and disease are specified, may not satisfy the utility requirement until sufficiently proven through testing.[47.1]

The Food and Drug Administration (FDA) approval process provides a useful yardstick by which one can measure adequacy of a specification's satisfaction of the utility requirement. The review process includes preclinical testing; Phase I limited human clinical trials for safety, tolerance and pharmacokinetics; Phase II pilot clinical trials for safety and efficacy; and Phase III expanded clinical trials for additional safety and efficacy data.[48] Plainly, FDA approval "is not

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44. *Brana*, 51 F.3d at 1563 (*in vitro* testing "against two specific types of human tumor cells" demonstrated utility of method of treating tumors); *In re* Jolles, 628 F.2d 1322, 1327 (C.C.P.A. 1980) (*in vivo* testing sufficient to show utility for pharmaceutical compositions and methods of treating leukemia).

45. *Cross*, 753 F.2d at 1050; *Nelson*, 626 F.2d at 857–58.

46. Fujikawa v. Wattanasin, 93 F.3d 1559, 1565 (Fed. Cir. 1996).

47. *In re* Irons, 340 F.2d 974 (C.C.P.A. 1965) (reversing requirement that applicant demonstrate utility with "[d]ouble blind tests" because use of evidence that skilled artisans will rely on "historical control" data "found to be statistically significant").

47.1. *In re* '318 Patent Infringement Litig., 583 F.3d 1317 (Fed. Cir. 2009); Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325 (Fed. Cir. 2005).

48. Nathenson v. Zonagen Inc., 267 F.3d 400, 404 (5th Cir. 2001) ("In order to market a drug in the United States, developers must first obtain the approval of the Food and Drug Administration (FDA). This approval process involves, among other things, conducting a series of clinical trials to establish the safety and efficacy of the drug. The maker of the drug then submits the results of these trials to the FDA as part of its New Drug Application (NDA). Phase I trials test the safety, dosage tolerance, and other pharmacokinetic properties of the drug; they also identify the primary side-effects, if any, that the drug may cause. During Phase II trials, researchers test the drug in a limited patient population to gather information about efficacy, optimal dosage levels, adverse effects, and safety risks. Phase III trials test the efficacy and safety of the drug in an expanded patient population at geographically dispersed trial sites."). See also section 2:4.2[A] above, for an overview of the FDA approval process.

a prerequisite for finding a compound useful within the meaning of the patent law."[49] Usefulness, particularly "in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development."[50] Thus, utility can generally be established before Phase I testing in humans.[51]

Ultimately, the law of utility for pharmaceutical inventions is grounded in considerations of practicality.

> Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.[52]

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49. *Brana*, 51 F.3d at 1568; *In re* Sichert, 566 F.2d 1154, 1160 (C.C.P.A. 1977) ("only a minimum level of safety [required] to meet section 101"); *In re* Anthony, 414 F.2d 1383, 1394 (C.C.P.A. 1969) ("No one, we suppose, would seriously maintain that, as a matter of policy, a composition unsafe for use by reason of extreme toxicity to the point of immediate death under all conditions of its sole contemplated use in treating disease of the human organism would nevertheless be useful within the meaning of the patent laws. But at the same time it must be recognized that 'safety' is a relative matter, and that absolute proof of complete safety is realistically impossible."); *In re* Hartop, 311 F.2d 249, 255, 257–58 (C.C.P.A. 1962) ("The use of drugs in medicine is frequently a matter of balancing risks to save a life. . . . Congress has recognized this problem and has clearly expressed its intent to give statutory authority and responsibility in this area to Federal agencies different than that given to the Patent Office.").
50. *Brana*, 51 F.3d at 1568.
51. *Id.*; *see also* M.P.E.P. §§ 2107.03, 2100–45 ("Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.").
52. *Brana*, 51 F.3d at 1568; *see also Nelson*, 626 F.2d at 856 ("It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility."); *but see Fisher*, 421 F.3d at 1378 (concerns that allowing EST claims "would result in an unnecessarily convoluted licensing environment . . . are not ones that should be considered in deciding whether the application for the claimed ESTs meets the utility requirement of § 101. . . . Congress did not intend for these practical implications to affect the determination of whether an invention satisfies the requirements set forth in 35 U.S.C. §§ 101, 102, 103, and 112").

§ 3:6.4 *Examples*

[A] Sufficient Disclosure

[A][1] Nelson v. Bowler[53]

Claim: 16-phenoxy-substituted prostaglandins.

Disclosure: Ability to influence blood pressure in rats *in vivo* and relax gerbil smooth muscle cells *in vitro*.

Holding: "[S]pecific pharmacological activities, i.e., smooth muscle stimulation and blood pressure modulation, were recognized as practical utilities" because "a correlation between test results and pharmacological activities has been established."

[A][2] Cross v. Iizuka[54]

Claim: Class of imidazole derivative compounds.

Disclosure: "[T]reatment of inflammation . . ." based on "strong inhibitory activity for thromboxane synthae in human or bovine platelet microsomes. . . ."

Holding: Disclosure of an *in vitro* utility that "is supplemented by the similar *in vitro* and *in vivo* pharmacological activity of structural, similar compounds" satisfies the practical utility requirement.

[A][3] *In re* Brana[55]

Claim: Specified compounds "for use as antitumor substances."

Disclosure: *In vivo* data in tumor models showing antitumor activity.

Holding: (1) PTO lacked basis to doubt applicant's asserted utility where "structurally similar compounds to those claimed . . . have been proven in vivo to be effective as chemotherapeutic agents"; (2) even if PTO had "met its initial burden thereby shifting burden to the applicants to offer rebuttal evidence," applicants evidence that claimed compounds "exhibited significant antitumor activity against the L1210 standard tumor model in vivo" was sufficient.

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53. *Nelson*, 626 F.2d at 857–58.
54. Cross v. Iizuka, 753 F.2d 1040, 1048, 1050–51 (Fed. Cir. 1985).
55. *In re* Brana, 51 F.3d 1560, 1564–65 (Fed. Cir. 1995).

[A][4] Fujikawa v. Wattanasin[56]

Claim: "[C]ompound and method for inhibiting cholesterol biosynthesis in humans and other animals."

Disclosure: Compounds within claimed genus coupled with data showing *in vitro* activity.

Holding: Article teaching "that *in vitro* testing is sometimes not a good indicator of how potent a compound will be *in vivo*" but implying "that compounds which are active *in vitro* will normally exhibit some *in vivo* activity" supports Board finding that "*in vitro* tests established a practical utility."

[B] Insufficient Disclosure

[B][1] Brenner v. Manson[57]

Claim: "[N]ovel process for making certain known steroids."

Disclosure: "The products of the process . . . have a useful, high anabolic-androgenic ratio" and are useful for increasing that ratio.

Holding: Rejected argument that prior art established utility by reporting that a homologue adjacent to the steroid produced by the claimed process had a tumor-inhibiting effect in mice.

[B][2] *In re* Kirk[58]

Claim: New class of steroids.

Disclosure: (1) High "biological activity"; and (2) useful "as intermediates in the preparation of compounds with useful biological properties."

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56. Fujikawa v. Wattanasin, 93 F.3d 1559, 1561–66 (Fed. Cir. 1996).
57. Brenner v. Manson, 383 U.S. 519, 520, 538 (1966).
58. *In re* Kirk, 376 F.2d 936, 937, 939, 945 (C.C.P.A. 1967).

Holding: (1) "[T]he nebulous expression 'biological activity' or 'biologic properties' appearing in the specification convey no . . . explicit indication of the usefulness of the compounds and how to use them," nor can a compound "be presumed" useful "simply because [it] is closely related . . . to other steroid compounds known to be useful"; and (2) "if a process for producing a product of only conjectural use is not itself 'useful' within § 101, it cannot be said that the starting materials for such a process—*i.e.*, the presently claimed intermediates are 'useful.'"

[B][3] Kawai v. Metlesics[59]

Claim: Class of benzodiazepine compounds.

Disclosure: "[E]ffects on the central nervous system. . . ."

Holding: Prior art showing similar compounds having anticonvulsant activity held by court as insufficient to satisfy how to use requirement.

[B][4] Rasmusson v. SmithKline Beecham[60]

Claim: "[M]ethod of treating human prostatic adenocarcinoma" by administering specified compound.

Disclosure: Specified compound known to be a selective 5-alpha-R inhibitor.

Holding: Applicant failed to prove that skilled artisan as of filing date "would have recognized" that specified compound "would be effective in treating prostate cancer."

§ 3:7 Patentable Subject Matter

Section 101 provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or *any* new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.[60.1]

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59. Kawai v. Metlesics, 480 F.2d 880, 890–91 (C.C.P.A. 1973).
60. Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1322–24 (Fed. Cir. 2005).
60.1. 35 U.S.C. § 101 (emphasis added).

"In choosing such expansive terms" in section 101, "modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope."[60.2]

Section 101 "specifies four independent categories of inventions or discoveries that are patent eligible: 'process[es],' 'machin[es],' 'manufactur[es],' and 'composition[s] of matter.'"[61] Congress intended "that the patent laws would be given wide scope."[62] "The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'"[63] The scope of these exceptions is further explained in the cases and in sections 3:7.1–3:8.2 and sections 7:6.2[A][2] and [B].

Claim construction is not always needed to determine whether a claim is directed to patentable subject matter.[63.1] In fact, courts have routinely held in the appropriate case that a claims failure to satisfy the patentable subject matter requirement can be adjudicated on a Rule 12(b)(6) motion to dismiss.[63.2]

§ 3:7.1 "Processes"

Section 100(b) provides its own definition of "process":

> The term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

The Supreme Court rejected the Federal Circuit's attempt to limit patentable "process" inventions to those that satisfied its "machine-or-transformation" test.[64] Nevertheless, the Court stated that its "precedents establish that the machine-or-transformation test is a useful and important clue, an investigative tool, for determining whether an invention is a patent-eligible 'process.'"[65]

60.2. Bilski v. Kappos, 561 U.S. 593, 601 (2010) (quoting Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980)).

61. *Bilski*, 561 U.S. at 593.

62. *Id*. at 601 (citing *Chakrabarty*, 447 U.S. at 308).

63. *Id*. (quoting *Chakrabarty*, 447 U.S. at 309).

63.1. Genetic Tech. Ltd. v. Merial LLC, 818 F.3d 1369, 1373–74 (Fed. Cir. 2016).

63.2. *Id*.

64. According to the Federal Circuit, prior to the Supreme Court's further ruling in *Bilski v. Kappos*, an invention only qualified as a "process" if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." *In re* Bilski, 545 F.3d 943, 954 (Fed. Cir. 2008), *aff'd*, 561 U.S. at 593 (2010).

65. *Bilski*, 561 U.S. at 604.

§ 3:7.2 "Manufactures" and "Compositions of Matter"

The courts have construed the meaning of "manufacture" and "composition of matter" in 35 U.S.C. § 101 consistent with their dictionary definitions. "Manufacture" has been interpreted to mean "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery."[66] Likewise, "composition of matter" has been interpreted to include "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids."[67]

§ 3:8 Patentable Subject Matter for Pharmaceutical Inventions

§ 3:8.1 "Processes"

Not long after the Supreme Court's pronouncement in *Bilski v. Kappos*,[68] the Federal Circuit, and ultimately the Supreme Court, had an opportunity in the *Prometheus* decisions to apply *Bilski* in a series of opinions to a patented diagnostic method for determining the appropriate dose of thiopurine, a drug used for certain gastrointestinal and auto-immune diseases. Table 3-1 summarizes the *Prometheus* and *Bilski* decisions.

Table 3-1

***Prometheus* and *Bilski* Decisions**

Decision	Court	Year	Test	Outcome
Bilski I[68.1]	CAFC	2008	machine-or-transformation test	claims held invalid
Prometheus I[68.2]	CAFC	2009	machine-or-transformation test	claims held valid

66. Am. Fruit Growers, Inc. v. Brogdex Co., 283 U.S. 1, 11 (1931).
67. Shell Dev. Co. v. Watson, 149 F. Supp. 279, 280 (D.D.C. 1957) (cited by *Chakrabarty*).
68. Bilski v. Kappos, 561 U.S. 593 (2010).
68.1. *In re* Bilski, 545 F.3d 943 (Fed. Cir. 2008), *aff'd*, 561 U.S. 593 (2010).
68.2. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 581 F.3d 1336 (Fed. Cir. 2009), *vacated and remanded*, 561 U.S. 1040 (2010).

Decision	Court	Year	Test	Outcome
Bilski II[68.3]	Supreme Court	2010	machine-or-transformation test an "investigative tool," "not sole test"	claims held invalid
Prometheus II[68.4]	Supreme Court	2010	machine-or-transformation test an "investigative tool," "not sole test"	vacating *Prometheus I*
Prometheus III[68.5]	CAFC	2010	machine-or-transformation test an "investigative tool," "not sole test"	claims held valid
Prometheus IV[68.6]	Supreme Court	2012	claims must contain more than a law of nature and conventional steps known by the scientific community	claims held invalid

[A] *Prometheus I*

The Federal Circuit, in *Prometheus I*, found that the patent claimed patentable subject matter. According to its then-acceptable machine-or-transformation test, which the Supreme Court subsequently ruled is not a requirement but is still a useful tool, a claimed process "is surely patent-eligible" if it is tied to a particular machine or transforms an article into a different thing.[69] However, "'the use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility,' and 'the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity.'"[70]

68.3. Bilski v. Kappos, 561 U.S. 593 (2010).
68.4. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 561 U.S. 1040 (2010).
68.5. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 628 F.3d 1347 (Fed. Cir. 2010), *rev'd*, 132 S. Ct. 1289 (2012).
68.6. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 132 S. Ct. 1289 (2012).
69. *Prometheus Labs.*, 581 F.3d at 1342.
70. *Id*.

The court found the claims satisfied its test by constituting a transformation because "[t]he transformation is of the human body following administration of a drug and the various chemical and physical changes of the drug's metabolites that enable their concentrations to be determined."[71] Measuring the level of the metabolites "is also transformative" because the levels "cannot be determined by mere inspection" and require "[s]ome form of manipulation, such as . . . high pressure liquid chromatography."[72] The court also stated that one "further requirement" must be met: the transformation requirement cannot be satisfied by "merely insignificant extra-solution activity."[73] The court found the transformations were central to the claims because they "are part of treatment regimes for various diseases using thiopurine drugs."[74]

[B] *Prometheus II*

The Supreme Court vacated *Prometheus I*,[74.1] described above, setting forth the basis on which courts could determine whether a medical diagnostic constituted a "process" under 35 U.S.C. § 101, and remanded it for further consideration in light of *Bilski*.

In *Bilski*, the Supreme Court held that its "precedents establish that the machine-or-transformation test is a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101. The machine-or-transformation test is not the sole test for deciding whether an invention is a patent-eligible 'process.'"[74.2]

On remand, the Federal Circuit again upheld the validity of the claims based on applying the machine-or-transformation test as a guidance.[74.3]

[C] *Prometheus III* and *IV*

In 2012, in *Prometheus IV*, the Supreme Court resolved, once and for all, the question whether "patent claims covering processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases determine whether a given dosage level is too low

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71. *Id*. at 1346.
72. *Id*. at 1347.
73. *Id*.
74. *Id*. at 1348.
74.1. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 581 F.3d 1336 (Fed. Cir. 2009), *vacated and remanded*, 561 U.S. 1040 (2010).
74.2. Bilski v. Kappos, 561 U.S. 593 (2010).
74.3. *Prometheus Labs.*, 628 F.3d at 1347.

or too high."[74.4] Contrary to the Federal Circuit's prior decisions in *Prometheus I* and *Prometheus III*, the Court held that "the processes are not patentable."

Eschewing use of the machine-or-transformation test it had sanctioned in *Bilski* as one way to analyze whether a process claim covers patentable subject matter, the Court stated that the question was: "do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?"[74.5] To answer the question, the Court analyzed the claim language.

First, the Court noted that any claim language that merely recited a law of nature would, without more, not be sufficient to qualify as eligible subject matter.[74.6] Next, the Court considered steps in the claim that "are not themselves natural laws" to see if they are "sufficient to transform the nature of the claim."[74.7] The Court concluded "that the three steps simply tell doctors to gather data from which they may draw an inference in light of the correlations."[74.8] "To put the matter more precisely, do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws? We believe that the answer to this question is no."[74.9]

74.4. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 132 S. Ct. 1289, 1294 (2012).

74.5. *Id*. at 1297.

74.6. *Id*. ("If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself."); *see also* buySAFE, Inc. v. Google, Inc., 765 F.3d 1350, 1353 (Fed. Cir. 2014) ("In defining the excluded categories, the Court has ruled that the exclusion applies if a claim involves a natural law or phenomenon or abstract idea, even if the particular natural law or phenomenon or abstract idea at issue is narrow.").

74.7. *Id*.

74.8. *Id*. at 1298.

74.9. *Id*. at 1297. *Accord* PerkinElmer, Inc. v. Intema Ltd., 496 F. App'x 65, 72–73 (Fed. Cir. 2013) (applying the reasoning of *Prometheus IV* and finding unpatentable under 35 U.S.C. § 101, claims to methods for determining risk of Down syndrome by measuring certain screening markers and comparing data points because the claims "recite an ineligible mental step and natural law, and no aspect of the method converts these ineligible concepts into patentable applications of those concepts" where the screening techniques involve "conventional steps, specified at a high level of generality").

[D] Post-*Prometheus*

[D][1] Alice v. CLS

In the *Alice* case, the Supreme Court revisited the question of patentable subject matter.[74.10] The Court characterized the "concern that drives this exclusionary principle as one of pre-emption."[74.11] Quoting its prior precedent, it noted that "[l]aws of nature, natural phenomena, and abstract ideas are 'the basic tools of scientific and technological work.'"[74.12] "'[M]onopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it,' thereby thwarting the primary object of the patent laws."[74.13] Quoting its *Prometheus* decision, the Court noted that in application "we must distinguish between patents that claim the 'buildin[g] block[s]' of human ingenuity and those that integrate the building blocks into something more, thereby 'transform[ing]' them into a patent-eligible invention."[74.14] "The former 'would risk disproportionately tying up the use of the underlying' ideas, and are therefore ineligible for patent protection. The latter pose no comparable risk of pre-emption, and therefore remain eligible for the monopoly granted under our patent laws."[74.15]

The Court referred to the "framework" it set out in *Prometheus* as follows:

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application. We have described step two of this analysis as a search for an "inventive concept"—*i.e.*, an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."[74.16]

74.10. Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014).
74.11. *Id*. at 2354.
74.12. *Id*. (quoting Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013)).
74.13. *Id*. (quoting Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1923 (2012)).
74.14. *Id*. at 2354 (quoting *Prometheus*, 132 S. Ct. at 1303, 1294).
74.15. *Id*. at 2354–55 (citations omitted).
74.16. *Id*. at 2355 (citations omitted).

In assessing whether the method claims at issue passed "step two" of the analytical framework described in *Prometheus*, the Court found *Prometheus* "instructive" in holding that "'[s]imply appending conventional steps, specified at a high level of generality,' was not '*enough*' to supply an 'inventive concept.'"[74.17] In analyzing the "additional elements," the Court first took "the claim elements separately" and then "as an ordered combination" and found that the additional elements did not add "enough" to transform the claim "into a patent-eligible invention."[74.18] With regards to the asserted system claims, the Court analyzed the additional limitations and determined that they were "purely functional and generic" and did not meaningfully limit the claims beyond a particular technical environment.[74.19] "Put another way, the system claims are no different from the method claims in substance."[74.20] Thus, the Court concluded that the system claims "add nothing of substance to the" unpatentable idea and were thus "patent ineligible under § 101."[74.21]

[D][2] Types of Claims

[D][2][a] Diagnostic Claims

The Federal Circuit, in a case where its prior decision had been vacated in view of the Supreme Court's decision in *Prometheus*,[74.22] found method claims that did not involve any transformative steps invalid for attempting to claim unpatentable subject matter. These method claims merely required "comparing" or "analyzing" a DNA sample sequence with a normal sequence, without requiring extracting or sequencing the sample as part of the claim. By reciting nothing more than the "mental steps" necessary to compare two different nucleotide sequences, the claims failed to cover patentable subject matter.[74.23] Furthermore, the Federal Circuit, in another case involving a related patent, found a claim to a method of comparing a sample prepared by "amplifying all or part of a BRCA1 gene" with the wild-type BRCA1 to identify any differences is patent ineligible subject

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74.17. *Id.* at 2357 (citations omitted).
74.18. *Id.* at 2359–60.
74.19. *Id.* at 2360.
74.20. *Id.*
74.21. *Id.*
74.22. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 653 F.3d 1329, 1349–55 (Fed. Cir. 2011) (*Myriad I*), *vacated*, 132 S. Ct. 1794 (2012) (*Myriad II*), *remanded to* 689 F.3d 1303 (Fed. Cir. 2012) (*Myriad III*).
74.23. *Myriad III*, 689 F.3d at 1334.

matter because: (1) "[t]he number of comparisons is unlimited" and therefore this step constitutes an unpatentable abstract idea; and (2) the remaining steps of amplification and sequencing the sample are routine.[74.24]

In a case involving "known laboratory techniques" applied to the inventors' discovery of "cell-free fetal DNA ('cffDNA') in maternal plasma and serum" to detect the small fraction of paternally inherited cffDNA to determine fetal characteristics such as gender, the Federal Circuit found that claims were directed to ineligible subject matter because: (1) "the existence of cffDNA in maternal blood is a natural phenomenon," (2) there was no alteration of the cffDNA, (3) "the method ends with paternally inherited cffDNA, which is also a natural phenomenon," and (4) the methods to detect cffDNA were "routine and conventional."[74.25] In other words, because "[t]he only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal plasma or serum," the claims were not directed to patent eligible subject matter.[74.26]

In a case involving "a method of detecting a coding region of a person's genome by applying and analyzing a linked non-coding region of that person's genome," the Federal Circuit held that the claims were directed to unpatentable subject matter.[74.27] The claimed invention is based on the discovery that "certain DNA sequences in coding regions (exons) of certain genes are correlated with non-coding regions (introns) within the same gene, non-coding regions in different genes, or non-coding regions of the genome that are not part of any gene."[74.28] The court, in conducting the step 1 analysis, determined that the claim was directed to a patent-ineligible concept because the claim "broadly covers essentially all applications, via standard experimental techniques, of the law of linkage disequilibrium to the problem of detecting coding sequences of DNA."[74.29] Because amplifying and analyzing DNA,

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74.24. *In re* BRCA1-and-BRCA2-Based Hereditary Cancer Test Patent Litig., 774 F.3d 755, 761–64 (Fed. Cir. 2014).

74.25. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015); CareDX, Inc. v. Natera, Inc., ___ F.4th ___ (Fed. Cir. 2022) (rejecting diagnostic claims under section 101 because, "as in *Ariosa*, the claims boil down to collecting a bodily sample, analyzing the cfDNA using conventional techniques, including PCR, identifying naturally occurring DNA from the donor organ, and then using the natural correlation between heightened cfDNA levels and transplant health to identify a potential rejection").

74.26. *Id*. at 1377–78.

74.27. Genetic Tech. Ltd. v. Merial LLC, 818 F.3d 1369, 1374–75 (Fed. Cir. 2016).

74.28. *Id*. at 1372.

74.29. *Id*. at 1375.

as claimed, was well-known, these physical steps were found to be insufficient, under step 2, to render the claim patent eligible.[74.30]

[D][2][b] Treatment Claims

Claims "directed to the single step of reviewing the effects of known immunization schedules, as shown in the relevant literature" which "do not include putting this knowledge to practical use" do not claim patentable subject matter.[74.31] On the other hand, claims that "require the further act of immunization in accordance with a lower-risk schedule" move "from abstract scientific principle to specific application" and thereby claim patentable subject matter.[74.32]

[D][2][c] Method of Making Claims

The Federal Circuit has "consistently held diagnostic claims unpatentable as directed to ineligible subject matter."[74.32.1] It also has "held that method of treatment claims are patent-eligible."[74.32.2] It found,

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74.30. *Id*. at 1377; *see also* Genetic Veterinary Scis., Inc. v. LABOKLIN GmbH, 933 F.3d 1302, 1317–18 (Fed. Cir. 2019) (claims directed to detecting a point mutation indicative of a hereditary canine disease directed to unpatentable subjection matter because they "begin and end with the with the point discovery of the HNPK mutation in the SUV39H2 gene" and nothing in the claim "suggests the invention of a new *method* for genotyping").

74.31. Classen Inmmunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1067 (Fed. Cir. 2011).

74.32. *Id*. at 1068; Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1136 (Fed. Cir. 2018) (method of treating schizophrenia using iloperidone directed to patent-eligible subject matter because it taught "a specific method of treatment for specific patients using a specific *compound* at specific *doses* to achieve a specific *outcome*" based on the patient's genotype); Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, 918 F.3d 1338, 1345 (Fed. Cir. 2019) (upholding method of treatment claims because they "require specific steps be taken in order to bring about a change in a subject, altering the subject's natural state").

74.32.1. Illumina, Inc. v. Ariosa Diagnostics, Inc., 967 F.3d 1319, 1325 (Fed. Cir. 2020) (citing Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1352 (Fed. Cir. 2019) (Moore, J., dissenting from denial of rehearing en banc) ("Since *Mayo*, we have held every single diagnostic claim in every case before us ineligible."); *see also, e.g.*, Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743 (Fed. Cir. 2019); Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352 (Fed. Cir. 2017); Cleveland Clinic Found. v. True Health Diagnostics LLC, 760 F. App'x 1013 (Fed. Cir. 2019)).

74.32.2. *Id*. (citing Endo Pharm. Inc. v. Teva Pharm. USA, Inc., 919 F.3d 1347 (Fed. Cir. 2019); Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, 918 F.3d 1338 (Fed. Cir. 2019); Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d. 1117 (Fed. Cir. 2018)).

however, a claim to a method of preparation of a DNA "fraction from a pregnant human female" that would be used to diagnose "fetal chromosomal aberration" to be neither a diagnostic claim nor a method of treatment. Instead, the court treated the claim as akin to a method of preparation because the "claimed methods achieve more than simply observing that fetal DNA is shorter than maternal DNA or detecting the presence of that phenomena. The claims include physical process steps that change the composition of the mixture, resulting in a DNA fraction that is different from the naturally occurring fraction in the mother's blood."[74.32.3]

The Federal Circuit has upheld other methods of making claims. For example, the court held that claims to a process for preserving hepatocytes comprising density gradient fractionation separation of previously frozen and thawed cells to recover and refreeze the viable cells was not directed to patent-ineligible subject matter.[74.33] "[T]he claims are simply not directed to the ability of hepatocytes to survive multiple freeze-thaw cycles," as the district court erroneously held, the claims "are directed to a new and useful laboratory technique for preserving hepatocytes."[74.34]

Similarly, the Federal Circuit upheld claims to a method of "sorting . . .individual particles" using "a flow cytometry apparatus" because, "[l]ike the claims in *Diehr*, the asserted claims 'describe in detail a step-by-step method' for accomplishing a physical process."[74.34.1]

[D][2][d] Method of Drug Screening Claims

A claim to a method of screening drug candidates was upheld because it included "the steps of growing transformed cells and determining those growth rates."[74.35] The court explained:

> It is rare that a new reaction or method is invented; much process activity is to make new compounds or products using established processes. Thus, once one has determined that a claimed composition of matter is patent-eligible subject matter, applying

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74.32.3. *Id*. at 1326.

74.33. Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1048 (Fed. Cir. 2016).

74.34. *Id*.

74.34.1. XY, LLC v. Trans Ova Genetics, LC, 968 F.3d 1323, 1331 (Fed. Cir. 2020) (claims "directed to purportedly improved method of operating a flow cytometry apparatus to classify and sort particles" using multiple detectors to detect signals from individual particles, conversion of the signals into "n-dimensional parameter data" and "rotationally alter[ing] that data to increase spatial separation" and facilitate sorting) (quoting Diamond v. Diehr, 450 U.S. 175, 184 (1981)).

74.35. *Myriad III*, 689 F.3d at 1333.

> various known types of procedures to it is not merely applying conventional steps to a law of nature. The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible.[74.36]

§ 3:8.2 "Manufactures" and "Compositions of Matter"

[A] *Diamond v. Chakrabarty*

The Supreme Court, in *Diamond v. Chakrabarty*, held that a living, genetically engineered bacterium capable of breaking down different components of crude oil was patentable under 35 U.S.C. § 101 because it constituted a "manufacture" or "composition of matter."[75] While not every discovery is patentable, Chakrabarty's invention was "not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character, [and] use.'"[76] On the other end of the spectrum, the Supreme Court held that a more broadly effective combination of certain strains of nitrogen-fixing bacteria, which the patentee discovered could be combined without interfering with each other, was not patentable subject matter—"like the heat of the sun, electricity, or the qualities of metals."[76.1]

Chakrabarty did not address the question of whether biological specimens found in nature, such as DNA sequences, proteins, and antibodies, are patentable under 35 U.S.C. § 101. Several other cases, however, support the patentability of biological specimens that have been purified and isolated.[77]

[B] *Association for Molecular Pathology v. Myriad Genetics*

[B][1] Myriad I, II, *and* III

After the Supreme Court's decision in *Prometheus IV*,[77.1] the Supreme Court granted certiorari and vacated the Federal Circuit's decision in *Myriad* for further determination in light of *Prometheus IV*.[77.2]

74.36. *Id*. at 1336.
75. Diamond v. Chakrabarty, 447 U.S. 303, 309–10 (1980).
76. *Id*. See also *infra* section 7:6.2[A][1] for a further discussion of *Chakrabarty*.
76.1. Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948).
77. *See infra* section 7:6.2[A][2] and [B].
77.1. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012) (*Prometheus IV*).
77.2. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 132 S. Ct. 1794 (2012) (*Myriad II*).

On remand, the Federal Circuit reached the same conclusions in its second opinion in *Myriad* as it did in its first.[77.3]

The Federal Circuit addressed the patentability of DNA sequences and distilled the following test from Supreme Court precedent in *Myriad I* and *Myriad III*:

> [T]he Supreme Court has drawn a line between compositions that, even if arrayed in useful combinations or harnessed to exploit newly discovered properties, have similar characteristics as in nature, and compositions that human intervention has given "markedly different," or "distinctive," characteristics.[78]

The court upheld the patentability of isolated DNA sequences from the BRCA1 and BRCA2 genes associated with the potential for breast cancer.[79] The reasoning, however, was not shared by the two judges on the three-judge panel who wrote in favor of reversing the district court's ruling that the claims did not cover patentable subject matter. Judge Lourie reasoned that the claims cover compositions that are "markedly different" from nature because the claimed "[i]solated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule."[80]

Judge Moore, in a concurring opinion, offered different reasoning for reversing the district court. Her analysis depended on the nature of the specific claims. Claims to cDNA presented the easiest case because "the claimed cDNA sequences do *not* exist in nature."[81] Claims to "shorter isolated DNA sequences" are "markedly different" from nature because they "have a variety of applications and uses in isolation that are new and distinct as compared to the sequence as it occurs in nature."[82] As for longer DNA strands, Judge Moore conceded that they present a "difficult issue" because they form a part

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77.3. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d 1303 (Fed. Cir. 2012) (*Myriad III*).

78. *Id*. at 1328.

79. *Id*. Judge Lourie's reasoning, however, may not apply to purified material such as some proteins or antibodies: "[I]solated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials." *Id*.

80. *Id*.

81. *Id*. at 1340 (Moore, J., concurring in part). She further explained that the claimed cDNAs lack the introns found in the natural DNA and differ from RNA because they have a complementary sequence of nucleotides and different base.

82. *Id*. at 1341.

of a naturally occurring sequence, and their isolation from nature may not result in utility that is new and distinct from what occurs in nature. She concluded that the danger of upsetting long-standing settled expectations supported upholding the patentability of even long strands:

> If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter. . . . But we do not decide this case on a blank canvas. . . . There are now thousands of patents with claims to isolated DNA, and some unknown (but certainly large) number of patents to purified natural products or fragments thereof. As I explain below, I believe we must be particularly wary of expanding the judicial exception to patentable subject matter where both settled expectations and extensive property rights are involved.[83]

[B][2] Myriad IV

The Supreme Court again granted certiorari in *Myriad*.[84] The Supreme Court reversed the judgment of the Federal Circuit regarding isolated DNA, holding that such naturally occurring genetic material is a product of nature and therefore not patent-eligible under 35 U.S.C. § 101.[85] The Court affirmed the judgment of the Federal Circuit holding that complementary DNA (cDNA) is a non-naturally occurring product and therefore patent-eligible.[86]

Justice Thomas delivered the unanimous opinion of the Court. In describing the claimed inventions at issue, the Court noted:

> It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13.[87]

The Court found that the acts of locating and isolating the DNA from its natural setting did not render the subject matter patentable.

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83. *Id*. at 1343.
84. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 694 (2012).
85. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116–19 (2013) (*Myriad IV*).
86. *Id*. at 2119.
87. *Id*. at 2116.

The Court compared the claims unfavorably with the claimed organism in *Chakrabarty*, a bacterium with four plasmids added by scientists, enabling it to break down components in crude oil:

> The *Chakrabarty* bacterium was new "with markedly different characteristics from any found in nature," due to the additional plasmids and resultant "capacity for degrading oil." In this case, by contrast, Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.[88]

The Court found the claimed genes to be more like the claimed mixture of naturally occurring bacteria held to be unpatentable in *Funk Brothers Seed Co*. because the bacteria had not been altered in any way.[89] Similarly, the Court found that the Myriad inventors discovered the location of the BRCA genes but did not alter them and "that discovery, by itself, does not render the BRCA genes 'new compositions of matter,' § 101, that are patent eligible."[90]

The Court noted the substantial research undertaken by the Myriad inventors to locate the BRCA genes but concluded that "extensive effort alone is insufficient to satisfy the demands of § 101."[91] Nor was the Court persuaded by the argument that the act of isolating the genes rendered them a non-naturally occurring, patent-eligible product because of the severing of chemical bonds: "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes."[92] The Court also rejected the argument that past Patent Office practice of awarding gene patents warranted upholding the patentability of the BRCA gene claims, noting that the United States in its *amicus* briefing argued that isolated DNA was not patentable, weighing against deferring to the PTO.[93]

The Court found that "cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments," and therefore affirmed the judgment of the Federal Circuit with respect to that issue.[94] In particular, the Court found that the removal of the noncoding intron sequences found in naturally occurring DNA,

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88. *Id*. at 2116–17 (internal citations omitted).
89. *Id*. at 2117.
90. *Id*.
91. *Id*. at 2118.
92. *Id*.
93. *Id*. at 2118–19.
94. *Id*. at 2119.

leaving only the exon sequences that code for amino acids, rendered cDNA distinct from natural DNA.[95] Thus, "the lab technician creates something new when cDNA is made" as opposed to isolating a product of nature, and cDNA is patent-eligible.[96]

The Court pointed out the limits of its opinion by commenting that there were no method claims before it and suggested that had Myriad created and claimed innovative methods of manipulating genes while searching for the BRCA1 and BRCA2 genes, this may have presented a different issue.[97] The Court noted, however, that the actual methods used by Myriad to isolate DNA were widely understood and widely used by geneticists at the time of Myriad's patents.[98] The Court further pointed out that the claims at issue did not involve *applications* of knowledge regarding the BRCA genes and many of the unchallenged claims were limited to such applications.[99] The Court also noted that DNA sequences in which the order of the naturally occurring nucleotides had been altered were not at issue and the Court offered no opinions on the patentability of claims to such sequences.[100]

[C] Post-*Myriad*

[C][1] Cloned Animal Claims

The Federal Circuit has since relied on *Myriad* in holding that a genetic clone of an animal is equally as patent-ineligible as the original animal.[101] Specifically, the Federal Circuit paralleled the Supreme Court's *Myriad* conclusion—"that 'isolated,' naturally occurring DNA strands are not eligible for patent protection"—and concluded that the claimed invention "'did not create or alter any of the genetic information' of its claimed clones, '[n]or did [it] create or alter the genetic structure of [the] DNA' used to make its clones."[102] The Federal Circuit reasoned that phenotypic differences and differences in mitochondrial DNA between a donor mammal and its clone were unclaimed, and thus were patent-ineligible because "the claims do not describe clones that have markedly different characteristics from the donor animals of which they are copies."[103] Moreover, the

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95. *Id*.
96. *Id*.
97. *Id*. at 2119–20.
98. *Id*.
99. *Id*. at 2120.
100. *Id*.
101. *In re* Roslin Inst. (Edinburgh), 750 F.3d 1333, 1337 (Fed. Cir. 2014).
102. *Id*. at 1337 (quoting *Myriad II*, 133 S. Ct. at 2116).
103. *Id*. at 1338–39.

Federal Circuit reasoned that phenotypic differences that were due to "environmental factors" were not a product of "any effort by the patentee" and thus, could not be enough to impart eligibility.[104] Lastly, the Federal Circuit adopted the reasoning of the district court that any temporal distinction between the donor and the clone cannot be enough to confer patent-eligibility because "that . . . is true of any copy of an original."[105] The Federal Circuit noted, however, that a "method of copying" may well be entitled to patent-eligibility.[106]

[C][2] Primer Claims

The Federal Circuit held claims to a "pair of single-stranded DNA primers" for BRCA1 patent ineligible despite the fact that "single-stranded DNA cannot be found in the human body" because (1) separating DNA from surrounding genetic material is not inventive and (2) the primers do not perform a significantly new function from their function in nature in view of the fact that DNA's complementarity is a function exploited in nature.[107]

[C][3] Food Supplements and Natural Products

The Federal Circuit held that claims to beta-alanine dietary supplements (which is an amino acid) were directed to potentially patentable subject matter because they claimed "specific treatment formulations that incorporate[d] natural products" that "ha[d] different characteristics and c[ould] be used in a manner that beta-alanine as it appears in nature cannot."[108] On the other hand, claims to milk with NR that has been isolated (as "compared to how NR naturally exists in milk") were not sufficient to confer patentability because "the asserted claims do not have characteristics markedly different from milk."[109]

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104. *Id*. at 1338.
105. *Id*. at 1339.
106. *Id*. at 1337.
107. *In re* BRCA1-and-BRCA2-Based Hereditary Cancer Test Patent Litig., 774 F.3d 755, 759–60 (Fed. Cir. 2014).
108. Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, 918 F.3d 1338, 1341, 1348–49 (Fed. Cir. 2019).
109. Chromadex, Inc. v. Elysium Health, Inc., 59 F.4th 1280, 1284 (Fed. Cir. 2023).

Chapter 4. Inventorship

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Chapter 4

Inventorship

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§ 4:1 General Principles of Inventorship

Inventorship issues can have a major impact on patent ownership and validity. Particularly in the context of the pharmaceutical and biotechnology industries, they can raise difficult legal issues with uncertain outcomes.

The patent statute does not directly define what one must do to be considered an inventor. Case law, which developed as a result of disputes over inventorship, provides some guidance on how to identify inventors. More frequently, the case law simply provides examples of what is not sufficient for inventorship.

Disputed inventorship issues broadly fall into two categories: (1) competing patents and applications subject to the pre-America Invents Act (AIA) versions of 35 U.S.C. § 102(g) and 35 U.S.C. § 135[1] can give rise to "priority disputes" to determine which of two or more competing inventors or groups of inventors made the invention first; and (2) disputes among several persons working together over who actually made the invention can give rise to proceedings known as "originality contests" under the pre-AIA law and derivation proceedings under the AIA. Priority disputes can arise when two or more patents or patent applications filed by different inventors for the same invention result in a proceeding known as an "interference." An interference is a Patent Office proceeding to determine which application should issue as a patent or which patent properly issued.[2] Originality contests and derivation proceedings can arise from a claim to inventorship or co-inventorship by a person not named in the patent. In a priority dispute, the issue is who was the first to invent, whereas "in an originality case the issue is not who is the *first* or *prior* inventor, but who *made* the invention."[3]

In litigation, inventorship is an issue of law.[5] There is a presumption that an issued patent names the correct inventors;[6] a challenge

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1. See *infra* section 4:1.1[B] for a discussion of pre-AIA priority disputes, and section 5:2.1 for a broader discussion of the AIA, Pub. L. No. 112-29, 125 Stat. 284.
2. Capon v. Eshhar, 418 F.3d 1349, 1351 (Fed. Cir. 2005) ("A patent interference is an administrative proceeding pursuant to 35 U.S.C. §§ 102(g) and 135(a), conducted for the purpose of determining which of competing applicants is the first inventor of common subject matter."). Interferences can also occur between a patent application and an issued patent or between issued patents. *See* 35 U.S.C. §§ 135(a), 291.
3. Sewall v. Walters, 21 F.3d 411, 415 (Fed. Cir. 1994) (quoting Applegate v. Scherer, 332 F.2d 571, 573 n.1 (C.C.P.A. 1964)) (emphasis added).
4. [Reserved.]
5. *Sewall*, 21 F.3d at 415 ("Determining 'inventorship' is nothing more than determining who conceived the subject matter at issue, whether that subject matter is recited in a claim in an application or in a count in an interference. Conception, and consequently inventorship, are questions of law that this court reviews de novo; of course, any facts found by the Board in reaching an inventorship holding are reviewed for clear error."); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986).
6. 35 U.S.C. § 282.

to the validity of an issued patent on the ground of misjoinder or incorrect inventorship must be established by clear and convincing evidence.[7]

§ 4:1.1 Overview of Statutory Provisions

Several different parts of the patent statute relate to inventorship. The following table provides a list of the provisions that are discussed in this chapter.

Statutory Section	Scope
§ 101	whoever "invents" patentable subject matter may obtain a patent
Pre-AIA § 102(f)	inventorship requirement for patentability
Pre-AIA § 102(g)	must be first U.S. inventor in a priority contest
§ 111(a)	patent application made by or authorized by inventor
§ 116	joint inventors
Pre-AIA § 135	interference proceeding
Post-AIA § 135	derivation proceedings
§ 256	correction of inventorship in an issued patent

[A] Priority Disputes and the AIA

The ability to challenge an invention on the basis that someone else invented it first flows from pre-AIA sections 102(g) and 135 of the patent statute.[7.1] On September 16, 2011, Congress enacted the Leahy-Smith America Invents Act (AIA), which, among other things, amended sections 102 and 135. Patent applications and patents that contain, or at any time during prosecution contained, at least one claim with an effective filing date of March 16, 2013, or later are subject to sections 102 and 135 as amended by the AIA.[7.2]

[B] Priority Disputes (Pre-AIA)

For patents with an effective filing date prior to March 16, 2013—the date that the modified first-to-file provisions of the Leahy-Smith America Invents Act (AIA) went into effect—a legal issue may arise

7. Hess v. Advanced Cardiovascular Sys., Inc., 106 F.3d 976, 979 (Fed. Cir. 1997); Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466, 1472 (Fed. Cir. 1997).
7.1. *See* pre-AIA 35 U.S.C. §§ 102, 135.
7.2. *See infra* section 5:2.1.

regarding who is the *first* inventor. Such a challenge can be made in the form of prior art under pre-AIA 35 U.S.C. § 102(g) or in the form of an interference proceeding under pre-AIA 35 U.S.C. § 135. As described below in section 4:1.5, the pre-AIA versions of 35 U.S.C. § 102(g) required that a patent only issue to the first inventor. The pre-AIA version of 35 U.S.C. § 135 outlined a proceeding called an interference that could be used to determine who is the first inventor when a patent application claims the same invention as another patent application or granted patent. When proving who was the first inventor, the challenger must prove conception,[7.3] diligence,[7.4] and reduction to practice[7.5] as well as prove that they did not abandon, suppress, or conceal the invention.[7.6]

[C] AIA's Elimination of Priority Disputes

As described in section 5:2.1[C][1], as part of the U.S. effort to conform its patent system with the rest of the world, the AIA changed 35 U.S.C. § 102 from a first-to-invent system to a first-to-file-or-disclose system. Patents with an effective filing date after March 16, 2013, will be subject to the post-AIA versions of 35 U.S.C. §§ 102 and 135. Because the AIA does away with the first-to-invent system, post-AIA 35 U.S.C. §§ 102 and 135 no longer contain provisions that bar a patent because someone else invented it first. In particular, pre-AIA 35 U.S.C. § 102(g) has been removed entirely and pre-AIA 35 U.S.C. § 135 has replaced interference proceedings with derivation proceedings.

Unlike an interference proceeding, which is concerned with who invented it first, a derivation proceeding is concerned with whether the idea was derived from someone else's work. Specifically, post-AIA 35 U.S.C. § 135(a) states:

> INSTITUTION OF PROCEEDING.
>
> **(1) In general.**—An applicant for patent may file a petition with respect to an invention to institute a derivation proceeding in the Office. The petition shall set forth with particularity the basis for finding that an individual named in an earlier application as the inventor or a joint inventor derived such invention from an individual named in the petitioner's application as the inventor or a joint inventor and, without authorization, the earlier application claiming such invention was filed. Whenever the Director determines that a petition filed under this subsection demonstrates

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7.3. *See infra* section 4:1.2.
7.4. *See infra* section 4:1.5[B].
7.5. *See infra* section 4:1.3.
7.6. *See infra* section 4:1.5[A].

> that the standards for instituting a derivation proceeding are met, the Director may institute a derivation proceeding.
>
> **(2) Time for filing.**—A petition under this section with respect to an invention that is the same or substantially the same invention as a claim contained in a patent issued on an earlier application, or contained in an earlier application when published or deemed published under section 122(b), may not be filed unless such petition is filed during the 1-year period following the date on which the patent containing such claim was granted or the earlier application containing such claim was published, whichever is earlier.
>
> **(3) Earlier application.**—For purposes of this section, an application shall not be deemed to be an earlier application with respect to an invention, relative to another application, unless a claim to the invention was or could have been made in such application having an effective filing date that is earlier than the effective filing date of any claim to the invention that was or could have been made in such other application.
>
> **(4) No appeal.**—A determination by the Director whether to institute a derivation proceeding under paragraph (1) shall be final and not appealable.

§ 4:1.2 Conception

[A] Requirements

Proof of conception, whether offered by a challenger to establish prior invention by another or co-invention by another, or offered by the patentee to establish a prior date of invention, requires corroboration. In the latter case, although the burden of persuasion remains firmly on the challenger and must be clear and convincing, the patentee bears the burden of production to demonstrate an earlier date of conception.[8]

"Conception is the touchstone of inventorship, the completion of the mental part of the invention."[9] It is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice."[10]

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8. Allergan, Inc. v. Apotex., Inc., 754 F.3d 952, 967 (Fed. Cir. 2014) ("While defendants bear the burden of persuasion to show that the Brandt references are prior art to the '404 patent by clear and convincing evidence, the patentee nevertheless must meet its burden of production to demonstrate an earlier conception date.").
9. *Id*.
10. *Hybritech*, 802 F.2d at 1376; Coleman v. Dines, 754 F.2d 353, 359 (Fed. Cir. 1985).

As the Federal Circuit has held, "the test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention. . . . An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan that he hopes to pursue."[11] Basically, "[d]etermining 'inventorship' is nothing more than determining who conceived the subject matter at issue . . . ."[12]

A conception must be operable and include every feature of the invention as claimed, as well as must be complete enough so that the inventor can describe the invention in sufficient detail to constitute an adequate written description.[13] The Federal Circuit described this latter requirement in *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*:[14]

> The conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention. These rules ensure that patent rights attach only when an idea is so far developed that the inventor can point to a definite, particular invention.

Accordingly, a vague notion of a goal to be achieved without a definite idea of how to achieve the goal in practice is not a complete conception. Nor can the inventive contribution be a general suggestion of

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11. Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994).
12. *Sewall*, 21 F.3d at 415.
13. *Id*. ("Conception is complete when one of ordinary skill in the art could construct the apparatus without unduly extensive research or experimentation."); *Coleman*, 754 F.2d at 359; Summers v. Vogel, 332 F.2d 810, 814 (C.C.P.A. 1964); *In re* Tansel, 253 F.2d 241, 243 (C.C.P.A. 1958).
14. *Burroughs Wellcome*, 40 F.3d at 1228. Thus, the test for an adequate conception of an invention is measured by the same standard that is used to determine when the written description of an invention is sufficient to support a particular claim. *See* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 930 n.10 (Fed. Cir. 2004) ("Although we have treated the issue in this case as one of written description, as it was argued and decided below, underlying that question is the fundamental issue whether Rochester actually invented the subject matter it claimed in the '850 patent as required by 35 U.S.C. § 102(f). . . . Here the patentee has done no more than invent a search method, *i.e.*, a method of identifying a selective COX-2 inhibitor, much less did it invent, as claimed in the '850 patent, a method of using any such compound to selectively inhibit COX-2 in humans. Under these circumstances, it might appear that the patentee also failed to satisfy the requirements of section 102(f).").

an approach to a problem or solution without the details for carrying out the general idea.[15]

[B] Proof of Conception Requires Corroboration

Challenging patentability based on prior claims to inventorship or co-inventorship must be based on corroborated evidence. "The law is unequivocal that an inventor's testimony respecting the facts surrounding a claim of derivation or priority of invention cannot, standing alone, rise to the level of clear and convincing proof. Throughout the history of the determination of patent rights, oral testimony by an alleged inventor asserting priority over a patentee's rights is regarded with skepticism."[16]

From an evidentiary standpoint, "[i]t is well established that when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony."[17] Each putative inventor must provide corroborating evidence of their contributions to the conception of an invention. Similar to conception of the entire invention, a contribution to conception is a "mental act which cannot be accurately verified without

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15. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property."); *see also infra* section 4:4 (description of the patentability of chemical compounds and nucleic acids).

16. Price v. Symsek, 988 F.2d 1187, 1194 (Fed. Cir. 1993); *see also Allergan*, 754 F.3d at 967 ("when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corroborating that testimony"); Chen v. Bouchard, 347 F.3d 1299, 1309 (Fed. Cir. 2003) ("That rule addresses the concern that a party claiming inventorship might be tempted to describe his actions in an unjustifiably self-serving manner in order to obtain a patent or to maintain an existing patent."); Hess v. Advanced Cardiovascular Sys., Inc., 106 F.3d 976, 980 (Fed. Cir. 1997) ("[T]he burden of showing misjoinder or non-joinder of inventors is a heavy one and must be proved by clear and convincing evidence.").

17. *Chen*, 347 F.3d at 1309–10 ("Evidence of the inventive facts must not rest alone on the testimony of the inventor himself."); *see also* Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461 (Fed. Cir. 1998) ("To show co-inventorship, however, the alleged co-inventor or co-inventors must prove their contribution to the conception of the claims by clear and convincing evidence."). *See infra* section 4:4.

corroboration."[18] The policy of this rule exists because "the temptation for even honest witnesses to reconstruct, in a manner favorable to their own position, what their states of mind may have been years earlier, is simply too great to permit a lower standard."[19]

The nature of the corroboration is subject to a "rule of reason" analysis of all the pertinent evidence.[20] Some factors that may be considered in weighing the sufficiency of corroboration include:[21]

(1) delay between the event and the trial,

(2) interest of corroborating witnesses,

(3) contradiction or impeachment,

(4) the corroborating witnesses' familiarity with details of alleged prior structure,

(5) improbability of prior use considering state of the art,

(6) impact of the invention on the industry, and

(7) relationship between witness and alleged prior user.

According to one court, unwitnessed lab notebooks, regardless of whether they may enable a person of ordinary skill in the art to make or practice the claimed invention, "*on their own* are insufficient to support a claim of co-inventorship."[23] It should be noted that the standard for corroborating conception does not apply to proof of reduction to practice.[24]

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18. Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466, 1474 (Fed. Cir. 1997).
19. *Hess*, 106 F.3d at 980; *see also Ethicon*, 135 F.3d at 1461 ("[A]n inventor's testimony respecting the facts surrounding a claim of derivation or priority of invention cannot, standing alone, rise to the level of clear and convincing proof.").
20. *Price*, 988 F.2d at 1195.
21. *Id*. at 1195 n.3.
22. [Reserved.]
23. Stern v. Trs. of Columbia Univ., 434 F.3d 1375, 1378 (Fed. Cir. 2006) (emphasis added); Gortatowsky v. Anwar, 442 F.2d 970, 972 (C.C.P.A. 1971) (holding that an inventor's laboratory notebook that was neither read nor witnessed and kept with suspect chronology could not provide the requisite corroboration for a reduction to practice); *cf*. Mikus v. Wachtel, 542 F.2d 1157, 1161 (C.C.P.A. 1976) (holding that an invention record, based on an unwitnessed laboratory notebook *and* results performed by technicians unaware of what they were testing, may provide sufficient evidence of conception but not reduction to practice under the rule of reason).
24. Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1169 (Fed. Cir. 2006) ("[N]o similar condition of 'corroboration' is imposed on an inventor's

The corroborating evidence of conception must corroborate each element of the claimed invention—in other words, it must "enable one skilled in the art to make the invention."[24.1] *Allergan, Inc. v. Apotex Inc.*[24.2] is instructive. "The district court found that the conception date of the '404 patent was in mid-2000 based on the following facts":

- "credible testimony" that inventor concluded that "topical application of bimatoprost would grow hair in mid-2000,"
- "credible testimony of meeting with patent attorneys" around 2000/2001 "to discuss the invention,"
- "internal Allergan memoranda reporting eyelash growth . . . in early 2000."[24.3]

The Federal Circuit reversed for lack of corroborating evidence because the only documentary evidence—the internal memoranda—referred to using "eyedrops" instead of the claimed "topical application."[24.4]

[C] Is There a Requirement That the Inventor Know That His Invention Will Work for Conception to Be Complete?

In one case, the Federal Circuit held that conception does not require proof that the invention will work. In *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*, the inventor conceived of the idea of using the specific chemical compound, AZT, as a treatment for AIDS.[25] The drug was later proven effective in human clinical trials conducted by the National Institutes of Health (NIH) in conjunction with the plaintiff. Although some experiments had been performed in mice, it was assumed for purposes of defendants' summary judgment motion that there was no reasonable scientific basis to believe AZT would be an effective treatment for AIDS until the human clinical trials demonstrated effectiveness. The defendants claimed the NIH scientists were co-inventors of the method of treatment claim because of their human clinical trial work, and took a license from the NIH. The Federal Circuit, however, affirmed the district court's finding

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notebook, or indeed on any documentary or physical evidence, as a condition for its serving as evidence of reduction to practice.").

24.1. Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994) ("Because it is a mental act, courts require corroborating evidence of a contemporaneous disclosure that would enable one skilled in the art to make the invention.").

24.2. Allergan, Inc. v. Apotex Inc., 754 F.3d 952 (Fed. Cir. 2014).

24.3. *Allergan*, 754 F.3d at 967–68.

24.4. *Id.* at 968 (reversing district court's finding of prior conception).

25. *Burroughs Wellcome*, 40 F.3d at 1223.

that the NIH scientists were not co-inventors. Conception was complete when plaintiff had the idea of using a specific, identified compound, AZT, for the specific purpose of treating AIDS. Lack of a reasonable basis to believe the method of treatment would be successful did not detract from the completeness of the conception, and testing to prove the utility of the method was not part of the conception of the method. The court explained:

> The question is not whether Burroughs Wellcome reasonably believed that the inventions would work for their intended purpose, the focus of the evidence offered by [the defendants], but whether the inventors had formed the idea of their use for that purpose in sufficiently final form that only the exercise of ordinary skill remained to reduce it to practice. . . . Whether or not Burroughs Wellcome believed the inventions would in fact work based on the mouse screens is irrelevant.[26]

The Burroughs Wellcome scientists were inventors because they had conceived of using a known specific chemical compound for a particular treatment, even though they had no basis to predict success.[27]

However, where the claimed invention requires that a method yield a certain result, to show conception that limitation must have been known to the inventor at the time of the alleged conception.[28] In *Burroughs Wellcome*, as described above, the court found sufficient

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26. *Id*. at 1231.
27. See MacMillian v. Moffett, 432 F.2d 1237 (C.C.P.A. 1970), where Moffett made a selection of sixty-nine compounds from 500 compounds known or suspected to have anticholorgenic activity for use in anti-perspirant. He gave the compounds to MacMillian, who tested them for activity. MacMillian found that only one of the sixty-nine compounds had outstanding activity. MacMillian claimed to be an inventor because his testing identified that compound and Moffett did not know which compound was surprisingly active until he tested the compounds. The court held that Moffett alone was the inventor. Moffett had done more than provide a general concept; he identified sixty-nine specific compounds and their intended use. The court held that the inventor need not know the unexpected properties, and that his reasons for selecting the compound were irrelevant.
28. *See* Hitzeman v. Rutter, 243 F.3d 1345, 1354 (Fed. Cir. 2001). But when the patent recites a limitation that is an inherent property of the claimed invention, *e.g.*, molecular weight, "specific conception of these properties is not required." *Id*.; Silvestri v. Grant, 496 F.2d 593, 599 (C.C.P.A. 1974) (finding that in a count directed to a form of ampicillin that recited the compound's molecular weight, it was "sufficient to possess the claimed compound and to characterize it by water count and infrared spectrograph, without demonstrating knowledge of the compound's molecular weight").

conception for the first five patents, which recited claims using AZT to treat AIDS, but not for the sixth patent, which required using AZT to increase T-lymphocytes in humans infected with the HIV virus. The court found that this invention was not conceived because there was uncertainty as to whether administering AZT actually would promote T-lymphocyte production—that is, whether the claimed result could be achieved, and there was no evidence "that the inventors thought AZT could raise a patient's T-cell levels."[29]

The Federal Circuit also addressed the conception requirements in *Hitzeman v. Rutter*.[30] That case was an interference relating to production of correctly assembled hepatitis B surface antigen in yeast. The senior party, Rutter, had actually produced the antigen in yeast with the correct particle size. The junior party, Hitzeman, attempted to show earlier conception of his portion of the interference count that was a method of producing hepatitis B of the correct particle size through expression in yeast. Only those antigens that formed approximately 22 nm particles were determined to be immunologically reactive and were useable in vaccines.

Hitzeman alleged that he had conceived of the method of expressing the hepatitis B antigen in yeast and had hoped it would produce particles of the authentic 22 nm size prior to Rutter's actual reduction to practice. Prior efforts to express the antigen in *E. coli* had not succeeded because the particles formed were not assembled in the correct size and were not useable in vaccines.

The Federal Circuit held that the particle size and sedimentation rate limitations were central to the patentability of the invention and were "material limitations of the counts, for which [the inventor] had the burden of establishing conception."[31] It held that Hitzeman, the party with the burden of proving conception in the interference proceeding below, only had a "hope" of achieving the claimed result. The court held that "[s]uch a bare hope is insufficient to establish conception."[32] Here, Hitzeman failed to show a reasonable expectation that the claimed result of the biological process would occur.[33]

Both *Hitzeman* and *Burroughs* involved method claims. While Hitzeman's "hope," without proof that his method would produce antigen particles of the authentic size, was not a sufficient conception of a count that claimed a method of producing the particles in yeast with the correct size, Burroughs' conception of a method of treating

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29. *Burroughs Wellcome*, 40 F.3d at 1231–32.
30. Hitzeman v. Rutter, 243 F.3d 1345 (Fed. Cir. 2001).
31. *Id*. at 1355.
32. *Id*. at 1357.
33. *Id*. at 1357–58.

AIDS with AZT was sufficient, although under the facts assumed for summary judgment, it could have had nothing more than a "hope" that the method of treatment would work because it had no reasonable basis to expect success.

The *Hitzeman* court distinguished *Burroughs* by noting that "Hitzeman chose to claim the invention by reciting the particular result of an intracellular process, *i.e.*, the production of 22 nm HBsAg particles," while *Burroughs* "concerned six patents directed toward administering a drug, AZT, to AIDS patients."[34] Five of the six *Burroughs* patents "recited various permutations of administering the AZT to patients, without reciting details of how the body would react to the drug."[35] Unlike *Hitzeman*, the *Burroughs* inventors of the claims in these five *Burroughs* patents, according to the court, "had sufficiently established conception of the limitations of the claims (*i.e.*, the drug itself and the intention to administer it to humans)."[36] It was "immaterial that the [*Burroughs*] inventors lacked a 'reasonable expectation' as to how non-claimed aspects of the drug would work."[37] The court likened Hitzeman's count to "the claims of the sixth patent discussed in *Burroughs*," which covered "a method of increasing the number of T-lymphocytes in a human infected with the [HIV] virus."[38] In contrast to the claims of the first five patents, Burroughs did not clearly conceive this method claim because there was "uncertainty as to whether administering AZT actually would promote T-lymphocyte production, *i.e.*, the claimed intended use."[39] Like the claims of the sixth patent in *Burroughs*, "Hitzeman failed to show that he had a reasonable expectation that the claimed result of the biological process would occur."[40] Accordingly, like the *Burroughs* court's ruling on the sixth patent, the *Hitzeman* court rejected Hitzeman's conception argument.

In *Rasmusson v. Smith-Kline Beecham Corp.*,[41] the Federal Circuit addressed a question that was in substance similar to the issue in *Burroughs*, although it arose under an enablement rubric. That case was an interference concerning the treatment of prostate cancer with the compound finasteride. Although the Rasmusson patent application disclosed the known compound finasteride and described its

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34. *Id.* at 1356, 1358.
35. *Id.* at 1358 (citing *Burroughs*, 40 F.3d at 1225 n.3).
36. *Id.*
37. *Id.*
38. *Id.*
39. *Id.*
40. *Id.*
41. Rasmusson v. Smith-Kline Beecham Corp., 413 F.3d 1318 (Fed. Cir. 2005).

use to treat prostate cancer, the Federal Circuit held that the application was not enabled because one of ordinary skill in the art would not have believed that the treatment would work (although it in fact did work). The court rejected the application as being "little more than respectable guesses."[42] Yet, in *Burroughs*, the inventors were found to have a complete conception of the method of treatment—which necessarily must be an enabled conception[43]—based on the idea of using a specific compound (AZT instead of finasteride) to treat a specific disease (AIDS instead of prostate cancer) with no more than a hope or "guess" that it would work.

[D] Unrecognized Accidental Creation Not Invention

Conception requires more than unrecognized accidental creation; it requires that the inventor appreciate that which he has invented. "An unrecognized and unappreciated duplication of an invention does not defeat the patent right of one who, though later in time, was the first to recognized that which constitutes the inventive subject matter."[44] As described in a preceding section, conception must be corroborated. Thus, the test results on which an inventor relies to show that the inventor appreciated that which he invented must show, by clear and convincing evidence to one of skill in the art, recognition of the claimed invention.[45] In *Invitrogen Corp. v. Clontech Laboratories, Inc.*,[46] the court found that the developer of a genetically engineered reverse transcriptase (RT) did not prove by clear and convincing evidence that, at the relevant time, he appreciated that his H7 and H8 RT were RNase H minus, a chemical compound which the developer hoped to create.[47]

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42. *Id*. at 1325.
43. Oka v. Youssefyeh, 849 F.2d 581, 583 (Fed. Cir. 1988) (conception of a compound "requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it").
44. Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052, 1063 (Fed. Cir. 2005) (quoting *Silvestri*, 496 F.2d at 597); Dow Chem. Co. v. Astro-Valcour, Inc., 267 F.3d 1334, 1341 (Fed. Cir. 2001) ("[T]he date of conception of a prior inventor's invention is the date the inventor *first appreciated* the fact of what he made.") (emphasis added).
45. *Invitrogen*, 429 F.3d at 1065; *Silvestri*, 496 F.2d 593 (requiring an objective basis corroborating the inventor's stated appreciation such that persons of ordinary skill in the art at the time of the recognition would have recognized the existence of the novel features); *see also supra* section 4:1.2[B] (discussion of the corroboration requirement).
46. Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052 (Fed. Cir. 2005).
47. *Id*. at 1066–69; *see also* Langer v. Kaufman, 465 F.2d 915, 919 (C.C.P.A. 1972) (holding that where an objective basis exists for identifying a

[E] Examples

[E][1] General Goal with No Specific Means for Implementation: Amax Fly Ash Corp. v. United States[48]

In this case, the patented method covered pumping fine particles of ash into burning mine shafts to block the shaft and deprive the fire of oxygen.

The defendant alleged that the plaintiff derived the invention from another who claimed to have made a general suggestion of using pneumatic trucks to blow fly ash into mines to extinguish mine fires. The court found the assertion of the alleged original inventor that he thought of using pneumatic trucks to blow fly ash into the mines was inadequate to become a conception because he had no conception of the specific means and processes involved in achieving the goal.[49] Further, the alleged original inventor had no expertise in any of the engineering problems that needed to be addressed to make the process a reality. At best, the court noted, the alleged original inventor had only a "general vague" idea of the use of pneumatic trucks to fight fires.

[E][2] Providing Goal to Be Achieved without Direction: Morgan v. Hirsch[50]

The patent issue claimed a process used to make a fabric of a certain design using a circular knitting machine.

The alleged inventor asserted that he had described the fabric to a third party prior to the named inventor's conception of the invention.[51]

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claimed compound, there must be evidence that the inventor timely considered it); Heard v. Burton, 333 F.2d 239, 243 (C.C.P.A. 1964) (finding no conception where inventor failed, before the critical date, to inspect the claimed compound's X-ray diffraction pattern, which was the only way that the claimed compound could have been identified).

48. Amax Fly Ash Corp. v. United States, 514 F.2d 1041, 1046–50 (Ct. Cl. 1975).

49. *Id*. at 1048–49.

50. Morgan v. Hirsch, 728 F.2d 1449, 1452 (Fed. Cir. 1984). Though not relevant for the discussion here, a portion of the underlying rationale in *Morgan* has been superseded by statute. *See* Kwon v. Perkins, 6 U.S.P.Q.2d (BNA) 1747 (B.P.A.I. 1988), *aff'd*, 886 F.2d 325 (Fed. Cir. 1989) (both patentability and priority questions are now within the power of the board to decide).

51. *Morgan*, 728 F.2d at 1452 ("[The alleged inventor] asked [the named inventors] if they could produce a fabric on circular knitting machines like the old and well-known raschel fabric, and they did.").

The court rejected the alleged inventor's argument, stating:

> "[A]sking someone to produce something without saying just what it is to be or how to do it is not what patent law recognizes as inventing. . . . All the record shows to us is that Trabal submitted successive samples which Morgan criticized, and for which he finally supplied the kind of yarn he wanted used, until he got what he wanted."[52]

Accordingly, the Federal Circuit affirmed the judgment of the Patent Office, which found that the appellee, who had filed the patent application first, held priority of conception over the alleged inventor.

[E][3] Carrying Out Confirming Experiments: Stern v. Trustees of Columbia University[53]

The patent at issue in this case was directed towards the use of prostaglandins in treating glaucoma.

The plaintiff sought to be added as co-inventor on the claimed invention because he carried out an experiment previously done by the inventor on different animals that the inventor already determined would be adequate models for prostaglandin research.[54]

The court rejected plaintiff's claim of co-inventorship, finding that the plaintiff's contribution to the claimed invention was insufficient to merit conception as co-inventor. The court specifically noted that plaintiff did not understand the effect of prostaglandins on glaucoma. Moreover, plaintiff merely provided routine work by "carr[ying] out an experiment previously done by [the named inventor]" on animals that the named inventor had already determined would be good models for his research.[55] Accordingly, the court affirmed the lower court's decision granting the defendant summary judgment on the ground that the plaintiff failed to present sufficient evidence to be added as co-inventor.[56]

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52. *Id.*; *see also* Eli Lilly & Co. v. Aradigm Corp., 376 F.3d 1352 (Fed. Cir. 2004) (where the invention related to use of a modified insulin, Lispro, for an inhalation delivery system. The court rejected the claim of an alleged co-inventor who testified that he always mentioned Lispro in discussing inhalable insulin with the named inventors, but did not testify that he had suggested that the use of Lispro would increase the absorption by the amount required by the claim).
53. Stern v. Trs. of Columbia Univ., 434 F.3d 1375 (Fed. Cir. 2006).
54. *Id.* at 1377.
55. *Id.* at 1378.
56. *Id.*

[E][4] Conception of Chemical Compounds

To show conception of a chemical compound, the researcher must have: "(1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it."[56.1] Utility is also required to patent a compound.[56.2] Whether one must conceive of this utility, or merely disclose and demonstrate it in the specification, has not been addressed by the courts.[56.3]

§ 4:1.3 Reduction to Practice

[A] Requirements

Reduction to practice can either be actual or constructive.

An invention is actually reduced to practice when it is shown to be suitable for its intended purpose.[57] Actual reduction to practice requires the making of an embodiment of the invention that includes all of the elements of the claim.[58]

In the context of prior art under pre-AIA 35 U.S.C. § 102(g)(2), the statute requires that the invention of the prior art have been made "in this country." The Federal Circuit has explained that "102(g)(2)

56.1. Oka v. Youssefyeh, 849 F.2d 581, 583 (Fed. Cir. 1988); Eli Lilly & Co. v. Crabtree, 485 F. Supp. 2d 982, 999–1000 (S.D. Ind. 2006), *aff'd*, 224 F. App'x 962 (Fed. Cir. 2007).

56.2. Brenner v. Manson, 383 U.S. 519, 535 (1966) ("Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing"); *In re* Fisher, 421 F.3d 1365, 1374 (Fed. Cir. 2005) ("claiming five particular ESTs which are capable of hybridizing with underlying genes of unknown function found in the maize genome" failed to satisfy utility requirement); *In re* Kirk, 376 F.2d 936, 941 (C.C.P.A. 1967) (finding that possessing "biological activity" or "useful biological properties" is too "nebulous" to convey the utility of the claimed steroid compounds).

56.3. Rey-Bellet v. Engelhardt, 493 F.2d 1380, 1385 (C.C.P.A. 1974) ("In the board's view then, even when the invention is a chemical compound which has been made and is defined by a count reciting no limitation related to its use, conception of that invention is not complete absent a conception of its utility. Engelhardt does not challenge this interpretation of the law. Accordingly, we will treat it as the law of this case although in our minds its applicability remains very much an open question. However, any resolution of this issue should be deferred until squarely presented and briefed by the parties to an appeal."); *Conception of a Chemical Compound—Is a Mental Formation of Utility Required?*, 4 J.P.O.S. 8 (1978) (arguing that "utility should be a necessary element of conception of a chemical compound").

57. *See* Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1578 (Fed. Cir. 1996).

58. *See* UMC Elecs. Co. v. United States, 816 F.2d 647, 652 (Fed. Cir. 1987).

allows conception to occur in another country, but in such circumstances requires the work constituting the reduction to practice to be performed in the United States by or on behalf of the inventor."[58.1] Reduction to practice can be considered on "behalf of the inventor" "if the inventor authorizes another to reduce his invention to practice," such as through a research agreement.[58.2]

In the context of an interference, the Federal Circuit has held that "[i]n order to establish an actual reduction to practice, the inventor must prove that: (1) he constructed an embodiment or performed a process that met all the limitations of the interference count; and (2) he determined that the invention would work for its intended purpose."[59] "To establish reduction to practice of a chemical composition, it is sufficient to prove that 'the inventor actually prepared the composition and knew it would work.'"[60]

The filing of a completed patent application is deemed a constructive reduction to practice.[61] To qualify, the application must comply with the requirements of section 112.[62]

[B] Proof of Reduction to Practice Requires Corroboration

In addition to the requirements outlined above, proof of actual reduction to practice requires the existence of sufficient evidence to corroborate inventor testimony.[63] While the corroboration requirement for both conception and reduction to practice is governed by "rule of reason" analysis, proof adequate to corroborate a conception will not necessarily suffice to corroborate a reduction to practice.[64]

58.1. Solvay S.A. v. Honeywell Int'l Inc., 742 F.3d 998, 1000 (Fed. Cir. 2014).

58.2. *Id*. at 1006–07.

59. Cooper v. Goldfarb, 154 F.3d 1321, 1327 (Fed. Cir. 1998).

60. Hahn v. Wong, 892 F.2d 1028, 1032–33 (Fed. Cir. 1989) (in proving actual reduction to practice, "[t]he inventor, however, must provide independent corroborating evidence in addition to his own statements and documents. . . . Such evidence 'may consist of testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor'") (internal citations omitted).

61. Hyatt v. Boone, 146 F.3d 1348, 1352 (Fed. Cir. 1998).

62. *Id*. See sections 5:4–5:6 for a discussion of the section 112 requirements.

63. Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1169 (Fed. Cir. 2006); *Cooper*, 154 F.3d at 1330 ("In order to establish an actual reduction to practice, an inventor's testimony must be corroborated by independent evidence.").

64. Singh v. Brake, 222 F.3d 1362, 1370 (Fed. Cir. 2000); Mikus v. Wachtel, 542 F.2d 1157, 1161 (C.C.P.A. 1976) (holding that an invention record, based on an unwitnessed laboratory notebook and results performed by

"Indeed, a notebook page may well show that the inventor conceived what he wrote on the page, whereas it may not show that the experiments were actually performed, as required for a reduction to practice."[65]

When the patentee constructively reduces his invention to practice by filing the patent application, there is no need for corroboration of the subject matter that is included in the application unless the patentee seeks to establish an effective date earlier than the filing date.[66]

§ 4:1.4 Simultaneous Conception and Reduction to Practice

In some situations, the conception—the complete mental picture of the invention—cannot be achieved until the invention is actually reduced to practice. This results in a "simultaneous conception and reduction to practice." The doctrine of simultaneous conception and reduction to practice was described in *Alpert v. Slatin*, a case concerning a catalyst:

> [T]his is considered to be one of those unusual cases where the work of conception must be considered to proceed simultaneously with the work of reduction to practice. This doctrine . . . is but rarely applied . . . to a residuum of cases where results at each step do not follow as anticipated, but are achieved empirically by what amounts to trial and error. In this type of research the inventor's mind cannot formulate a completed invention until he finally performs a successful experiment.[67]

In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,[68] the Federal Circuit applied the doctrine to a case involving the isolation and discovery of a nucleic acid sequence encoding the protein erythropoietin (EPO). The court held that a claim to the nucleic acid sequence encoding EPO was not invented until the gene had been isolated and sequenced so its structure could be determined:

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technicians unaware of what they were testing, may provide sufficient evidence of conception but not reduction to practice under the rule of reason).

65. *Singh*, 222 F.3d at 1370.
66. *Hyatt*, 146 F.3d at 1352; Kawai v. Metlestics, 480 F.2d 880, 886 (C.C.P.A. 1973) ("[T]he written specification in the application is the evidence proving the invention of that which is reduced to practice . . . .").
67. Alpert v. Slatin, 305 F.2d 891, 894 (C.C.P.A. 1962).
68. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991).

> [W]hen an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.[69]

Because conception of a nucleic acid sequence claimed as an isolated sequence requires actual knowledge of the sequence, and knowledge of the sequence is not possible until it is isolated, the conception of the nucleic acid sequence cannot be complete until the sequence is obtained.[70]

§ 4:1.5 Priority

Although the focus of this chapter is on inventorship per se, the following sections outline the most basic concepts in deciding competing claims as to who is the first inventor. As described above in section 4:1.1[B], priority disputes regarding who was the first inventor are still applicable to patents that have an effective filing date prior to March 16, 2013. These disputes can arise between competing groups of inventors, each attempting to claim the same subject matter. Such disputes are known as interferences and are governed by a complex set of procedural rules.[71] In addition, these disputes can arise in the context of a dispute over prior art. In prior art disputes, the Patent Office or courts can be called upon to determine the date of invention of a patent whose validity is being challenged, or the date of an invention asserted as prior art.

The pre-AIA version of 35 U.S.C. § 102(g) outlines the rules governing an inventor's right to priority in an interference proceeding. It provides, in relevant part, that a person shall be entitled to a patent unless:

> (1) during the course of an interference . . . another inventor involved . . . establishes . . . that before such person's invention thereof the invention was made by such other inventor and not *abandoned, suppressed, or concealed*, or
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> (2) before such person's invention thereof, the invention was made in this country by another inventor who had not *abandoned, suppressed, or concealed* it. In determining priority

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69. *Id*.

70. Although often associated with biotechnology inventions, the doctrine of simultaneous conception and reduction to practice is older than biotechnology. *See* Smith v. Bousquet, 111 F.2d 157 (C.C.P.A. 1940) (insecticide). For a further discussion of the concept of simultaneous conception and reduction to practice in the context of nucleic acid inventions, see *infra* section 4:4.2.

71. *See* 35 U.S.C. § 135; 37 C.F.R. §§ 1.601–1.690; M.P.E.P. § 2300 *et seq.*

> of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the *reasonable diligence* of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.[72]

The following sections address the "not abandoned, suppressed or concealed" and "reasonable diligence" requirements.

[A] Abandoned, Suppressed, or Concealed

There are two types of abandonment, suppression, or concealment: (1) cases in which the inventor *intentionally* or *actively* abandons, suppresses, or conceals his invention, and (2) cases in which a *legal inference* of abandonment, suppression, or concealment can be drawn based on an unreasonable delay in making the invention publicly known.[73] An inventor acts with intentionality when "designedly, and with the view of applying it indefinitely and exclusively for his own profit, [he] withholds his invention from the public."[74] Mere passage of time, as well as the status of work as "secret," do not necessarily mean that a patent has been abandoned, suppressed, or concealed; there must be evidence that the inventor deliberately delayed filing in order to prolong the period during which the invention is maintained in secret.[75]

Moreover, the failure to make the invention publicly available, either by filing a patent, describing the invention in a public document, or using the invention publicly, within a reasonable time after making the invention, may constitute abandonment, suppression, or concealment.[76] While each case involving abandonment, suppression, or concealment must be considered on its facts,[77] the law is clear that an inventor need only use reasonable efforts in disclosing his invention to the public.[78]

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72. Pre-AIA 35 U.S.C. § 102(g) (emphasis added).
73. Flex-Rest, LLC v. Steelcase, Inc., 455 F.3d 1351, 1358 (Fed. Cir. 2006); Dow Chem. Co. v. Astro-Valcour, Inc., 267 F.3d 1334, 1342 (Fed. Cir. 2001).
74. Paulik v. Rizkalla, 760 F.2d 1270, 1273 (Fed. Cir. 1985) (en banc) (quoting Kendall v. Winsor, 62 U.S. 322, 328 (1858)).
75. *Flex-Rest*, 455 F.3d at 1358; E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1436 n.5 (Fed. Cir. 1988) ("Because work is 'secret' does not necessarily mean that it has been 'abandoned, suppressed, or concealed.'").
76. *Flex-Rest*, 455 F.3d at 1359; *Dow Chem.*, 267 F.3d at 1342.
77. *Paulik*, 760 F.2d at 1275.
78. *Flex-Rest*, 455 F.3d at 1359; *see also* Lutzker v. Plet, 843 F.2d 1364, 1367 (Fed. Cir. 1988) (finding that a delayed filing due to commercialization efforts or improvements not reflected in the patent application is

[B] Diligence in Reducing Invention to Practice

If a party in an interference is last to reduce but is first to conceive the invention, that party will be entitled to the patent based on prior conception if he exercised reasonable diligence from a time before the other party's conception date to his own reduction to practice date.[79] The requirement of reasonable diligence by the first to conceive the invention but last to reduce it to practice is "to assure that the invention was not abandoned or unreasonably delayed by the first inventor during the period after the second inventor entered the field."[80] Reasonable diligence is a question of fact and inventor testimony as to diligence must be corroborated.[81] The factual inquiry is whether the evidence shows a reasonably continuing effort to reduce the invention to practice. However, "[u]nlike the legal rigor of conception and reduction to practice, diligence and its corroboration can be shown by a variety of activities . . . ."[82]

§ 4:2 Joint Inventorship: Distinguishing Inventive from Non-Inventive Contributions

Rarely does a modern inventor in the pharmaceutical industry work completely alone. An inventor may have many assistants who carry out various tasks involving different levels of skill related to the research and eventual reduction to practice of the invention. An inventor will also frequently consult with others on a range of technical issues. Accordingly, issues often arise as to whether an individual's contributions to an invention make that person a joint inventor.

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inexcusable); *cf. Dow Chem.*, 267 F.3d at 1343 (distinguishing *Lutzker* from cases in which an invention is disclosed to the public by commercialization).

79. *See* Brown v. Barbacid, 436 F.3d 1376, 1378 (Fed. Cir. 2006).
80. *Id*. at 1379.
81. *Id*. at 1380; see also *supra* sections 4:1.2[B] and 4:1.3[B] for a discussion of the corroboration requirement.
82. *Brown*, 436 F.3d at 1380; Lacotte v. Thomas, 758 F.2d 611, 613 (Fed. Cir. 1985) (finding that the testimony of the inventor and his notebook records were adequately corroborated by his obtaining relevant supplies and the testimony of his associate); Bey v. Kollonitsch, 806 F.2d 1024, 1030 (Fed. Cir. 1986) (diligence shown by attorney's work in preparing patent application); Scott v. Koyama, 281 F.2d 1243, 1248 (Fed. Cir. 2002) (diligence shown by inventor's efforts to locate a construction company capable of building a manufacturing plant for practicing the claimed process on a large scale); *In re* Jolley, 308 F.3d 1317, 1327 (Fed. Cir. 2002) (diligence was shown by activity to obtain necessary supplies and laboratory glassware and by testing of related materials).

§ 4:2.1 Statutory Provision: Sections 101, 116, and 256

Whoever "invents" patentable subject matter may obtain a patent.[83] "When an invention is made by two or more persons jointly, they shall apply for a patent jointly . . . ."[84] Instead of affirmatively stating the requirements for being a joint inventor, section 116 of the patent statute only describes what is not required. That section states:

> Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent.[85]

Finally, section 256 provides that if "through error an inventor is not named in an issued patent and such error arose without deceptive intention on his part, the [patent office] may . . . issue a certificate correcting such error."[86] Although section 116 applies to patent applications and section 256 applies to issued patents, "the pertinent statutory language is virtually identical, and the burden of proof"—clear and convincing evidence—"is the same under both sections."[87] Inventors and co-inventors are presumed to be correctly named in the patent.[88]

§ 4:2.2 Requirements for Joint Invention

The Federal Circuit has recognized that section 116 "sets no explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor. Rather, a joint invention is simply the product of a collaboration between two or more persons working together to solve the problem addressed."[89]

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83. 35 U.S.C. § 101.
84. 35 U.S.C. § 116.
85. *Id*.
86. 35 U.S.C. § 256.
87. The policy concerns involved do not permit a lower standard than clear and convincing evidence. *See* Hess v. Advanced Cardiovascular Sys. Inc., 106 F.3d 976, 980 (Fed. Cir. 1997) ("[T]here is an equally strong temptation for [alleged co-inventors] who consulted with the inventor and provided him with materials and advice to reconstruct . . . the extent of their contribution . . . . In these circumstances, it would be inappropriate to permit a lower standard than clear and convincing evidence.").
88. Amax Fly Ash Corp. v. United States, 514 F.2d 1041, 1047 (Ct. Cl. 1975).
89. Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466, 1473 (Fed. Cir. 1997).

As with inventorship in general, joint inventorship is based on a determination with respect to the conception of the invention. Accordingly, "to be a joint inventor, an individual must make a contribution to the conception of the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention."[90] Furthermore, an inventor need not make a contribution to every claim in the patent. "A contribution to one claim is enough."[91]

[A] Determining Co-Inventorship

The analysis of whether the inventors are properly named is a two-step process: First the "claim must be construed." "The second step is then to compare the alleged contributions of each asserted co-inventor with the subject matter of the properly construed claim to then determine whether the correct inventors were named."[92]

[B] Assistance and Knowledge from One of Ordinary Skill Does Not Make One an Inventor

As a general principle of law, an inventor may obtain assistance in carrying out tasks that are within the ordinary skill of the art, and may also obtain information from others concerning the state of the art in the field of the invention (or related areas) without thereby acquiring as a joint inventor one who assists him. Further understanding of this general principle is best obtained from a review of several joint inventorship dispute cases.

In *Stern v. Trustees of Columbia University*,[93] plaintiff Stern sought to be added as a co-inventor to a patent disclosing a method for using prostaglandins in the treatment of glaucoma. Stern conducted experiments in the laboratory of the named inventor, Bito, which showed that topical application of a single dose of prostaglandin reduced intraocular pressure (IOP) in rhesus monkeys and cats. Bito conceived the patent at issue while studying the effects of repeated prostaglandin

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90. *Id.*; *see also* Trovan, Ltd. v. Sokymat SA, 299 F.3d 1292, 1302 (Fed. Cir. 2002); BJ Servs. Co. v. Halliburton Energy Servs., Inc., 338 F.3d 1368, 1373 (Fed. Cir. 2003) ("Conception is the touchstone of inventorship, and each joint inventor must contribute in some significant manner to the conception of the invention."); Univ. of Colo. Found., Inc. v. Am. Cyanamid Co., 342 F.3d 1298, 1308 (Fed. Cir. 2003); Frank's Casing Crew & Rental Tools, Inc. v. PMR Techs., Inc., 292 F.3d 1363, 1373 (Fed. Cir. 2002); Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998); Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1460 (Fed. Cir. 1998).
91. *Ethicon*, 135 F.3d at 1460; *see also infra* section 4:3.3.
92. *Trovan*, 299 F.3d at 1302 (citation omitted).
93. Stern v. Trs. of Columbia Univ., 434 F.3d 1375 (Fed. Cir. 2006).

application on the IOP in rhesus monkeys. The Federal Circuit affirmed the decision of the lower court finding that Stern failed to present clear and convincing evidence of inventorship. The court found that Stern did not understand the effect of prostaglandins on IOP and did not conceive of the idea to use prostaglandins to reduce IOP. Instead, Stern "simply carried out an experiment previously done by Bito on different animals—animals that Bito had al ready [sic] determined would be good models for prostaglandins research."[94] The court held that Stern's contributions were insufficient to support a claim of co-inventorship.[95]

In *Hess v. Advanced Cardiovascular Systems*,[96] two doctors sought to develop an improved balloon angioplasty catheter, but were unable to find a satisfactory material from which to make the balloon. They then consulted with a technical advisor from a materials manufacturer, who suggested the successful material, and explained techniques for making the balloon and sealing it using the material. The doctors eventually succeeded with the suggested materials, and the advisor claimed to be a co-inventor of the balloon catheter. The Federal Circuit affirmed the finding that the advisor was not a co-inventor.[97] The court agreed that he did nothing more than explain the state of the art concerning materials available and inform the inventors of the available materials and their uses.[98] He had no experience with the catheters, did not conceive of the balloon catheter invention, and did not partake in the day-to-day work on the invention project.[99]

Quoting from *O'Reilly v. Morse*,[100] the Supreme Court's 1853 decision holding that Samuel Morse's discussions with scientists did not make those scientists co-inventors of the telegraph, the Court said:

> No invention can possibly be made, consisting of a combination of different elements . . . without a thorough knowledge of the properties of each of them, and the mode in which they operate

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94. *Id*. at 1378.
95. *Id*.
96. Hess v. Advanced Cardiovascular Sys., 106 F.3d 976 (Fed. Cir. 1997).
97. *Id*. at 980.
98. *Id*. at 981 ("The principles [the advisor] explained to [the doctors] were well known and found in textbooks. . . . The extensive research and development work that produced the catheter was done by [the doctors].").
99. *Id*. at 980–81 ("Although the doctors followed and utilized some of [the advisor's] suggestions . . . the district court justifiably concluded . . . that it was [the doctors], and not [the advisor] who actually conceived and made the patented invention and that [the advisor's] contributions to the inventions did not constitute the conception necessary to establish co-inventorship.").
100. O'Reilly v. Morse, 56 U.S. 62 (1853).

> on each other. And it can make no difference, in this respect, whether [the inventor] derives his information from books, or from conversation with men skilled in the science. If it were otherwise, no patent, in which a combination of different elements is used, could ever be obtained.[101]

Accordingly, one who merely teaches an actual inventor about concepts that are already known in the art does not become an inventor.[102]

The contribution of a joint inventor cannot be based merely on carrying out routine work.[103] Accordingly, an inventor should be able to employ others to, for example, synthesize molecules that can be made with routine skill, run screening tests within routine skill, and the like without acquiring joint inventors.

Similarly, the selection of materials to be included in a composition of matter conceived by another does not make one a co-inventor.[104] In *Boehringer Ingelheim Animal Health, Inc. v. Schering Plough Corp.*,[105] defendant claimed that a patent on the method of growing and isolating PRRS virus was invalid for failure to name two alleged co-inventors who had collected infectious materials from pig organs that were used to infect cells and then culture and identify the virus. The court held the defense of incorrect inventorship lacked merit:

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101. *Hess*, 106 F.3d at 981; *see also* Shatterproof Glass Corp. v. Libby-Owens Ford Co., 758 F.2d 613, 624 (Fed. Cir. 1985) ("An inventor 'may use the services, ideas, and aid of others in the process of perfecting his invention without losing his right to a patent.'") (quoting Hobbs v. U.S. Energy Comm'n, 451 F.2d 849, 864 (5th Cir. 1971)); *In re* Herschler, 591 F.2d 693 (C.C.P.A. 1979) (one who tested various formulas and ideas supplied by another was not a co-inventor); Mattor v. Coolegem, 530 F.2d 1391, 1393 (C.C.P.A. 1976) (assistant was "another pair of hands" for inventor, carrying out tasks under instructions from the inventor).

102. *Pannu*, 155 F.3d at 1351; *Hess*, 106 F.3d at 980; *Fina Oil*, 123 F.3d at 1473 ("The basic exercise of the normal skill expected of one skilled in the art, without an inventive act, also does not make one a joint inventor. Therefore, a person will not be a co-inventor if he or she does no more than explain to the real inventors concepts that are well known and the current state of the art.") (citation omitted).

103. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1575–76 (Fed. Cir. 1996); Sewall v. Walters, 21 F.3d 411, 415 (Fed. Cir. 1994).

104. Caterpillar Inc. v. Sturman Indus., Inc., 387 F.3d 1358 (Fed. Cir. 2004) (identification of preferred alloy for use in spool value with residual magnetic latching was not a significant contribution to overall invention, where claim was not limited to alloy and persons of ordinary skill could have identified suitable alloys).

105. Boehringer Ingelheim Animal Health, Inc. v. Schering Plough Corp., 984 F. Supp. 239 (D.N.J. 1997).

> The court agrees that had Collins and Bonfield [the two alleged co-inventors] not provided Harris [the inventor] with the inoculum containing the virus, they would not have been able to isolate the virus, but that does not mean that they should be entitled to joint inventorship rights. Harris might have obtained the necessary material from Collins and Benfield, but the patent does not claim a compound. It claims a method developed exclusively by Harris.[106]

Accordingly, the use of biological materials supplied by another should not give rise to joint inventorship with the supplier for inventions made or discovered from use of the material.

In *Bard Peripheral Vascular, Inc. v. W.L. Gore & Associates, Inc.*,[106.1] the Federal Circuit held that a scientist's identification of "ePFTE as a promising material for vascular grafts" was insufficient to qualify as co-inventorship of a prosthetic vascular grafts using ePFTE fibrils of a specified length.[106.2] Although that scientist had conceived of the need for the specified length he never communicated that to the named inventor and the mere suggestion of ePFTE by itself was insufficient because "many grafts that were made of ePTFE failed."[106.3] Even if the unnamed scientist "had achieved conception prior to" the named inventor, the named inventor "arrived at conception on his own, and, thus" the unnamed inventor gets no credit for the inventor's independent reduction to practice based on his own conception of the specified fibril length.[106.4]

Whether an assistant who provides advice on the state of the art for some aspect of the invention is an inventor, is unlikely to be a clear-cut issue, because the line between contributing to conception and educating the inventor about the state of the art is more easily drawn in theory than in practice.

It appears from the Federal Circuit's decision in *Pannu v. Iolab Corp.*[107] that one may become a co-inventor by suggesting a prior art component to be assembled as part of the invention. There, two parties, Pannu and Link, collaborated on the invention of a single piece snag-resistant intraocular lens. One party, Link, claimed to be the sole inventor because Pannu had published the substance of his contribution in the prior art more than one year before the collaboration

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106. *Id*. at 260.
106.1. Bard Peripheral Vascular, Inc. v. W.L. Gore & Assocs., Inc., 776 F.3d 837 (Fed. Cir. 2015).
106.2. *Id*. at 846.
106.3. *Id*.
106.4. *Id*. at 847.
107. Pannu v. Iolab Corp., 155 F.3d 1344 (Fed. Cir. 1998).

occurred. The Federal Circuit ruled that this publication in the prior art did not disqualify Pannu from being a joint inventor:

> It is undisputed that Pannu and Link collaborated in the development and production of one-piece prototype embodiments of the invention. Link cannot claim the status of a sole inventor simply because Pannu had disclosed his ideas to Link and others more than a year earlier. During the meeting with Link, Pannu was doing more than simply providing Link with well-known principles or explaining the state of the art; he was contributing his ideas concerning the snag-resistant elements to a total inventive concept. Because it is undisputed that the invention was conceived while Link and Pannu were engaged in a collaborative enterprise and it is furthermore undisputed that Pannu conceived significant aspects of the invention, Pannu is certainly at least a co-inventor.[108]

Pannu v. Iolab Corp. is consistent with the rule that one does not become a co-inventor by merely explaining the state of the art to the inventor.[109] It has long been the law that an invention may consist of a new combination of old, prior art elements.[110] A combination invention may be made by one inventor or more than one inventor, each of whom contributes the conception of issuing a prior art element in the new contribution. Although Pannu's contribution to the joint invention was the use of a prior art element, the court's holding can be justified because he did participate, through his collaboration with Link, in the conception of the combination of that element with other elements of the invention.

By contrast, in *Acromed Corp. v. Sofamor Danek Group, Inc.*,[111] a party claiming to be a co-inventor of a surgical spinal plate was found not to be a co-inventor based on a contribution that was within the routine skill of the art. The plate had slots along its length for the insertion of screws. The alleged co-inventor cut recesses in the plate along the slots to prevent the attached bolts from slipping along the slots and ruining alignment. The court held that he was not a co-inventor. His contribution was nothing more than routine skill used to carry out the instructions of the inventor to modify the plate so that the nut "sinks in" and cannot move.

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108. *Id.* at 1351.
109. *Hess*, 106 F.3d at 980.
110. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985); Orthopedic Equip. Co. v. United States, 702 F.2d 1005, 1012 (Fed. Cir. 1983).
111. Acromed Corp. v. Sofamor Danek Grp., Inc., 253 F.3d 1371 (Fed. Cir. 2001).

The difference between *Acromed* and *Pannu* is that in *Acromed* the alleged inventor used a routine technique to implement the conception of the inventor (having the nuts sink in to prevent movement), while in *Pannu* the alleged co-inventor suggested part of the combination of the elements that made the invention, although the suggested element was already in the prior art.

As the Federal Circuit has noted, however, the determination of whether a person is a joint inventor is "fact specific, and no bright-line standard will suffice in every case."[112] Whenever others are connected to research leading to an important invention, there are risks of claims of joint invention. The best protection is to resolve the issues of ownership by agreements entered before the work begins. Well maintained and corroborated documentation of both research and ideas will also provide protection when disputes arise.

In *Dana-Farber Cancer Institute v. Ono Pharmaceutical Co.*, the Federal Circuit refused "to hold categorically that research made public before the date of conception of a total invention cannot qualify as a significant contribution to conception of the total invention."[112.1] "[S]uch a rule would ignore the realities of collaboration, especially that collaboration generally spans a period of time and may involve multiple contributions."[112.2] The court held that "a collaborative enterprise is not negated by a joint inventor disclosing ideas less than the total invention to others, especially when, as here, the collaborators had worked together for around one year prior to the disclosure, and the disclosure occurred just a few weeks prior to conception."[112.3]

§ 4:3 Incorrect Inventorship

§ 4:3.1 Statutory Overview and Standard of Proof

A patent that does not name the correct inventors is invalid under section 102(f) of the patent statute.[113] A party challenging a patent must prove incorrect inventorship by clear and convincing

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112. Univ. of Colo. Found., Inc. v. Am. Cyanamid Co., 342 F.3d 1298, 1308 (Fed. Cir. 2003).

112.1. Dana-Farber Cancer Inst. v. Ono Pharm. Co., 964 F.3d 1365, 1372 (Fed. Cir. 2020).

112.2. *Id*.

112.3. *Id*.

113. Pannu v. Iolab Corp., 155 F.3d 1344, 1348–49 (Fed. Cir. 1998) ("[S]ection 102(f) provides that '[a] person shall be entitled to a patent unless he did not himself invent the subject matter sought to be patented.' Since the word 'he' refers to the specific inventive entity named on the patent, this subsection mandates that a patent accurately list the correct inventors of a claimed invention.") (citations omitted); Schultz v. Green, 136 F.3d

evidence.[114] Unnamed inventors may bring suit under section 256 to correct inventorship and be added to the patent.[115] The same clear and convincing evidence standard applies to such actions.

§ 4:3.2 Consequences of Naming the Wrong Inventors

Failure to name the correct inventors renders a patent invalid.[116] Although inventors are named for the entire patent, the analysis of whether a claim is invalid because of incorrect inventorship is, like other grounds for invalidity, determined on a claim-by-claim basis.[117] Because inventors may be named on a patent if they contributed to the conception of any claim[118] and because the patent need not identify which inventors relate to which claims, invalidity of a claim because of incorrect inventorship should arise only when a required inventor is missing from the patent entirely. If an inventor is named on the patent but is not an inventor of any claims of a multiple claim patent, in theory only one claim might be invalid. Since the multiple inventors are not assigned to particular claims, it is not clear how one could determine which of the claims on a patent with an additional and incorrect inventor are invalid.

§ 4:3.3 Correction of Inventorship

[A] Statutory Basis: Section 256

The rather drastic consequence of invalidity, however, need not be the ultimate outcome of an incorrect inventorship. The statute allows for correction if the error was not the result of deceptive intent. Section 256 provides for correction of inventorship of a patent, preserving the validity of the patent:

> Whenever . . . through error an inventor is not named in an issued patent and such error arose without any deceptive intention on his part, the Director may, on application of all the parties and assignees, with proof of the facts and such other requirements as may be imposed, issue a certificate correcting such error.[119]

786, 792 (Fed. Cir. 1998); Gemstar-TV Guide Int'l, Inc. v. ITC, 383 F.3d 1352, 1381 (Fed. Cir. 2004); Jamesbury Corp. v. United States, 518 F.2d 1384, 1395 (Ct. Cl. 1975).

114. Canon Comput. Sys., Inc. v. Nu-Kote Int'l, Inc., 134 F.3d 1085, 1089 (Fed. Cir. 1998).

115. Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461 (Fed. Cir. 1998).

116. 35 U.S.C. § 102(f).

117. *Gemstar-TV*, 383 F.3d at 1382 ("Because co-inventors need not contribute to the subject matter of every claim in the patent, inventorship is determined on a claim-by-claim basis.").

118. 35 U.S.C. § 116.

119. 35 U.S.C. § 256.

[B] Deceptive Intent

The Federal Circuit has described an incorrect inventorship as a "technical defect"[120] and has interpreted section 256 as permitting the amendment of the patent in the case of an omitted inventor, provided *the omitted inventor* had not engaged in deceptive intent.[121] Deceptive intent of the patentee or named inventors does not preclude an amendment to correct inventorship, although it could be a basis for an inequitable conduct allegation.

In *Stark v. Advanced Magnetics, Inc.*,[122] the plaintiff alleged that he was omitted as an inventor on a patent by reason of deceptive intent on part of the patentee, who was also sued for fraud. The district court held that the allegations that the omission was due to deceptive intent precluded a claim under section 256 to amend the patent to plaintiff as an inventor. On appeal, the Federal Circuit reversed, holding that only the deceptive intent of the omitted inventor is relevant, not that of the patentee. It stated:

> In the event of nonjoinder of an inventor, this error must occur 'without any deceptive intention on his part.' The clause 'on his part' refers to the antecedent inventor, *meaning that the omitted inventor* must not have engaged in any deception related to the non-joinder.[123]
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> * * *
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> In other words, the statute allows correction in all misjoinder cases featuring an error and in those nonjoinder cases where *the unnamed inventor* is free of deceptive intent.[124]

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120. *Nu-Kote*, 134 F.3d at 1089 ("Incorrect inventorship is a technical defect in a patent that may be easily curable."); 35 U.S.C. § 256 ("The error of omitting inventors or naming persons who are not inventors shall not invalidate the patent in which such error occurred if it can be corrected as provided in this section.").
121. Stark v. Advanced Magnetics, Inc., 119 F.3d 1551, 1554 (Fed. Cir. 1997).
122. *Id*. at 1552.
123. *Id*. at 1555 (emphasis added).
124. *Id*. (emphasis added). The Federal Circuit went on to describe that any remedy for deceptive intent on the part of the patent owner or named inventors must be under the standard of inequitable conduct. "While irrelevant to the question of correcting inventorship, Stark's allegations of fraud may . . . have implications under the inequitable conduct doctrine." *Id*. at 1556; *see also* Pannu v. Iolab Corp., 155 F.3d 1344, 1350 (Fed. Cir. 1998) ("Nonjoinder may be corrected 'on notice to all parties concerned' and upon a showing that the error occurred *without any deceptive intent on the part of the unnamed inventor*.") (emphasis added); Trovan, Ltd. v. Sokymat SA, 299 F.3d 1292, 1301 (Fed. Cir. 2002) ("[T]o the extent that fewer than the true inventors are named on a patent, the patent may be

[C] Comment: An Odd Policy

While the construction of section 256, precluding correction only if the omitted inventor was guilty of deceptive intent, follows from the statutory language, it is difficult to imagine a case where an inventor would be motivated to conspire to deceptively have himself not named on a patent to his invention.[125] The usual allegation is the opposite—that the patentee and named inventors deliberately excluded another inventor.

It is also a strange policy to allow correction of inventorship if the named inventor was guilty of deceptive intent in excluding another co-inventor, but to bar correction of inventorship if the person omitted from the patent was guilty of deceptive intent, even if the named inventors and patent owners were innocent of wrongdoing. Yet, that is clearly the law.

[D] Correction of Inventorship Versus Inequitable Conduct

As explained earlier,[126] correction of the inventorship on the patent is permitted as long as the omitted inventor was not guilty of deceptive intent. Deceptive intent, however, of the named inventors (or others involved in the prosecution of the patent) in incorrectly naming or omitting inventors can provide a basis for inequitable conduct rendering the patent unenforceable.[127]

The way to address and avoid inequitable conduct with respect to inventorship is by disclosure of the inventorship issue to the Patent Office during prosecution. Known allegations by another that he is a co-inventor, as well as lawsuits or disputes in other forms, should be fully disclosed to the Patent Office. Where the alleged but unnamed inventor has made his claim to be a joint inventor, or sole inventor in a written form, the writings should be given to the Patent Office to remove the allegation that the applicant distorted the unnamed alleged inventor's role.

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corrected to so reflect as long as the nonjoinder was done without deceptive intent on the part of the person erroneously left off the patent.").

125. If one were trying to avoid a prior art reference under section 102(a) or (e), by having the patent inventorship the same as the prior art to avoid the prior art being the work of "another," a motive to deceive might arise if the omitted inventor would benefit from the patent issuance.

126. *See supra* section 4:3.3[B].

127. *Stark*, 119 F.3d at 1556; Frank's Casing Crew & Rental Tools, Inc. v. PMR Techs., Ltd., 292 F.3d 1363, 1370 (Fed. Cir. 2002) (affirming finding of unenforceability because of inequitable conduct in "deliberately failing to name an inventor"; holding that unenforceability of the patent applied to the innocent omitted inventor as well as the wrongdoing applicants).

§ 4:3.4 Procedure for Correcting Inventorship

[A] Correction During Litigation

The procedure for correcting inventorship in the course of litigation contemplates an initial finding of incorrect inventorship, followed by a separate hearing on notice under section 256.[128] The patent owner must claim the right to correct under section 256 and then establish its right to correct, or the patent will be invalid:[129]

(1) "When a party asserts invalidity under § 102(f) due to nonjoinder, a district court should first determine whether there exists clear and convincing proof that the alleged unnamed inventor was in fact a co-inventor."

(2) "Upon such a finding of incorrect inventorship, a patentee may invoke section 256 to save the patent from invalidity . . . [and] be given an opportunity to correct inventorship pursuant to that section." Correction requires:

  (a) proper "notice and hearing of all parties concerned" and

  (b) "a showing that the error occurred without any deceptive intent on the part of the unnamed inventor."

The fact that a patentee can correct inventorship does not by itself avoid invalidity for improper inventorship. The patentee must actually:

> claim entitlement to relief under the statute and the court must give the patentee an opportunity to correct the inventorship. If the inventorship is successfully corrected, section 102(f) will not render the patent invalid. On the other hand, if the patentee does not claim relief under the statute and a party asserting invalidity proves incorrect inventorship, the court should hold the patent invalid for failure to comply with section 102(f).[130]

[B] Correcting Inventorship in the Patent Office

Inventorship may also be corrected under section 256 by petition to the Commissioner of the Patent Office. The same standards that are applicable in litigation apply in the Patent Office.[131]

To demonstrate the right to correct inventorship, the patentee must show that an error had been made. If the error was the omission

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128. *Pannu*, 155 F.3d at 1348–50.
129. *Id.* at 1350–51.
130. *Id.*
131. 35 U.S.C. § 256.

of an inventor, the patentee must show that the omitted inventor did not act with deceptive intent.

§ 4:3.5 Adding Inventors Can Add Joint Owners

Correcting inventorship saves the patent from invalidity but may not solve ownership problems.[132] If an inventor must be added to the patent and that added inventor does not have an obligation to assign to the current patent owner, the effect can be as devastating as if the patent were invalid. The new joint inventor would be free to license another, such as a defendant in an infringement litigation, and deprive the former owner of exclusive rights.

Several cases demonstrate the danger that unnamed co-inventors can present to patent ownership, especially when they team up with infringers or competitors.

[A] Examples

[A][1] Ethicon, Inc. v. U.S. Surgical Corp.[133]

The patent owner, Ethicon, had acquired patent rights from the sole named inventor, Yoon. Yoon and Ethicon sued U.S. Surgical for infringement of their patent on a trocar, a type of surgical instrument. The parties stipulated to the intervention of Choi as defendant-intervenor, who asserted that he was an unnamed co-inventor of the patent and had granted U.S. Surgical a license under the patent.

Yoon, a medical doctor, had collaborated with Choi, an electronics technician, for approximately eighteen months in developing a trocar. After their collaboration ended, Yoon filed a patent application for the trocar without informing Choi or including him on the patent. The Patent Office issued Yoon the patent; Yoon then granted an exclusive license to Ethicon. U.S. Surgical became aware of Choi after Ethicon's suit against it, and obtained from him a retroactive license to practice his inventions. Choi also agreed to assist U.S. Surgical in any suit concerning the patent; in return, U.S. Surgical promised to pay Choi, depending on whether it would be able to continue to practice and market the invention.

The court affirmed the dismissal of the patent infringement because Choi, found to be a joint inventor at trial, had not consented to join as a plaintiff.[134] Further, the court held that Choi could no

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132. See *infra* section 4:5 for a discussion of patent ownership as it relates to inventorship.

133. Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456 (Fed. Cir. 1998).

134. *Id*. at 1468 ("[A]s a matter of substantive law, all co-owners must ordinarily consent to join as plaintiffs in an infringement suit.").

longer consent because the license he had given to the defendant barred any infringement suit subsequent to the license.[135]

The *Ethicon* case highlights the dangers of collaborating without proper agreements assigning patent rights to the entity sponsoring the collaboration. It also illustrates the risk that a jilted collaborator will form an alliance with the patentee's competitor.

[A][2] Burroughs Wellcome Co. v. Barr Laboratories, Inc.[136]

In *Burroughs Wellcome*, the defendants similarly tried the strategy of acquiring rights from a potential, but unnamed, co-inventor. The plaintiff, Burroughs Wellcome, owned patents covering various preparations of a drug, AZT, used to treat patients infected with HIV. The plaintiff filed infringement suits against the defendants, who sought to manufacture and market a generic version of the drug. In turn, the defendants asserted that the National Institutes of Health (NIH) scientists who performed human clinical trials to demonstrate the drug's effectiveness in humans were co-inventors of the method of treatment claims. Further, the defendants claimed they had obtained a license from the NIH to manufacture and market AZT, and that the patents were therefore unenforceable.

At the time the inventions were allegedly conceived, Burroughs Wellcome employed all of the named inventors. Around the same time Burroughs Wellcome began searching for a cure for AIDS caused by HIV infection, NIH scientists also began looking for effective AIDS treatments. Burroughs Wellcome contacted a scientist at the NIH, one of the alleged unnamed co-inventors, and agreed to have him test compounds supplied by Burroughs Wellcome. Burroughs Wellcome first conducted its own tests of AZT, the results of which led Burroughs Wellcome to begin preparing a patent application for the drug. Only then did Burroughs Wellcome supply the AZT to the NIH for testing.

The defendants alleged that the confirmation testing by the NIH on AZT's effectiveness against HIV was an essential part of the inventive process, such that the NIH scientists should have been named as joint inventors. Ultimately, the defendants' strategy of acquiring rights from a potential co-inventor did not succeed, as the appeals

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135. *Id*. ("Because Choi, [the unnamed co-inventor], did not consent to an infringement suit against U.S. Surgical and indeed can no longer consent due to his grant of an exclusive license with its accompanying 'right to sue,' [the plaintiff's] complaint lacks the participation of a co-owner of the patent.").

136. Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1227–28 (Fed. Cir. 1994).

court rejected the defendants' arguments and affirmed the district court's ruling on five of the six patent claims that the NIH scientists were not co-inventors because conception was already complete when the plaintiffs identified AZT as a treatment of HIV.[137]

[A][3] Ortho-McNeil Pharmaceuticals, Inc. v. Mylan Laboratories, Inc.[138]

In *Ortho-McNeil Pharmaceuticals*, the plaintiff patent holder and licensees sued the defendants, generic drug manufacturers, for patent infringement because defendants sought to manufacture and distribute a generic version of the drug levofloxacin. The defendants asserted as a defense, among other things, that two scientists employed by a non-party laboratory had conceived of levofloxacin prior to the named inventors. The court rejected this defense, finding insufficient evidence to support defendants' assertions. The court gave only limited weight to the testimony of the one of the scientists alleged as an unnamed prior inventor, noting that "[a]s a rival inventor and expert witness for [defendants], he clearly has some interest in the outcome of the litigation."[139]

§ 4:4 Inventorship Issues for Particular Types of Inventions

§ 4:4.1 Chemical Inventions

A large proportion of pharmaceutical patents relate to chemical compounds that are claimed as compounds specified by their chemical formulas. Biotechnology-related inventions involving nucleic acid sequences of DNA or RNA or amino acid sequences of proteins are also common, and while they are usually discovered in very different ways than small synthetic chemical drug molecules, they are treated in law as chemical compounds and governed by the same standards of conception.[140]

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137. The appeals court did, however, vacate the district court's holding that the record supported the plaintiff's conception as a matter of law for one of the six patents. The appeals court found that evidence existed in the record that the named inventors may not have conceived of the invention prior to the study by the alleged unnamed co-inventors. *Id*. at 1232. See *supra* section 4:1.2 for a discussion of conception.
138. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W. Va. 2004).
139. *Id*. at 737.
140. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("A gene is a chemical compound in our law, albeit a complex one, and it is well established that . . . the inventor be able to define it so as

The invention of a chemical compound requires conception of the chemical structure and a method for making it.[141] When the method of making the compound is a matter of routine knowledge among those who are skilled in the art, the conception may be deemed complete when the compound is described.[142]

The Federal Circuit, in *Board of Education ex rel. Board of Trustees of Florida State University v. American Bioscience, Inc.*,[143] covered a number of issues relating to chemical compound inventions. It emphasized the need to focus on what is claimed when determining inventorship. The case involved a patent claiming the anti-cancer drug Taxol® and two other compounds. Researchers at Florida State University (FSU) had identified a related group of compounds and developed methods to synthesize them. The FSU researchers had also identified certain substituents that produced both radiosensitizing and cytotoxic effects on the compounds they had made.

A former employee of the FSU lab became an employee for the patentee, where similar research was ongoing. The patentee's scientists, with the help of the FSU former employee, made the compounds claimed in their patent. The claimed compounds contained a particular side chain never used at FSU. Thus, FSU never made these compounds.

During the subsequent litigation, FSU asserted that its scientists were co-inventors of the compounds claimed in defendant's patent. The district court agreed with FSU. (It also held the patent unenforceable for inequitable conduct because the defendant did not disclose that one co-inventor formerly worked at FSU where prior art compounds had been made.) The Federal Circuit reversed.

The Federal Circuit held that the prior artwork at FSU on related compounds and synthesis methods did not make the FSU employees co-inventors of the patented compounds. The FSU scientists never

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to distinguish it from other materials, and to describe how to obtain it."); Fiers v. Revel, 984 F.2d 1164, 1169 (Fed. Cir. 1993) ("[C]onception of DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility.").

141. Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466, 1473 (Fed. Cir. 1997) ("Conception of a chemical substance requires knowledge of both the specific chemical structure of the compound and an operative method of making it."); Oka v. Youssefyeh, 849 F.2d 581, 583 (Fed. Cir. 1988) (conception of a chemical compound "requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it").

142. *Oka*, 849 F.2d at 583; *see also* Coleman v. Dines, 754 F.2d 353 (Fed. Cir. 1985).

143. Bd. of Educ. *ex rel*. Bd. of Trs. of Fla. State Univ. v. Am. Bioscience, Inc., 333 F.3d 1330 (Fed. Cir. 2003).

had a conception of the specific compounds claimed in the patent at issue regardless of the importance of their prior work and the investigation of properties of related structures. The court held:

> Invention requires conception, and 'conception does not occur unless one has a mental picture of the structure of the chemical . . . or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property . . . .' Moreover, general knowledge regarding the anticipated biological properties of groups of complex chemical compounds is insufficient to confer inventorship status with respect to specifically claimed compounds.[144]

FSU argued that its scientists were co-inventors because they had developed a method for making the complex compound, and that the FSU former employee had used his knowledge of that method in synthesizing the compound for defendant. FSU argued that since conception of a compound required both the idea of the compound's structure and a method of making it, the inventor of the method used to make the compound should have been a co-inventor. The Federal Circuit rejected that argument:

> [D]espite the fact that Nadizadeh may have developed a method of making PNIP[145] and other taxol derivatives, the record in the present case indicates that he did not conceive the claimed compounds; only [defendant's] inventors were in possession of both the structure of the claimed compounds and an operative method of making those compounds. The fact that similar compounds had been made at FSU in the past by using essentially the same method is of no consequence, because neither that method nor those similar compounds themselves are claimed in the '653 patent.[146]

The court noted that even if the FSU former employee hired by defendant had learned how to make the compounds from FSU, that knowledge would not make FSU scientists joint inventors, because the imparting of general knowledge and techniques does not alone make one the co-inventor of later inventions made by employing those techniques.[147]

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144. *Bd. of Educ.*, 333 F.3d at 1340 (quoting *Amgen*, 927 F.2d at 1206).
145. A pre-synthesized compound.
146. *Bd. of Educ.*, 333 F.3d at 1342.
147. *Id.* ("Although Tao [the FSU former employee hired by defendant] may have learned the beta-lactam method from Nadizadeh [an FSU scientist], teaching skills or general methods that somehow facilitate a later invention, without more, does not render one a co-inventor.").

The Federal Circuit did acknowledge that if the FSU scientists had actually assisted in making the claimed compounds, it would be possible that they were joint inventors:

> If Tao, Soon-Shiong, and Desai [defendant's inventors] had conceived the structures of the claimed compounds, but were then unable to make them without Nadizadeh's help, Nadizadeh might have been a co-inventor. That is not this case, however.[148]

The Federal Circuit thus clearly recognizes only some forms of assistance as sufficient to establish joint inventorship. On one hand, if the alleged joint inventor merely teaches the inventor a general method that could be applied to make the claimed compound and the inventor utilizes that method as applied to his invention, there is no joint inventorship. On the other hand, if the alleged joint inventor teaches the inventor how to make his claimed compound after the inventor tried and failed, joint inventorship will be found.

Certain questions, however, remain unanswered: If the inventor had failed to make the compound, but then asked the alleged joint inventor about the synthesis method without telling him about the specific compound that he was trying to make, would the person providing the synthesis information be a joint inventor or not? Should it matter that the synthesis method told to the inventor was not one that was known in the prior art? Should the outcome be different if the inventor was not able to make the compound, but the alleged joint inventor actually succeeded in making the compound using prior art methods that were not known to the inventor?

The distinction made by the Federal Circuit could create uncertainty of inventorship when information about making the compound derives from another source.

§ 4:4.2 Nucleic Acid and Sequence Claims

The development of biotechnology has created a number of difficult questions regarding inventorship. Many biotechnology inventions involve isolated nucleic acid sequences, such as an isolated gene encoding some useful protein. Unlike traditional organic chemistry, where the inventor usually conceives of a chemical structure, then makes and tests it, the inventor of an isolated nucleic acid sequence usually cannot describe the sequence of the gene that is the target of the research until it is made and sequenced. Before that time, the inventor only has a goal and method or strategy to obtain the gene, but not the actual gene or knowledge of its structure.

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148. *Id.*

Because there is no means *a priori* to define the sequence a gene performing a certain role will have, the invention is said to come into existence with a "simultaneous conception and reduction to practice."[149] Unlike the chemical compound that can be drawn first and then synthesized, the DNA sequence invention must be obtained in its physical form, that is, actually reduced to practice before it can be described.

Having conceived of an idea of a strategy for obtaining a DNA sequence is not sufficient to constitute a conception of, and therefore not an invention of, the sequence. The seminal Federal Circuit case of *Fiers v. Revel*[150] involved a three-way interference among Sugano, Fiers, and Revel, on a DNA sequence that encodes for human fibroblast interferon-beta (Beta-IF). Fiers contended that he was entitled to priority because he was the first to conceive of a method for isolating the DNA, and expert testimony supported Fiers' argument that this method would have enabled one of skill in the art to obtain the DNA. The Board held that Fiers' conception of a method for obtaining the DNA sequence did not amount to conception of the DNA sequence itself, even assuming that the method would have been successful.[151]

> Irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility.[152]

While the Federal Circuit in *Amgen, Inc. v. Chugai Pharmaceutical Co.*[153] acknowledged that a chemical could be claimed by its method of preparation, it held that Fiers could not claim the nucleic acid sequence as a compound per se by conceiving only a method for finding it:

> We also reject Fiers' argument that the existence of a workable method for preparing a DNA establishes conception of that material. Our statement in *Amgen* that conception may occur, *inter alia*, when one is able to define a chemical by its method of preparation requires that the DNA be claimed by its method of preparation. . . . Before reduction to practice, conception only of a process for making a substance, without a conception of a structural or

149. *Amgen*, 927 F.2d at 1206.
150. Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993).
151. *Id*. at 1168.
152. *Id*. at 1169.
153. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991).

> equivalent definition of that substance, can at most constitute a conception of the substance claimed as a process. Conception of a substance per se without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties.[154]

In the context of examining the written description requirement, the Federal Circuit again held in *Regents of the University of California v. Eli Lilly & Co.*[155] that the written description requirement was not satisfied for a claim to plasmids containing "human insulin cDNA" because the patent specification disclosed only rat insulin DNA and an example of how to obtain the human insulin DNA sequence. Had the question been whether the conception of the human insulin DNA sequence was complete with possession of the rat insulin DNA sequence and an idea of how to obtain the human sequence, the answer would necessarily have been that there was not yet a complete conception of the human DNA sequence of insulin, just as there was no complete description.

Application of the simultaneous conception and reduction to practice standard is simple enough when applied between different inventive teams contesting who was the first inventor. But, a far less clear application of this standard arises when deciding which member(s) within one inventive team are inventors of the sequence (nucleic or amino acid).

At least one type of nucleic acid research team will consist of someone who develops a cloning strategy for finding the desired gene in a particular biological sample. Others will be involved in the process of making genetic libraries and screening them with nucleic acid hybridization of antibodies if proteins are being sought, and those people could make important decisions on screening techniques as well as make important judgments based upon visual inspection of genetic libraries as to when a positive clone is found. Still others may be more removed from the project and run laboratory equipment, such as the machines that sequence DNA or proteins.

If the conception is not complete until the sequence of the claimed nucleic acid is known, is the first person to have a complete conception the person who reads the sequence off of the sequencing machine? That person, however, might be a technician with no connection to the research program at all, who simply ran a routine process with no inventive input. It would be illogical for the sequencer to be the sole

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154. *Fiers*, 984 F.2d at 1169.

155. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1567 (Fed. Cir. 1997).

inventor, and contrary to the usual rule that one is not made a joint inventor by carrying out tasks calling for only the exercise of routine skill.[156]

In *Fina Oil & Chemical Co. v. Ewen*,[157] the Federal Circuit explained that the doctrine of simultaneous conception and reduction to practice is relevant to priority disputes (that is, to determine which of two or more inventors or groups of inventors were the first to make the invention), but was not to be applied mechanically to exclude those who contributed to the invention from joint inventorship. The court held:

> The doctrine of simultaneous conception and reduction to practice applies to the conception of the entire invention. Thus, it is applied in priority disputes to determine priority of conception as between one patent or application and another application. Conception and reduction to practice of the entire claimed invention may be relevant to establish that a first person conceived of an invention before another person entered the scene, and that the first person is therefore the sole inventor. However, the doctrine cannot be used, as the district court did here, to show that because the first person did not conceive or reduce to practice the entire claimed invention, he or she did not at least contribute in some significant way to the ultimate conception.[158]

The court went on to say that "a joint inventor must contribute in some significant manner to the conception of the invention,"[159] and found that there were at least issues of fact whether the asserted joint inventor's experiments and ideas prior to the actual successful reduction to practice contributed to the invention.

Because the contribution to the conception must be a significant one when measured against the full scope of the invention,[160] a claim to an isolated genomic sequence is logically invented by one who made a significant contribution to actually obtaining the claimed sequence and identifying it. In *Regents of the University of California v. Synbiotics Corp.*[161] and *Brown v. Regents of University of California*,[162] both courts applied this analysis. A claim of co-inventorship was made to a patent

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156. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1575–76 (Fed. Cir. 1996); Sewall v. Walters, 21 F.3d 411, 415 (Fed. Cir. 1994).
157. Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466 (Fed. Cir. 1997).
158. *Id*. at 1474.
159. *Id*. at 1473.
160. Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998).
161. Regents of Univ. of Cal. v. Synbiotics Corp., 849 F. Supp. 740 (S.D. Cal. 1994).
162. Brown v. Regents of Univ. of Cal., 866 F. Supp. 439 (N.D. Cal. 1994).

claiming the isolated feline immunodeficiency virus (FIV). The claimant, Brown, had maintained an animal shelter and observed that some cats appeared to be suffering from a disease like AIDS. She took the cats to the later-named inventors at the University of California and explained her suspicion about the previously unknown feline disease. The later-named inventors at the university used materials from the cats to isolate the FIV causing the illness. Both courts considering the issue ruled that Brown was not a co-inventor of the claim to the isolated FIV, because she had no role in the process of isolating the virus even though she was the first person to observe that the virus might exist and to supply the animals from which the virus was isolated. While Brown had an important role in the ultimate identification of the virus, she did not have a role in the particular invention claimed.[163]

§ 4:5 Inventorship and Ownership

The inventor is the owner of the invention in the absence of an agreement to assign rights to another. The law requires that the inventor must apply for the patent.[164] Identifying all the correct inventors is therefore an important task in preparation of any patent application.[165]

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163. *See also* Bd. of Educ. *ex rel*. Bd. of Trs. of Fla. State Univ. v. Am. Bioscience, Inc., 333 F.3d 1330 (Fed. Cir. 2003) (discussed *supra* section 4:4.1, where a claimant's background research into a general group of compounds, their utilities and methods of synthesizing them was not sufficient to support a claim of inventorship to three specific chemical compounds that were not conceived or made by the claimant).

164. 35 U.S.C. § 111(a) ("An application for patent shall be made, or authorized to be made, by the inventor, except as otherwise provided in this title, in writing to the Director.").

165. Proposed section 118 of the Patent Reform Act of 2005 would allow the application for a patent to be made in the name of the owner rather than the inventor. Section 118 provides:

> A person to whom the inventor has assigned or is under an obligation to assign the invention may make an application for patent. A person who otherwise shows sufficient proprietary interest in the matter may make an application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is appropriate to preserve the rights of the parties. If the Director grants a patent on an application filed under this section by a person other than the inventor, the patent shall be granted to the real party in interest and upon such notice to the inventor as the Director considers to be sufficient.

Patent Reform Act of 2005, H.R. 2795, 109th Cong. § 4.

Patents are treated like other personal property. An applicant for a patent (that is, the inventors) may assign any of their interest in the patent by an instrument in writing.[166] Unless the assignment is recorded in the Patent Office within three months of its date, the assignment shall be void as against a subsequent good faith purchaser for value who purchases without notice.[167]

§ 4:5.1 Inventions by Employees

[A] Employment Agreements

The fact that the invention is made by an employee does not alone give the employer rights to the invention. Inventions by non-government employees will be owned exclusively by the employee unless the employer has an employment agreement requiring assignment of those rights to the employer or the doctrine of shop rights requires such assignment. Ownership of inventions by certain government employees is governed by executive order and statute.[168] An employer's rights in its employee's invention are generally a matter of agreement between the two. Where part of the duties of the employee was to exercise inventive skills for the employer's benefit, inventions made in the course of the employment belong to the employer.[169]

However, in most companies the obligation of an employee to assign inventions to the company is not left to inference from the nature of the employee's duties, but is covered by an explicit written agreement entered at the time of employment. In general, such agreements unequivocally provide that the employer owns all inventions

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166. 35 U.S.C. § 261.

167. *Id*.

168. *See* Exec. Order No. 10,096, 15 Fed. Reg. 389 (1950) (providing for a uniform patent policy for the government with respect to inventions made by government employees and for the administration of such policy); 37 C.F.R. § 501.6 (criteria for the determination of rights in and to inventions made by government employees); 15 U.S.C. § 3710d(a) (allowing federal government employees to retain patent rights in their inventions if the federal employer chooses not to patent the invention or otherwise develop it).

169. Wommack v. Durham Pecan Co., 715 F.2d 962, 965 (5th Cir. 1983) ("That an invention was conceived or developed while the inventor was employed by another does not alone give the employer any right in the invention. The employer must show that a mutual understanding existed between the inventor and his employer that the inventor was employed to exercise his inventive faculties for the employer's benefit. If the employer proves this, he acquires ownership of the patent. . . . Alternatively, if the employee was not hired to invent, the employer may establish a shop right.").

made by the employee in the course of his employment and that the employee is obligated to assign inventions made during his employment to the employer, including the obligation to execute any papers necessary to document or effectuate the assignment.

Many agreements between employer and employee require the employee to assign inventions "conceived or first reduced to practice" during the employment. Statutory provisions and regulations governing federal employee obligations to assign inventions to the government have the same result in mind.[170] While such language may be justified in an effort to obligate assignment in all possible circumstances where the employee may have rights to an invention, the actual reduction to practice, first or otherwise, of an invention conceived by another does not give rights to the invention. The one who conceived the invention is the owner, although in some situations, such as simultaneous conception and reduction to practice,[171] it may be difficult to separate the persons responsible for the conception. A clearer way to achieve the same end is to require assignment to the employer of any rights to an invention the employee acquires by reason of activities during his employment.[172]

[B] Shop Rights

In the absence of an agreement, either express or implied by the nature of the employee's duties, that requires employee to assign inventions to the employer, the employee owns his own invention. An employer who has no right to an assignment of an employee's invention, however, may obtain a "shop right" to an employee's invention, which is a non-exclusive and royalty-free license that permits the employer to use the invention in the course of its own business.[173]

A shop right does not follow automatically from the employment relationship. A variety of different legal theories have been used to find a shop right, including implied license and estoppel. The Federal Circuit has held that:

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170. *See* Exec. Order No. 10,096, 15 Fed. Reg. 389 (1950) ("The Government shall obtain the entire right, title and interest in and to all inventions made by any Government employee (1) during working hours, or (2) with a contribution by the Government of facilities, equipment, materials, funds, or information, or of time or services of other Government employees on official duty, or (3) which bear a direct relation to or are made in consequence of the official duties of the inventor.").
171. *See supra* section 4:1.4.
172. *Id.*; 37 C.F.R. § 501.6.
173. McElmurry v. Ark. Power & Light Co., 995 F.2d 1576, 1582 (Fed. Cir. 1993); Cal. E. Labs., Inc. v. Gould, 896 F.2d 400, 402 (9th Cir. 1990).

> [T]he proper methodology for determining whether an employer has acquired a shop right in a patented invention is to look to the totality of the circumstances on a case-by-case basis and determine whether the facts of a particular case demand, under principles of equity and fairness, a finding that a shop right exists. In such an analysis, one should look to such factors as the circumstances surrounding the development of the patented invention and the inventor's activities respecting that invention, once developed, to determine whether equity and fairness demand that the employer be allowed to use that invention in his business.[174]

Factors such as the use of the employer's resources in making the invention may support the finding of the shop right.

Whether an employer, who has obtained a shop right, has the right to sell the patented invention or prohibit others from using it also depends on the facts out of which the shop right arises.[175] For example, in *Flannery Bolt Co. v. Flannery*,[176] the defendant invented a bolt while employed by plaintiff corporation. The business of the plaintiff involved the manufacturing of bolts for sale, which the defendant knew. Thus, the court held that "[t]he only use of a shop right to the plaintiff was the right to sell the [bolts] that it had manufactured in accordance with the invention and this right equity gave it."[177] Conversely, where an employee invents a tool or process that its employer in turn uses in its shop, but where the employer is not in the business of making or selling what the employee has created, the employer should not have the right to sell the employee's invention.

Because the shop right is a non-exclusive license to the employer, the employee may license others to practice the invention. Therefore, in industries in which exclusive rights are critical, such as the pharmaceutical industry, the shop right is generally inadequate to protect the employer's investment in the development of a product.

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174. *McElmurry*, 995 F.2d at 1581–82.

175. Gonnocci Revocable Living Tr. v. Three M Tool & Mach., Inc., Case No. 02-74796, 2006 U.S. Dist. LEXIS 38871, at *8 (E.D. Mich. June 13, 2006) ("[T]he rights encompassed under the shop right doctrine are not universal. . . . In other words, the rights encompassed depend upon the facts and circumstances of each case.").

176. Flannery Bolt Co. v. Flannery, 86 F.2d 43, 44 (3d Cir. 1936).

177. *Id. See also* Gemco Eng'g & Mfg. Co. v. Henderson, 84 N.E.2d 596, 599 (Ohio 1949) ("Where an employee, even though not hired to invent, develops an invention in his employer's shop at the expense of his employer, equity will intervene to protect the employer against later exclusive adverse claims of the employee-inventor by giving the employer a shop right in the invention thereby *enabling the employer to make, use and sell the device invented by the employee*.") (emphasis added).

There is no reason for a company to rely on a "shop right" if it uses employment agreements obligating the employees to assign inventions made during the employment to the company.

[C] The Rights of Joint Inventors in the Absence of Agreement or Shop Rights

[C][1] Joint Ownership

When an invention is made by more than one inventor jointly, each of the co-inventors has an equal and undivided interest in the invention. Each can license or practice the invention without the consent of, and without accounting to, the other co-inventors for any profits made. The rights of joint inventors are statutory:

> In the absence of any agreement to the contrary, each of the joint owners of a patent may make, use, offer to sell, or sell the patented invention within the United States, or import the patented invention into the United States, without the consent of and without accounting to the other owners.[178]

In the case where co-inventors are all employees of the same company with an obligation to assign the invention to the company, the joint inventor rights are not material because ownership will reside with the company. Accordingly, inventions developed by more than one employee of a single company without outside collaboration should not present problems due to joint inventorship if agreements to assign inventions are in place.

Situations arise, however, where co-inventors are from different companies or entities.[179] For example, an invention may be made by persons from different companies due to a joint venture, collaboration, or scientists from different universities may have collaborated on an invention. Thus, whenever there has been input to the invention process by persons who are not under an obligation of assignment to a single entity, an investigation into the possible existence of joint inventorship rights is warranted.

[C][2] Entire Patent—Not Claim-by-Claim

By statute, in the absence of any agreement to the contrary, each of the joint owners of a *patent* has the right to practice the invention and license others without the permission of, or an accounting to, their co-inventors.[180] The statute is not worded in terms of joint ownership

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178. 35 U.S.C. § 262.
179. *See supra* section 4:3.5.
180. 35 U.S.C. § 262.

of *inventions* or *claims*. Instead it refers to *patents*. The statute treats the patent as a unit and does not divide joint ownership on a claim-by-claim basis. Thus, each joint inventor has equal rights in the patent without regard to the relative degree of their contribution.

The rule that joint inventors jointly own a patent allows each joint owner to freely practice or license the patent without accounting to the other joint owners. In addition, the law allows joining a co-inventor who made an inventive contribution to only one claim of a multi-claim patent.[181] Together, these provisions can result in a co-inventor of a narrow claim of a patent having rights to a much broader invention described in other claims of the patent. A co-inventor may have contributed to the conception of any one claim in the patent, but as a joint inventor on the patent, would have rights to all the claims in that patent.[182]

The Federal Circuit observed that when Congress amended section 116 to allow a joint inventor to be joined on a patent if he contributed to any one claim, it did not amend section 262, which gave joint inventors named on the patent individual ownership of the entire patent.[183] The court stated:

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181. 35 U.S.C. § 116. A person may be named as a co-inventor of a patent if he has contributed to the conception of a single claim in the patent. The criteria for naming a joint inventor on a patent are set forth in 35 U.S.C. § 116:

> When an invention is made by two or more persons jointly, they shall apply for patent jointly and each make the required oath, except as otherwise provided in this title. Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent.

182. For example, one inventor may have independently invented an important therapeutic molecule, and a co-inventor may have contributed to a method of using the drug by discovering the optimal dosage for a specific therapy. If the claim to the method of treatment with the particular dosage is included in the same patent as the therapeutic molecule, the co-inventor, absent a contrary agreement, would have equal undivided rights to the patent including the claim to the molecule itself. If the company owning the molecule rights wanted to patent the method of treatment with the co-inventor's contribution and did not or could not get an assignment of rights from the co-inventor, the method of treatment claims should be filed in a separate application, leaving the claims to the molecule with only the sole inventor of that invention named.

183. Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1465–66 (Fed. Cir. 1998).

> This rule presents the prospect that a co-inventor of only one claim might gain entitlement to ownership of a patent with dozens of claims. As noted, the Patent Act accounts for that occurrence: "Inventors *may* apply for a patent jointly even though . . . each did not make a contribution to the subject matter of every claim." 35 U.S.C. Section 116 (emphasis added). Thus, where inventors choose to cooperate in the inventive process, their joint inventions may become joint property without some express agreement to the contrary. In this case, Yoon must now effectively share with Choi ownership of all the claims, even those which he invented by himself. Thus, Choi had the power to license rights in the entire patent.[184]

By stating that under section 116 inventors *may* apply for a patent jointly, the Federal Circuit apparently emphasized that joinder of inventions is permissive, not mandatory.

Thus, the *Ethicon* case serves to caution against including in the same patent application claims to which an inventive contribution has arguably been made by someone who is not obligated to assign his patent rights to the company filing the patent application.[185] If there is any issue of joint inventorship, such claims can be pursued in a divisional application. This would safeguard against a joint inventor, based on an inventive contribution to a less valuable aspect of the technology, having rights to all the claims of a patent containing valuable inventions.[186]

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184. *Id*. at 1466.

185. For example, the invention of a pharmaceutical compound may have clearly been made by a single chemist with an obligation of assignment, but a potential invention relating to course of treatment or dosage could have been developed by others outside the company. In such a situation, one would not want a joint inventor dispute to put at risk rights to the basic compound that are otherwise clear by including a claim for a particular dosage or treatment regime with potentially disputed inventorship in the same patent.

186. Taking this approach requires careful consideration of double patenting issues. A narrower application may issue ahead of a broader more basic invention and create obviousness-type double patenting issues. If the patent with the narrower claim that might have inventorship issues is filed on the same day as the broader patent, however, a terminal disclaimer should be able to solve the problem without loss of term under the current twenty-year-from-filing-date term.

§ 4:6 Anticipating and Resolving Joint Invention Issues

§ 4:6.1 Putting Agreements in Place

The best time to address joint inventorship issues is before beginning research that might lead to an invention. All research-based companies should have agreements with their employees requiring assignment of inventions made during employment to the company. But that is not enough. Collaborations with universities, other companies, doctors performing clinical trials, contractors performing work on development or testing, and government researchers, could give rise to an invention made jointly (or entirely) by a person not in the employ of the company and who does not have an obligation to assign his inventions to the company. Furthermore, in such situations, the outside inventor may have a pre-existing obligation to assign inventions he makes to his own employer or others. This can further complicate settlement efforts after the invention is made. An agreement concerning ownership of inventions made at the outset of any collaboration with non-employees will clarify ownership and reduce the risks of inventorship disputes by eliminating the economic consequences of different inventorship scenarios.

§ 4:6.2 Including Warranties of Freedom to Assign

A research collaboration agreement requiring assignment of an invention should contain warranties concerning any pre-existing obligations to assign inventions by the outside collaborator to others. If there are assignment obligations, the entity entitled to the assignment must be brought within the agreement to achieve full protection.

The research collaboration agreement should also contain warranties concerning whether any government funding has been, or will be, connected with the work done by the collaborator. Involvement of the federal government as a collaborating party or as a financer of the research triggers statutory provisions concerning assignment and ownership of invention rights. Private parties are not free to acquire all rights to the complete exclusion of the government.[187]

§ 4:6.3 Inventorship Checklists Before Research Begins

The following checklists should be considered before the start of a research program and re-visited during the project's life:

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187. See *infra* section 12:3 for a discussion of federal government-funded research.

Employees:

- Written agreements for all employees, requiring assignments of all inventions made during the course of employment.[188]

Record Keeping:

- Encourage (require) employees involved in research to record their general ideas, hypotheses, and concepts, even before performing actual experiments.[189]
- Date and witness writings.
- Make sure laboratory notebooks, and also memoranda reporting research plans and results are dated and witnessed.
- Institute a routine process for assuring compliance with record-keeping requirements.[190]
- Make sure all records are retained.
- Implement a backup system for storage of notebooks and other records, a task made easier with the advent of computer storage and record scanning.

Consultants and Outside Laboratories:

- Enter a written agreement that will clearly establish the ownership of a resulting invention at the outset of any collaboration.
- Make sure that any outside laboratory or consultant has in place the proper agreements to assign inventions from all subordinate employees.
- When dealing with universities, make sure that the assignment agreements extend to any students who may work on the project, whether as part of their studies or for compensation.

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188. Such agreements are particularly critical to the pharmaceutical industry where so much of the company's worth depends on inventions and patents.

189. While maintenance of laboratory notebooks recording actual experimental work is routine, the recording of ideas and conceptions before they are proven by experiments is done less often. Recording a complete conception, for example, use compound *X* to treat disease *Y*, can establish an invention date before the proof of the concept is obtained.

190. Consider an "audit." For example, can your scientists working on a project describe what they are trying to achieve and show documentation of who developed the idea and when?

- Written agreements with outside collaborators or consultants should include warranties against any pre-existing obligation of the collaborator or consultant to assign inventions to another.
- Be on the alert for clauses in any license agreements providing rights to research tools that require the user of the research tool to assign or cross-license any resulting inventions.[191]

Government Funding:

- Inquire whether there is any government funding or collaboration with government agencies by any outside consultant or collaborator.[192]

Suppliers:

- Be on the alert for clauses in supply agreements (particularly supply of chemicals or biological materials) that could give the supplier rights to any inventions made by use of the supplies.
- Obtain a release of claims for intellectual property rights to inventions made with materials supplied from an outside source, particularly if the materials supplied are unusual.

Patent Prosecution:

- The patent attorney should give consideration to issues of inventorship for each claim when the application is being prepared, and for each claim added or amended during prosecution. Dropped claims may require deleting some co-inventors.
- If there are claims where joint inventorship would impact ownership, consider filing those jointly invented (or potential jointly invented) claims in a separate application.
- All actual and even potential disputes or doubts about inventorship relating to any pending or new patent application should be fully disclosed to the Patent Office to protect against a charge of inequitable conduct.
- Where possible, the allegations of an omitted alleged inventor should be provided to the Patent Office in the alleged inventor's own words.

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191. Sometimes these agreements are not reviewed as carefully as they should because of the relatively low dollar value associated with the agreement.

192. Entering into a collaboration with a government-funded laboratory might make resulting patent rights subject to a government license and march-in rights or even risk loss of rights for failure to comply with the disclosure and election requirements. *See infra* section 12:3.

Chapter 5. Patentability

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Chapter 5

Patentability

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§ 5:1 Introduction

The Patent Office acts as the gatekeeper, preventing applicants from obtaining patents with claims to subject matter that does not satisfy the requirements for patentability. Once the Patent Office is satisfied the requirements are met, a patent will issue. Patents then confer the legal power to exclude others from engaging in activities falling within the scope of their claims. The validity of these claims, however, is subject to challenge. Accused infringers can argue the Patent Office made a mistake or was not privy to information that demonstrates invalidity. If a claim covers something that is not useful (utility), that the named inventor did not first invent (inventorship), that is not new (anticipation), or that covers obvious variations (obviousness); if the patent application was not timely filed (statutory bars); or if the patent specification fails to provide a disclosure of the invention sufficient to describe it (written description), to teach the use of it (enablement) or to reveal any best mode of the invention known to the inventors at the time of filing (best mode), the claim should be rejected by the Patent Office, or, if already issued, invalidated by a court.[1]

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1. For more in-depth treatment, see the following: on the law of utility (chapter 3), inventorship (chapter 4), anticipation (section 5:2), obviousness (section 5:3), written description (section 5:4), enablement (section 5:5), best mode (section 5:6), and indefiniteness (section 5:7). Although best mode is still a requirement for patentability, under the Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, 125 Stat. 284, best mode is no longer a ground for invalidity for cases filed on or after September 16, 2011. *See* 35 U.S.C. § 282(b)(3)(A) ("The following shall be defenses in any action involving the validity or infringement of a patent . . . any requirement of section 112, except that the failure to disclose the best mode shall not be a basis on which any claim of a patent may be canceled or held invalid or otherwise unenforceable.").

The boundaries for defining public knowledge for purposes of ascertaining whether a claimed invention is novel (that is, not anticipated) and not obvious is generally referred to as prior art. The statutory provisions defining anticipation set forth the definition for prior art and are explained in the section on anticipation.[2]

Patent applications can also be rejected and issued patents found invalid for statutory or non-statutory double patenting.[3] Double patenting occurs when the same inventor or patent owner attempts to obtain more than one patent with different expiration dates on the same invention or nonobvious variations on the same invention. Finally, patents can be rendered unenforceable for inequitable conduct even if they satisfy all of the validity requirements if the applicant deceived the patent office during prosecution of the patent.[4] Validity is determined on a claim-by-claim basis; patents can have claims that are valid and other claims that are found to be invalid. Unenforceability, on the other hand, renders all claims in a patent unenforceable.

§ 5:1.1 Presumption of Validity

Issued patents are presumed valid.[5] The presumption of validity "provides that a challenger must overcome that presumption to prevail on an invalidity defense."[6] This means that "a jury or a court may reach a conclusion that a patent remains valid solely on the failure of the patent challenger's evidence to convincingly establish the contrary."[7] The presumption of validity "can only be overcome by clear and convincing evidence of facts to the contrary."[8] The presumption cannot be avoided by "asserting a 'practicing prior art' defense to literal infringement under the less stringent preponderance of the evidence standard."[9]

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2. The AIA made changes to what constitutes prior art. *See infra* sections 5:2.1 and 5:2.3.
3. *See infra* section 5:8.
4. *Id*.
5. 35 U.S.C. § 282 ("A patent shall be presumed valid.").
6. Microsoft Corp. v. i4i Ltd., 131 S. Ct. 2238, 2245 (2011); *see also* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 930 (Fed. Cir. 2004).
7. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1570 (Fed. Cir. 1986).
8. Minton v. Nat'l Ass'n of Sec. Dealers, Inc., 336 F.3d 1373, 1376 (Fed. Cir. 2003); *see also* Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1253 (Fed. Cir. 2004); Poly-America, L.P. v. GSE Lining Tech., Inc., 383 F.3d 1303, 1308 (Fed. Cir. 2004); Juicy Whip, Inc. v. Orange Bang, Inc., 292 F.3d 728, 736 (Fed. Cir. 2002); U.S. Surgical Corp. v. Ethicon, Inc., 103 F.3d 1554, 1563 (Fed. Cir. 1997).
9. Tate Access Floors, Inc. v. Interface Architectural Res., Inc., 279 F.3d 1357 (Fed. Cir. 2002).

The presumption of validity has no applicability in a reexamination.[10] The presumption of validity cannot be defeated by uncorroborated oral testimony.[11]

It may be easier to satisfy the burden of proving invalidity if the prior art was not presented to the examiner.[12] Nevertheless, the presumption of validity still must be overcome by clear and convincing evidence in cases where the evidence before the jury was not submitted to the PTO; the applicable standard does not depend upon the

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10. *In re* Etter, 756 F.2d 852, 858 (Fed. Cir. 1985).

11. *See* Woodland Tr. v. Flowertree Nursery, Inc., 148 F.3d 1368, 1371 (Fed. Cir. 1998) ("Although an appellate court is indeed in a poor position to assess credibility, there is a very heavy burden to be met by one challenging validity when the only evidence is the oral testimony of interested persons and their friends, particularly as to long-past events. Corroboration of oral evidence of prior invention is the general rule in patent disputes."); Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1473 (Fed. Cir. 1997) ("An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself."); Jamesbury Corp. v. Litton Indus. Prods., Inc., 756 F.2d 1556, 1563 (Fed. Cir. 1985) (oral unsupported testimony of expert does not overcome by clear and unsupported convincing evidence the presumption of validity); Lockheed Aircraft Corp. v. United States, 553 F.2d 69, 75 (Ct. Cl. 1977) ("the oral testimony of witnesses, speaking only from memory in regard to past transactions has, in the absence of contemporaneous documentary or physical evidence, consistently been found to be of little probative value").

12. Microsoft Corp. v. i4i Ltd., 131 S. Ct. 2238, 2251 (2011) (noting that "if the PTO did not have all material facts before it, its considered judgment may lose significant force"); *see also* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1745 (2007) ("the rationale underlying the presumption—that the PTO, in its expertise, has approved the claim—seems much diminished here" where a prior art reference was not disclosed); Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253 (Fed. Cir. 2012) (holding that whether the PTO considered the asserted prior art during examination affects the weight of the reference in evaluating obviousness rather than the ultimate standard requiring clear and convincing evidence of invalidity); WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1355 (Fed. Cir. 1999); Eli Lilly & Co. v. Zenith Goldline Pharm., 2001 U.S. Dist. LEXIS 18361, at *13 n.3 (S.D. Ind. Oct. 12, 2001) ("The prior art compounds upon which Zenith relies here were not only before the examiner, they were described in detail in the '547 patent itself."); Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467 (Fed. Cir. 1990) ("[T]he burden of showing, by clear and convincing evidence, the invalidity of [patent claims] . . . is especially difficult when the prior art was before the PTO examiner during prosecution of the application."); *cf.* Kappos v. Hyatt, 132 S. Ct. 1690, 1700 (2012) ("Though the PTO has special expertise in evaluating patent applications, the district court cannot meaningfully defer to the PTO's factual findings if the PTO considered a different set of facts.").

individual facts of each case.[13] The Supreme Court noted, however, that when evidence submitted to the jury was not presented to the PTO or when there is a dispute regarding whether the jury and PTO did, in fact, receive different evidence, "the jury may be instructed to evaluate whether the evidence before it is materially new, and if so, to consider that fact when determining whether an invalidity defense has been proved by clear and convincing evidence."[14]

On the other hand, "persuading a fact finder that an expert agency is incorrect on a proposition is likely to be a greater forensic challenge to the advocate than showing the proposition to be incorrect in the absence of a contrary expert-agency determination."[15]

§ 5:1.2 Independent and Dependent Claims

Dependent patent claims are claims that contain all of the limitations of the independent claim upon which they depend.[16] Both dependent and independent claims "shall be presumed valid independently

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13. *See* Microsoft Corp. v. i4i Ltd., 131 S. Ct. 2238, 2250 (2011) ("Nothing in § 282's text suggests that Congress meant to depart from that understanding to enact a standard of proof that would rise and fall with the facts of each case. Indeed, had Congress intended to drop the heightened standard of proof where the evidence before the jury varied from that before the PTO—and thus to take the unusual and impractical step of enacting a variable standard of proof that must itself be adjudicated in each case—we assume it would have said so expressly.") (internal citation omitted); *see also Sciele Pharma Inc.*, 684 F.3d at 1260 ("The burden does not suddenly change to something higher—'extremely clear and convincing evidence' or 'crystal clear and convincing evidence'—simply because the prior art references were considered by the PTO. In short, there is no heightened or added burden that applies to invalidity defenses that are based upon references that were before the Patent Office. The burden is always the same, clear and convincing evidence.").
14. Microsoft Corp. v. i4i Ltd., 131 S. Ct. 2238, 2251 (2011); *cf.* Volterra Semiconductor Corp. v. Primarion, Inc., 2011 WL 4079223, at *10 (N.D. Cal. Sept. 12, 2011) (when the record reflects that the same evidence was presented to the jury and the PTO, the type of jury instruction suggested in *i4i* is not appropriate).
15. Intercontinental Great Brands v. Kellogg N. Am. Co., Nos. 2015-2082 and 2015-2084, 2017 WL 3906853, at *11, 869 F.3d 1336, 1350 (Fed. Cir. Sept. 7, 2017); *see also* Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253, 1260–61 (Fed. Cir. 2012) ("[I]t may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered. Importantly, whether a reference was before the PTO goes to the weight of the evidence, and the parties are of course free to, and generally do, make these arguments to the fact finder.").
16. 35 U.S.C. § 112, ¶ 3.

of the validity of other claims."[17] Thus, "dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim."[18] Furthermore, since a dependent claim is normally narrower than the independent claim upon which it depends, a dependent claim is often held to be valid over the prior art once the independent claim is found valid over the prior art.[19] A dependent claim will be invalidated, however, if it fails to "incorporate by reference all the limitations of the claim to which it refers" and "then specify a further limitation of the subject matter."[20] In other words, the dependent claim will be invalid if it does not narrow the scope of the independent claim, even if the dependent claim covered otherwise patentable subject matter.[21]

§ 5:1.3 Claim Construction Issues Relevant to Validity

As a general proposition, the "more narrowly a claim is construed, the more likely the claim may be upheld in light of the prior art."[22] During prosecution of a patent application, the patent office will interpret claims broadly to minimize the risk that a patent is issued improperly.[23] As for issued claims, courts have sometimes relied on the maxim that "claims should be so construed, if possible, as to sustain their validity."[24] The Federal Circuit, however, observed in an en

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17. Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 942 (Fed. Cir. 1992).
18. *Id*.
19. *See* Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1256 n.4 (Fed. Cir. 1989) ("Because we conclude that claim 1 is not anticipated, claim 2, which is dependent on claim 1, need not be separately discussed.").
20. Pfizer, Inc. v. Ranbaxy Labs. Ltd., 457 F.3d 1284, 1291 (Fed. Cir. 2006) (applying 35 U.S.C. § 112, ¶ 4); *see also* Curtiss-Wright Flow Control Corp. v. Velan, 438 F.3d 1374, 1380 (Fed. Cir. 2006) ("Reading an additional limitation from a dependent claim into an independent claim would not only make that additional limitation superfluous, it might render the dependent claim invalid" for failing to add a limitation to those recited in the independent claim, as required by 35 U.S.C. § 112, ¶ 4.).
21. *Pfizer*, 457 F.3d at 1292 ("We recognize that the patentee was attempting to claim what might otherwise have been patentable subject matter.").
22. Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 767 (Fed. Cir. 1988).
23. *See In re* Yamamoto, 740 F.2d 1569, 1571 (Fed. Cir. 1984) ("The PTO broadly interprets claims during examination of a patent application since the applicant may amend his claims to obtain protection commensurate with his actual contribution to the art. This approach serves the public interest by reducing the possibility that claims, finally allowed, will be given broader scope than is justified. Applicants' interests are not impaired since they are not foreclosed from obtaining appropriate coverage for their invention with express claim language.") (citations omitted).
24. Rhine v. Casio, Inc., 183 F.3d 1342, 1345 (Fed. Cir. 1999).

banc opinion that the maxim has not been applied "broadly."[25] The court has "certainly not endorsed a regime in which validity analysis is a regular component of claim construction."[26] The maxim has been limited "to cases in which 'the court concludes, after applying all the available tools of claim construction, that the claim is still ambiguous.'"[27] If the claim remains ambiguous, determining whether applying the maxim is appropriate "depends on the strength of the inference that the PTO would have recognized that one claim interpretation would render the claim invalid, and that the PTO would not have issued the patent assuming that to be the proper construction of the term."[28]

In any event, it is clear that "claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses."[29]

§ 5:1.4 Grounds for Invalidity

Although patents enjoy a presumption of validity, there are certain grounds on which a patent can be invalidated.[30] A patent will be invalidated according to 35 U.S.C. § 282(b)(2) if it fails to satisfy

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25. Phillips v. AWH Corp., 415 F.3d 1303, 1327 (Fed. Cir. 2005) (en banc).
26. *Id*.
27. *Id*. (citations omitted).
28. *Id*. at 1328; *see also* Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n, 871 F.2d 1054, 1065 (Fed. Cir. 1989) (construing claims to preserve their validity "does not justify reading into a claim a limitation that it does not contain and that the patentee deleted from the claim during prosecution"); E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1434 (Fed. Cir. 1988) (claims are not to be "saved" by reading extraneous limitations into them).
29. SmithKline Diagnostics, Inc. v. Helena Labs. Corp., 859 F.2d 878, 882 (Fed. Cir. 1988). The fact that a claim must be construed the same way for validity and infringement does not mean that invalidity can "be proved by merely establishing that one 'practices the prior art.'" Zenith Elecs. Corp. v. PDI Commc'ns Sys., Inc., 522 F.3d 1348, 1363–64 (Fed. Cir. 2008); Tate Access Floors, Inc. v. Interface Architectural Res., Inc., 279 F.3d 1357 (Fed. Cir. 2002) ("Where an accused infringer is clearly practicing only that which was in the prior art, and nothing more, and the patentee's proffered construction reads on the accused device, meeting this [clear and convincing] burden of proof should not prove difficult. Nevertheless, accused infringers are not free to flout the requirement of proving invalidity by clear and convincing evidence by asserting a 'practicing prior art' defense to literal infringement under the less stringent preponderance of the evidence standard.").
30. *See generally* 35 U.S.C. § 282(b)(2), (b)(3) (enumerating affirmative defenses for patent infringement based on invalidity of the patent or any claim in suit).

"any ground specified in part II of [the Patent Act] as a condition for patentability," which includes the utility, subject matter eligibility, novelty, and nonobviousness requirements of the Act.[31] A patent will also be invalidated according to 35 U.S.C. § 282(b)(3) for "failure [of the patent] to comply with (A) any requirement of [35 U.S.C.] section 112, except that the failure to disclose the best mode shall not be a basis on which any claim of a patent may be canceled or held invalid or otherwise unenforceable; or (B) any requirement of section 251." Courts, however, will not permit third-party challenges to internal decisions made by the PTO, such as permitting improper revival of an abandoned application[32] or other irregularities during prosecution,[33] as a means of invalidating an issued patent, unless covered by section 282(b).

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31. *See* Aristocrat Techs. Austl. Pty Ltd. v. Int'l Game Tech., 543 F.3d 657, 661–62 (Fed. Cir. 2008) ("While there are most certainly other factors that bear on the validity or the enforceability of a patent, utility and eligibility, novelty, and nonobviousness are the only so-called conditions of patentability.").

32. *See id*. at 660–63 (concluding that improper revival does not provide an affirmative defense leading to invalidity because it did not fit within the framework of section 282(b)); *see also* Schultz v. iGPS Co., 2011 WL 37839 (N.D. Ill. Jan. 3, 2011) (holding that an affirmative defense based on improper reinstatement does not lead to invalidity, unless inequitable conduct is pleaded); Allied Tube & Conduit Corp. v. John Maneely Co., 125 F. Supp. 2d 987 (D. Ariz. 2000) (finding improper reinstatement is not covered under section 282(b) and, thus, does not lead to invalidity); Cal. Med. Prods., Inc. v. Tecnol Med. Prods., Inc., 921 F. Supp. 1219 (D. Del. 1995) (same).

33. *See* Magnivision, Inc. v. Bonneau Co., 115 F.3d 956 (Fed. Cir. 1997) (holding that "prosecution irregularities," such as an examiner's failure to make a written record of a phone call between himself and an applicant, do not serve as a basis for invalidity); *accord Aristocrat Techs.*, 543 F.3d at 663 ("Once a patent has issued, the procedural minutiae of prosecution have little relevance to the metes and bounds of the patentee's right to exclude."); Norian Corp. v. Stryker Corp., 363 F.3d 1321 (Fed. Cir. 2004) (holding that, absent inequitable conduct, an applicant's factually misleading statement to the PTO about the contents of a reference was not a basis for invalidity); Ateliers de la Haute-Garonne v. Bröetje Automation-USA Inc., 819 F. Supp. 2d 389 (applicant's check for issue fee bounced and PTO later accepted an undocumented payment in violation of its rules held not a basis to challenge validity); Rowe Int'l Corp. v. Ecast, Inc., 586 F. Supp. 2d 924 (N.D. Ill. 2008) (missing new oath in CIP application held not a basis to challenge validity); *see also* Exxon Corp. v. Phillips Petroleum Co., 265 F.3d 1249 (Fed. Cir. 2001) (holding procedural issues during interference proceeding cannot be collaterally attacked).

§ 5:2 Anticipation: An Invention Must Be Something New*

An invention must be new when discovered by an inventor to qualify for patent protection. This fundamental requirement assures "that ideas in the public domain remain there for the free use of the public."[34] The determination of whether an inventor's idea qualifies for protection is made by comparing the inventor's idea to knowledge deemed to be in the public domain. The public body of knowledge, referred to as prior art, is defined by the patent statute. When a patent claim covers an idea that was fully disclosed in a single place in the prior art, that claim is not valid. This is referred to as anticipation.

Section 5:3, below, addresses the requirement that an invention be nonobvious to qualify for patent protection. Like anticipation, obviousness requires a comparison of the invention with the prior art; therefore, courts have had occasion to compare anticipation and obviousness. Often, it has been said that anticipation is the "epitome of obviousness."[35] Nevertheless, they arise out of separate statutory requirements, "novelty under 35 U.S.C. § 102 and nonobviousness under 35 U.S.C. § 103 . . . and therefore [they are] separate defenses available in an infringement action."[36]

The following sections provide an overview of the anticipation requirement.

§ 5:2.1 Statutory Provisions: Sections 101 and 102 and the AIA

The requirement that a patent claim not be anticipated by the prior art flows from sections 101 and 102 of the patent statute.[37] Section 101 requires that a patentable invention be "new." It specifies "the type of subject matter that is eligible for patent protection."[38] Section 102 "covers in detail the conditions relating to novelty."[39]

On September 16, 2011, Congress enacted the Leahy-Smith America Invents Act (AIA), which, among other things, amended section 102. Patent applications and patents that contain, or at any time during prosecution contained, at least one claim with an effective

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34. Aronson v. Quick Point Pencil Co., 440 U.S. 257, 262 (1979).
35. *In re* Kalm, 378 F.2d 959, 962 (C.C.P.A. 1967).
36. Cohesive Tech., Inc. v. Waters Corp., 543 F.3d 1351, 1363–65 (Fed. Cir. 2008) (describing cases distinguishing anticipation and obviousness).
37. *See* 35 U.S.C. §§ 101, 102.
38. Diamond v. Diehr, 450 U.S. 175, 189 (1981).
39. *Id*.

filing date of March 16, 2013, or later are subject to section 102 as amended by the AIA.[40]

[A] Section 102 (Pre-AIA)

Section 102 (pre-AIA) prescribes circumstances in which an applicant is not entitled to a patent either because the claimed invention was not the first to invent the claimed subject matter[41] or because the applicant waited too long before filing the patent application.[42]

Pursuant to section 102(a), (e), and (g), one is not entitled to a patent if, before the invention by the applicant, the invention was:

(1) "known or used by others in this country";

(2) "patented or described in a printed publication in this or a foreign country";

(3) described in a published patent application that was filed in the United States;

(4) described in a patent that was "granted on an application for patent by another filed in the United States"; or

(5) "made in this country by another inventor who had not abandoned, suppressed or concealed it."

Under section 102(b), an inventor is not entitled to a patent if, more than a year before the priority date of the inventor's U.S. patent application, the invention was (1) "patented or described in a printed publication in this or a foreign country"; or (2) "in public use or sale in this country."[43] Thus, section 102(b) "encourages an inventor to enter the patent system promptly, while recognizing a one year period of public knowledge or use or commercial exploitation before the patent application must be filed."[44]

Section 102(d) bars issuance of a patent if the invention was "first patented or caused to be patented" by the applicant or his legal representative, in a foreign country, on an application filed more than twelve months prior to the filing of the inventor's U.S. application.

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40. *See infra* section 5:2.1[D].
41. 35 U.S.C. § 102(a), (e), (g).
42. 35 U.S.C. § 102(b), (d).
43. 35 U.S.C. § 102(b).
44. Woodland Tr. v. Flowertree Nursery, Inc., 148 F.3d 1368, 1370 (Fed. Cir. 1998).

[B] Section 102 (AIA)

[B][1] Overview

Section 102(a), as amended by the AIA, prescribes the circumstances in which an applicant is *not* generally entitled to a patent:

(1) the inventor did not file a patent application before the claimed invention was available to the public;[45] or

(2) the inventor was not the first to file an application for the claimed subject matter.[46]

Section 102(b), as amended by the AIA, sets forth exceptions to section 102(a) which provide that an inventor who is *not* the first to file but *was* the first to disclose, or the source of the first disclosure or first patent application, may qualify for an exception to the first-to-file rule.[47] The discussion below outlines the differences in section 102 as it stood before the AIA and as amended by the AIA, including a description of the change from a first-to-invent system to a first-to-file-or-disclose system,[48] examples of what constitutes prior art under the first-to-invent and first-to-file-or-disclose systems,[49] a delineation of the expanded geographic scope of prior art under the AIA,[50] tables summarizing the changes,[51] and an explanation of whether the pre-AIA regime or the AIA regime applies to a particular patent or patent application.[52]

[B][2] Scope of Prior Art

More specifically, unless an exception under section 102(b) applies, pursuant to section 102(a)(1), one is not entitled to a patent if, "before the effective filing date of the claimed invention," it was:

- "patented,"
- "described in a printed publication,"
- "in public use,"

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45. 35 U.S.C. § 102(a)(1).
46. 35 U.S.C. § 102(a)(2) (bars the invention only if the first-filed application publishes, is deemed published, or issues as a patent).
47. 35 U.S.C. § 102(b).
48. *See infra* section 5:2.1[C][1].
49. *See infra* section 5:2.1[C][2].
50. *See infra* section 5:2.1[C][3].
51. *See infra* section 5:2.1[C][4].
52. *See infra* section 5:2.1[D].

- "on sale,"
- "otherwise available to the public,"[53] or
- "described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b)" that "names another inventor."[54]

Each of these categories, with the exception of the newly added "otherwise available to the public," corresponds to a category of prior art under the pre-AIA section 102.[55]

[B][3] Exceptions to Defined Scope of Prior Art

Under section 102(b)(1), a disclosure under section 102(a)(1) "made 1 year or less before the effective filing date of a claimed invention shall not be prior art" if:

- "the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor"; or
- "the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor."

In addition, under section 102(b)(2), a disclosure under section 102(a)(2) shall not be prior art if it was:

- "obtained directly or indirectly from the inventor or a joint inventor";
- "publicly disclosed by" an inventor or another who obtained it from an inventor before it was effectively filed under section 102(a)(2); or
- owned by the same person who owned or was the beneficiary of an obligation of assignment of the invention "not later than the effective filing date of the claimed invention."

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53. 35 U.S.C. § 102(a)(1).
54. 35 U.S.C. § 102(a)(2). Note the priority date of a prior patent for purposes of establishing its prior art date can extend back to its foreign filing date.
55. See *infra* section 5:2.3 for a discussion of the case law on various types of prior art defined by pre-AIA section 102.

[C] Differences Between Pre-AIA and AIA Versions of Section 102

[C][1] Change from First-to-Invent to First-to-File-or-Disclose

The AIA amended section 102 to change the U.S. patent system from a first-to-invent to a first-to-file-or-disclose system to achieve greater conformity to the rest of the world, which largely employs a first-to-file system. Prior public disclosure of the inventor's work within one year of filing can overcome prior art,[56] but such prior art can no longer be overcome by showing an earlier date of invention.[57]

This new one-year grace period still leaves differences with most foreign jurisdictions. A "public" disclosure by, or obtained from, an inventor is not prior art if the inventor files a patent application within one year of the disclosure.[58] Such a disclosure, however, will cause a forfeiture of foreign patent rights in countries that do not have such a grace period (that is, have an absolute novelty bar).

Interferences (disputing who invented first) have been replaced with derivation proceedings (disputing whether one derived the invention form the other).[59] Swearing behind a reference based on the date of invention has been eliminated.[60] Secret prior art, except for earlier-filed, not-yet-published applications, has been eliminated.[61]

The AIA adds to the scope of prior art by including "or otherwise available to the public before the effective filing date of the claimed invention" in section 102(a).

[C][2] First-to-File-or-Disclose Examples

The timelines in Fig. 5-1 exemplify the differences between the first-to-invent pre-AIA system and the AIA's first-to-file-or-disclose system.

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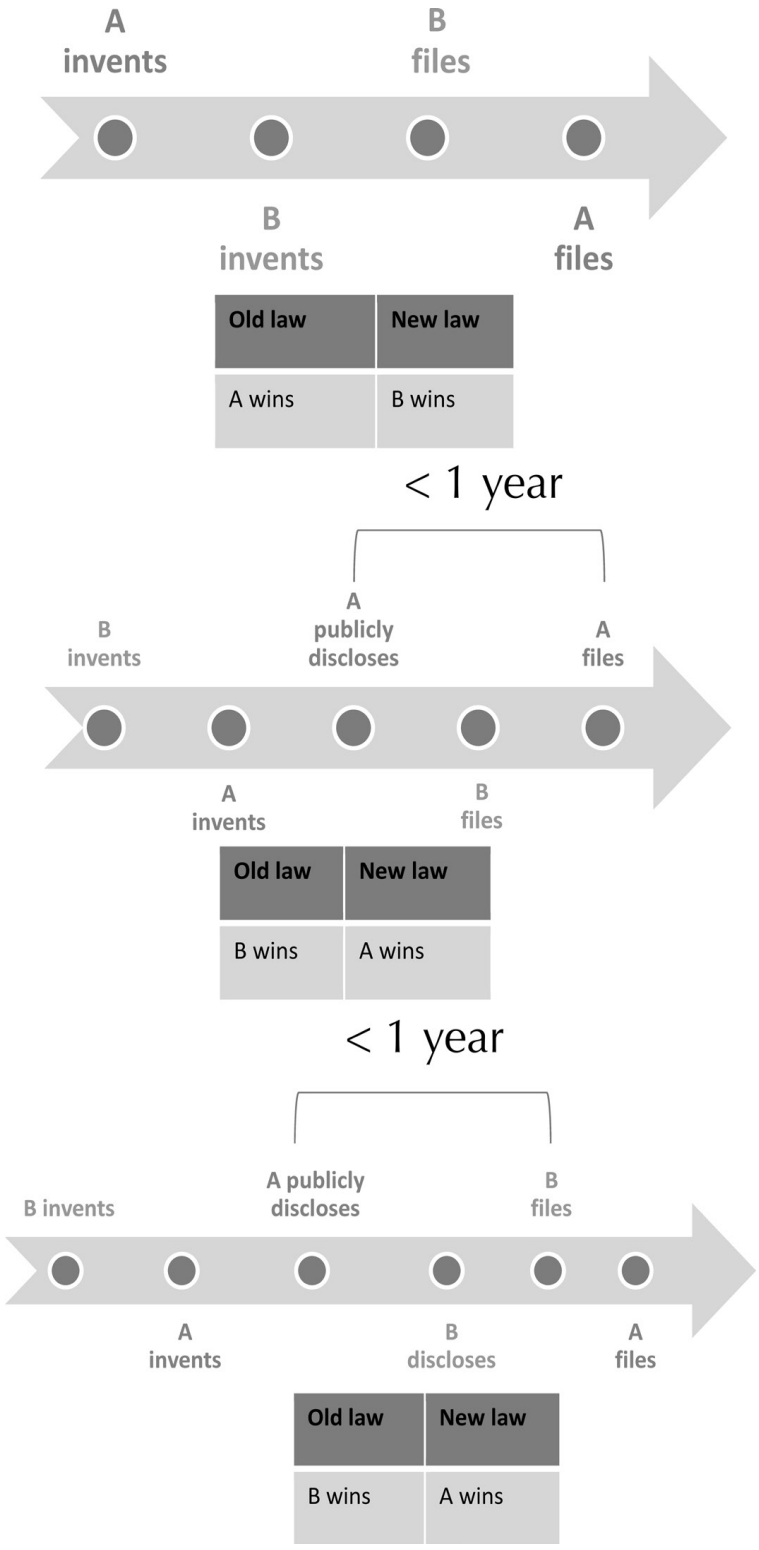
56. 35 U.S.C. § 102(b)(1) (AIA).
57. *Compare* 35 U.S.C. § 102(a), (b) (pre-AIA), *with* 35 U.S.C. § 102(a), (b)(2) (AIA).
58. 35 U.S.C. § 102(b)(1) (AIA).
59. *Compare* 35 U.S.C. §§ 102(g) *and* 135 (pre-AIA), *with* 35 U.S.C. §§ 102(b)(2) and 135 (AIA).
60. *Compare* 35 U.S.C. § 102(a) ("before the invention thereof"), 102(e) ("before the invention by the applicant for patent"), *and* 102(g) ("before such person's invention thereof") (pre-AIA), *with* 35 U.S.C. § 102(a) ("before the effective filing date") *and* 102(b) ("before the effective filing date") (AIA).
61. *See* 35 U.S.C. § 102(g)(2) (pre-AIA) ("before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it").

Fig. 5-1

First to Invent (Old Law) Versus First to File (New Law)



[C][3] New Geographic Scope for Scope of Prior Art

The category of art "known or used by others" is no longer restricted in section 102(a) to "in this country," as depicted in Table 5-1.

Table 5-1

Geographic Scope Compared to Prior Statute

Type of art	Former §§ 102(a) & (b)	New § 102(a)(1)
Known or used by others[62]	U.S. only	Anywhere in world
Patented	Anywhere in world	Anywhere in world
Printed Publication	Anywhere in world	Anywhere in world
Public use/On Sale	U.S. only	Anywhere in world

[C][4] Summary of Changes

Tables 5-2 and 5-3 summarize other differences between the pre-AIA and AIA versions of section 102.

Table 5-2

Earlier Filed Application Art Compared to Prior Statute

Type of art	Former § 102(e)	New § 102(a)(2)
Prior application filed by another, published or issued in the U.S.	Prior art if filed prior to applicant's date of invention	Prior art if filed prior to applicant's date of filing and if filed prior to the inventor's public disclosure within one-year grace period
	U.S. priority date or date of PCT application if it designates the U.S. and is published in English	U.S. priority date or § 119 foreign filing date

62. As amended by the AIA, section 102(a)(1) uses the broader phrase "otherwise available to the public."

Type of art	Former § 102(e)	New § 102(a)(2)
Invention by another	Invention by another (even one who files first) overcome by showing an earlier date of invention **("Interference" proceedings)**	Prior filing of application by another overcome by showing that the invention was obtained from the inventor **("Derivation" proceedings)**

Table 5-3

Summary of Changes

	Former § 102	AIA
Known or used by others/in public use or on-sale	U.S. only	Anywhere in world
Competing inventors	First to invent wins (with reasonable diligence between conception and reduction to practice)	First to file wins, unless derived from other inventor or second filer has prior disclosure within 1-year grace period
1-year grace period	Patent, printed publication, public use or on-sale: prior art if before the date of invention or > 1 year before application's filing date	Public disclosure by (or obtained from) the inventor if < 1 year before his effective filing date, overcomes later disclosures
Prior filed application published or issued in the U.S.	Bars patent if prior to date of invention	Bars patent if prior to date of filing, unless derived from inventor or inventor has public disclosure < 1 year before filing application

[D] Determining Which Version of Section 102 Applies

Section 146(n)(1) of title 35 determines which patents and patent applications will be subject to the AIA. They are a patent or patent application

that contains or contained at any time—

(A) a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after the effective date described in this paragraph; or

(B) a specific reference under section 120, 121, or 365(c) of title 35, United States Code, to any patent or application that contains or contained at any time such a claim.

§ 5:2.2 *Requirements for Anticipation*

[A] Art Must Include All Elements of a Claim to Anticipate

If an invention was previously "known," "used," "patented," "described," or "made" and is, therefore, unpatentable under section 102, the invention is said to have been "anticipated." "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference."[63] "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention."[64] Thus, analyzing whether a prior art reference anticipates a patent claim is a two-step process. First, the claim must be construed; and second, the prior art reference must be compared to the properly construed claim.[65] Anticipation is then a question of fact.[66] The burden of proving a patent anticipated "is particularly high when the prior art was before the examiner during prosecution of the application."[67]

Anticipation requires that the reference must disclose the invention "without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings

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63. Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991); *but see* Procter & Gamble Co. v. Nabisco Brands Inc., 711 F. Supp. 759, 762 (D. Del. 1989) ("The prior art need not . . . state the elements of the claim in identical language."); *see also* Akzo N.V. v. U.S. Int'l Trade Comm'n, 808 F.2d 1471, 1479 (Fed. Cir. 1986).
64. *Scripps Clinic*, 927 F.2d at 1576.
65. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 (Fed. Cir. 2003). The anticipation test, stated differently, is "[t]hat which would *literally* infringe if later in time anticipates if earlier than the date of invention." Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747 (Fed. Cir. 1987); *see also* Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001) (same). See chapter 10 for a description of infringement.
66. *Scripps Clinic*, 927 F.2d at 1576.
67. Brown v. 3M, 265 F.3d 1349, 1354 (Fed. Cir. 2001).

of the cited reference."[68] "Because the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'"[69] This does not mean, however, that when determining whether the claim of a prior art patent anticipates one is unable to look to relevant portions of the specification because that is the normal way to read a patent reference.[70]

[B] Art May Anticipate Based Only on Limited Consideration of Information Beyond the Reference

In deciding whether a prior art reference anticipates the invention at issue, consideration of evidence outside the reference is appropriate only "to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention."[71] "The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference."[72] A claim is not anticipated "if it is necessary to prove facts

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68. *In re* Arkley, 455 F.2d 586, 587–88 (C.C.P.A. 1972) ("Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection.").

69. Net Moneyin, Inc. v. Verisign, Inc., 545 F.3d 1359, 1369 (Fed. Cir. 2008); *see also* Therasense, Inc. v. Becton, Dickinson & Co., 593 F.3d 1325 (Fed. Cir. 2010) ("We agree with Abbott, therefore, that when read in its entirety, the instruction is incorrect because it makes sufficient, for purposes of anticipation, a prior art disclosure of individual claim elements that 'could have been arranged, in a way that is not itself described or depicted in the anticipatory reference.'").

70. *In re* Schaumann, 572 F.2d 312, 317 (C.C.P.A. 1978) (reading claim 1 of the prior art patent in combination with portion of specification passage there was "no alternative since claim 1 itself did not define the expression 'lower alkyl radical'").

71. *Scripps Clinic*, 927 F.2d at 1576; *see also* Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc., 726 F.2d 724 (Fed. Cir. 1984) (anticipation must be found in a single reference, although other references may be used to interpret an allegedly anticipating reference).

72. Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc., 344 F.3d 1186, 1192 (Fed. Cir. 2003) (quoting Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1369 (Fed. Cir. 2003)). Note, however, that it "is well established that the claims of a patent cited as a reference are

beyond those disclosed in the reference in order to meet the claim limitations."[73] If one must "reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not § 102 anticipation, but § 103 obviousness."[74]

[C] Art Must Be Enabling to Anticipate

A prior art reference may be anticipatory even if the disclosed invention was not actually made.[75] However, the prior art reference must be an enabling disclosure. In other words, a prior art reference is not anticipatory if it "fails to 'enable one of skill in the art to reduce the disclosed invention to practice.'"[76]

[C][1] Level of Disclosure

The level of disclosure necessary to enable a prior art reference must be considered in view of the patent's level of disclosure,[77] although some discrepancy may be allowed due to teachings of the intervening prior art dated after the date of the art at issue and before the date of invention.

[C][2] Enablement for Section 102(b) Art

Section 102(b) prior art is any patent, printed publication in any country or public use or sale in the United States "more than a year

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part of the disclosure of that reference and may properly be considered in determining the question of anticipation." *In re* Schaumann, 572 F.2d 312, 317 n.11 (C.C.P.A. 1978).

73. *Scripps Clinic*, 927 F.2d at 1576.

74. *Id*. at 1577.

75. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1379 (Fed. Cir. 2001).

76. *Amgen*, 314 F.3d at 1354 (quoting *In re* Borst, 345 F.2d 851, 855 (C.C.P.A. 1962)); *see also* Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys., 804 F.2d 659, 665 (Fed. Cir. 1986) (a "§ 102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it'") (quoting *In re* Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985)); Akzo N.V. v. U.S. Int'l Trade Comm'n, 808 F.2d 1471, 1479 (Fed. Cir. 1986) ("the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public"). See *infra* section 5:5 for a discussion of enablement.

77. Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1569 (Fed. Cir. 1988) ("The disclosure [in the reference] is at least at the same level of technical detail as the disclosure in the . . . patent. If disclosure of a computer program is essential for an anticipating reference, then the disclosure in the . . . patent would fail to satisfy the enablement requirement.").

before the priority date of the inventor's U.S. patent application."[78] For a section 102(b) reference to anticipate, it must be enabling. This enablement requirement, however, does not apply to prior public use.[79] Furthermore, "[t]he standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112."[80] "[A] prior art reference need not demonstrate utility [which is incorporated into the enablement standard] in order to serve as an anticipating reference under section 102."[81]

The question arises, "At what point in time should the adequacy of the disclosure be measured?" A reference dated ten years before the filing date might disclose a claimed compound but no route of synthesis. The law, however, permits one to assess adequacy of the disclosure for satisfying enablement based on later prior art knowledge, so long as that art predates the critical date (one year prior to the filing date) of the patent or application in question.[82]

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78. 35 U.S.C. § 102(b).
79. *See infra* section 5:2.3[B][2].
80. Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325 (Fed. Cir. 2005) (citing *In re* Hafner, 410 F.2d 1403, 1405 (C.C.P.A. 1969)) ("[A] disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is . . . entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim.").
81. *Rasmusson*, 413 F.3d at 1326; *In re* Gleave, 560 F.3d 1331, 1335 (Fed. Cir. 2009) ("a reference need disclose no independent use or utility to anticipate a claim under § 102.").
82. *In re* Sasse, 629 F.2d 675, 681 (C.C.P.A. 1980) (permitting reliance on prior art predating the anticipatory section 102(b) reference to find the section 102 (b) reference enabled); *In re* Samour, 571 F.2d 559, 563 (C.C.P.A. 1978) ("The critical issue under 35 U.S.C. § 102(b) is whether the claimed subject matter was in possession of the public more than one year prior to applicant's filing date—not whether the evidence showing such possession came before or after the date of the primary reference."); *accord In re* LeGrice, 301 F.2d 929, 937 (C.C.P.A. 1962) ("[B]efore any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge and of the particular art and be in possession of the invention."); Cohen v. U.S. Corset Co., 93 U.S. 366, 377 (1876) (the prior art "in connection with the known state of the art at the time when it was filed and published, was sufficient to enable" skilled artisan to "to make the patented corset").

[D] Art May Anticipate by Inherency

"[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is . . . inherent, in the single anticipating reference."[83] A missing feature is inherent if it "is necessarily present" or is "the 'natural result flowing from' the explicit disclosure of the prior art."[84] This is true even for a chemical process that produces only "trace" amounts of a compound.[85] "The mere fact that a certain thing may result from a given set of circumstances is insufficient to prove anticipation."[86]

A product is "inherently anticipated where it was the natural result of the prior art process, even when it would be possible to prevent the formation of the product through 'extraordinary measures.'"[87] Accordingly, the Federal Circuit found no clear error when a district court refused to find inherent anticipation of a method to treat hair loss by locally administering one of genus of compounds to the skin because an expert "persuasively testified that a 'properly applied

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83. Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003); Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc., 344 F.3d 1186, 1192 (Fed. Cir. 2003) ("A claim limitation is inherent in the prior art if it is necessarily present in the prior art, not merely probably or possibly present."); EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1349 (Fed. Cir. 2001) ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.").

84. *Schering Corp.*, 339 F.3d at 1377, 1379 (missing feature inherent if "necessarily present"; "a limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art") (citation omitted); *see also* SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005) ("Apotex did not need to prove that it was impossible to make PHC anhydrate in the United States that contained no PHC hemihydrate, but merely that 'the [prior art] is sufficient to show that the natural result flowing from the operation as taught would result in' the claimed product.").

85. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1345 (Fed. Cir. 2005).

86. Cont'l Can Co. v. Monsanto Co., 948 F.2d 1264, 1268–69 (Fed. Cir. 1991) (quoting *In re* Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981) ("Inherency . . . may not be established by probabilities or possibilities.")); *In re* Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.").

87. Allergan, Inc. v. Apotex Inc., 754 F.3d 952, 961 (Fed. Cir. 2014) (quoting Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1349 (Fed. Cir. 1999)).

drop' would not transfer to the skin" when practicing the prior art method of administering some of the same compounds using an eye dropper.[88]

Recognition of the invention in the prior art is not required to show anticipation by inherency.[89] Consequently, "the fact that a characteristic is a necessary feature or result of a prior art embodiment (that is sufficiently described and enabled) is enough for inherent anticipation, even if the fact was unknown at the time of the prior invention."[90]

The issue of inherent anticipation has arisen in numerous cases involving pharmaceutical patents. The following cases illustrate the principle of inherent anticipation.

[D][1] Examples of Inherent Anticipation[91]

Schering Corp. v. Geneva Pharmaceuticals, Inc.[92]

Claim:	The non-drowsy antihistamine compound descarboethoxyloratadine (DCL), its fluorine analogs, and salts.
Prior Art:	Patent disclosing Loratadine.
Inherent Property:	The body metabolizes Loratadine to form DCL.
Holding:	"DCL necessarily and inevitably forms from loratadine under normal conditions" and therefore anticipates.[93]

88. *Allergan*, 754 F.3d at 960–61.
89. *Schering Corp.*, 339 F.3d at 1377; *cf.* Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356, 1367 (Fed. Cir. 2017) (reversing finding of inherency because "[n]o expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomib and mannitol, or that the resulting ester would have the long-sought properties and advantages").
90. Toro Co. v. Deere & Co., 355 F.3d 1313, 1320–21 (Fed. Cir. 2004).
91. See *infra* section 7:4.5[A][1] for a description of additional cases of inherent anticipation involving method of treatment claims.
92. Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373 (Fed. Cir. 2003).
93. *Id.* at 1378.

In re Crish[94]

Claim:	Specific oligonucleotide sequence having promoter activity for the human involucrin gene.
Prior Art:	Analyzed phenotype of mice injected with hINV isolated from same plasmid that served as source of oligonucleotide sequenced for the claim and described how to obtain isolated hINV.
Inherent Property:	Nucleotide Sequence
Holding:	"The only arguable contribution to the art that Crish's application makes is the identification of the nucleotide sequence of the promoter region of the [involucrin gene]. However, . . . the identification and characterization of a prior art material also does not make it novel."[95]

Abbott Laboratories v. Geneva Pharmaceuticals, Inc.[96]

Claim:	"Anhydrous Form IV crystalline of" terazosin hydrochloride (anti-hypertensive drug).
Prior Art:	Third-party sales of terazosin hydrochloride.
Inherent Property:	Sales subsequently determined to be of Form IV terazosin hydrochloride.
Holding:	Finding anticipation because "[t]he fact that the parties to the sales transactions did not know they were dealing in Form IV at the time of the sales is therefore irrelevant to the question whether it was 'on sale' before the critical date."[97]

94. *In re* Crish, 393 F.3d 1253 (Fed. Cir. 2004); *but see In re* Recombinant DNA Tech. Patent & Contract Litig., 30 U.S.P.Q.2d (BNA) 1881 (S.D. Ind. 1994) (denying summary judgment that claim to human proinsulin anticipated by prior patent that named human proinsulin protein without providing amino acid sequence because prior art only provided sequence with 90% confidence).
95. *Schering Corp.*, 393 F.3d at 1258.
96. Abbott Labs. v. Geneva Pharm., Inc., 182 F.3d 1315 (Fed. Cir. 1999).
97. *Id.* at 1318.

In re Cruciferous Sprout Patent Litigation[98]

Claim: Method for producing and consuming cruciferous sprouts, "containing high Phase 2 enzyme-inducing potential and non-toxic levels of indole glucosinolates."

Prior Art: Eating and preparing cruciferous sprouts.

Inherent Property: High Phase 2 enzyme-inducing potential and non-toxic levels of indole glucosinolates in the sprouts.

Holding: "Brassica does not claim to have invented a new kind of sprout, or a new way of growing or harvesting sprouts. Rather, Brassica recognized that some sprouts are rich in glucosinolates and high in Phase 2 enzyme-inducing activity while other sprouts are not. . . . [A] sprout's glucosinolate content and Phase 2 enzyme-inducing potential are inherent characteristics of the sprout."[99]

[D][2] Examples of No Anticipation by Inherency[100]

Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research[101]

Claim: "[T]ransgenic rodent comprising a diploid genome comprising a transgene encoding a heterologous APP polypeptide . . . expressed to produce a human APP polypeptide . . . processed to ATF-betaAPP in a sufficient amount to be detectable."[102]

Prior Art: Patent stating "that transgenic animals containing the mutated gene can be used in Alzheimer's disease (AD) research and therapy."[103]

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98. *In re* Cruciferous Sprout Patent Litig., 301 F.3d 1343 (Fed. Cir. 2002).
99. *Id.* at 1350.
100. See *infra* section 7:4.5[A][2] for a description of additional cases where courts have found no inherent anticipation involving method of treatment claims.
101. Elan Pharm. v. Mayo Found. for Med. Educ. & Research, 304 F.3d 1221 (Fed. Cir. 2002).
102. *Id.* at 1226.
103. *Id.* at 1224–25.

Inherent Property: Infringer asserts that "a successful transgenic procedure and ensuing enzymatic cleavage will [inherently] produce ATF-betaAPP."[104]

Holding: "General instructions to conduct such failure-prone activities as gene transfer between humans and animals, and the ensuing uncertainties with respect to gene expression and enzymatic cleavage of the mutated human protein with animal enzymes, do not meet the legal criteria of 'anticipation' of the successful product of transgenic activity."[105] The inherent property "was not shown by Mullan, and there was no evidence that the formation and detection of ATF-betaAPP in the transgenic mouse brain with the Swedish mutation was known to person of ordinary skill."[106]

Glaxo Inc. v. Novopharm Ltd.[107]

Claim: Compound ranitidine hydrochloride in its Form 2 crystalline polymorph.

Prior Art: A patent claimed ranitidine and its hydrochloride salt; example 32 resulted in the Form 2 polymorph in all 13 tests performed by Novopharm's experts.

Inherent Property: Novopharm argued the Form 2 polymorph was inherent in the prior patent.

Holding: Example 32 of the ranitidine patent "could yield crystals of either polymorph," as evidenced by tests performed by Glaxo's expert, therefore it did not inherently anticipate.[108]

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104. *Id.* at 1229.
105. *Id.* at 1228.
106. *Id.* at 1229.
107. Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043 (Fed. Cir. 1995).
108. *Id.* at 1047.

Millennium Pharmaceuticals, Inc. v. Sandoz Inc.[109]

Claim:	A boronate ester of bortezomib and D-mannitol.
Inherent Property:	Lyophilized bortezomib in the presence of a known bulking agent (mannitol) results in the formation of the claimed compound.
Holding:	Reversing the district court's finding of inherency because "[n]o expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomib and mannitol, or that the resulting ester would have the long-sought properties and advantages."[110]

[E] Art Disclosed Species Anticipates Genus Claim

"When a claim covers several structures or compositions, either generally or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art."[111] Thus, in the case of chemical compound patents, which often claim thousands of compounds by reciting a basic structure and listing numerous possible substituents that may appear at various locations in the molecule, "a single prior art species within the patent's claimed genus reads on the generic claim and anticipates."[112]

There is an exception to the general rule that a species anticipates a genus. An inventor claiming a genus may be able to avoid a species anticipation by showing that the inventor possessed the species before its prior art date.[113]

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109. Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356 (Fed. Cir. 2017).
110. *Id.* at 1367.
111. Brown v. 3M, 265 F.3d 1349, 1351 (Fed. Cir. 2001).
112. Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1346 (Fed. Cir. 1999); *see also In re* Gosteli, 872 F.2d 1008, 1010 (Fed. Cir. 1989) ("Section 102(e) bars the issuance of a patent if its generic claims are anticipated by prior art disclosing individual chemical species."); Titanium Metals Corp. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985) (finding anticipation "when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art").
113. *See In re* Stempel, 241 F.2d 755, 759 (C.C.P.A. 1957) ("[A]ll the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show."); *but see In re* Tanczyn, 347 F.2d 830, 831–32 (C.C.P.A. 1965).

[F] Art Disclosed Genus Generally Does Not Anticipate Species Claim

Generally, a claim to a large genus of compounds anticipates only those particular compounds within the genus that are expressly recited.[114] However, where a prior art reference discloses either a small genus of compounds or a small preferred subgenus of a larger genus, this description may anticipate all species falling within the described class even without specifically reciting the species.[115] In *In re Petering*,

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114. *In re* Petering, 301 F.2d 676 (C.C.P.A. 1962); *see also* Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356 (Fed. Cir. 2012) (prior art reference disclosing "variety of oral compositions" including chewing gum, toothpaste, mouth rinses and lozenges with various types of ingredients such as "cooling agents" including WS-3, WS-23, and one other that were "particularly preferred" and "menthol as one of 23 listed flavoring agents," and one which was "among the 'most suitable'" anticipated on summary judgment a claim to gum that contained WS-23 and menthol); Impax Labs., Inc. v. Aventis Pharm., Inc., 468 F.3d 1366, 1383 (Fed. Cir. 2006) (finding no anticipation of method of using riluzole because "riluzole is just one of hundreds of compounds included in formula I" of the prior patent); Metabolite Labs. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367 (Fed. Cir. 2004) ("A prior art reference that discloses a genus still does not inherently disclose all species within that broad category."); Corning Glass Works v. Sumitomo Elec. U.S.A., 868 F.2d 1251, 1262 (Fed. Cir. 1989) (rejecting argument that "a claim to a genus would inherently disclose all species"); *In re* Benno, 768 F.2d 1340, 1346 (Fed. Cir. 1985) ("The scope of a patent's claims determines what infringes the patent; it is no measure of what it discloses. A patent discloses only that which it describes, whether specifically or in general terms, so as to convey intelligence to one capable of understanding."); *In re* Luvisi, 342 F.2d 102, 107 n.2 (C.C.P.A. 1965).

115. Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356 (Fed. Cir. 2012) (holding that claim to a species of the combination of two ingredients was anticipated by reference disclosing genus of three "particularly preferred" cooling agents combined with one of the "most suitable" of twenty-three flavoring agents); Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001); Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006) ("a very small genus can be a disclosure of each species within the genus"); *Petering*, 301 F.2d at 682; *In re* Schaumann, 572 F.2d 312, 316–17 (C.C.P.A. 1978) ("When we also consider that claim 1 of [the prior art] patent, read in conjunction with the signification given the expression 'alkyl radical' in the specification, embraces a very limited number of compounds closely related to one another in structure, we are led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name."); Schering Corp. v. Precision-Cosmet Co., 614 F. Supp. 1368, 1373 (D. Del. 1985) ("The general rule is that a prior genus does not anticipate a later species. If, however, it is possible to derive a class of compounds of lesser scope

one court concluded that a prior art patent describing a class containing twenty compounds had "described to those of ordinary skill in the art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name."[116] The *Petering* principle, however, does not apply where the prior art fails to identify "a definite and limited class of compounds that enable[ ] a person of ordinary skill in the art to at once envisage each member of this limited class."[117]

Disclosure of a large number of compounds, or other embodiments of subject matter relating to a claimed invention, should not be mistaken for a mere generic disclosure of a genus. A patentee cannot avoid anticipation by arguing that the anticipating disclosure is located among numerous other non-anticipating embodiments.[118]

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than the genus disclosed in a prior art reference on the basis of preferences ascertainable from the remainder of the reference, anticipation may be found.") (citations omitted).

116. *Petering*, 301 F.2d at 682; *cf. Altofina*, 441 F.3d at 999 ("temperature range of over 100 degrees" not sufficiently small genus to count under *Petering* as a disclosure of inclusive sub-temperature ranges).

117. Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp., 50 F.4th 147 (Fed. Cir. 2022) (holding "that the Board did not err in finding that a class of 957 predicted salts that may result from the 33 disclosed compounds and eight preferred acids, some of which may not even form under experimental conditions, is insufficient to meet the 'at once envisage' standard set forth in *Petering*"); Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1376 (Fed. Cir. 2006).

118. *In re* Gleave, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (finding anticipation based on prior art list of over 1, 400 oligodeoxynucleotide sequences); Merck & Co. v. Biocraft Labs., 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the '813 [prior art] patent discloses a multitude of effective combinations does not render any particular formulation less obvious."); *In re* Sivaramakrishnan, 673 F.2d 1383 (C.C.P.A. 1982) (reference anticipates under section 102(b) even though disclosing the claimed invention among twenty other embodiments); *Ex parte* A, 17 U.S.P.Q.2d (BNA) 1716, 1718 (B.P.A.I. 1990) ("The tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of those compounds is 'described,' as that term is used in 35 U.S.C. § 102(a), in that publication. A similar conclusion would be appropriate with respect to the approximately 1.5 million compounds in the Bielstein Handbook."); *cf. In re* Wiggins, 488 F.2d 538, 543 (C.C.P.A. 1973) ("The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference. If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer

[G] Art's Use of Equivocal Language Generally Does Not Defeat Anticipation

The fact that a reference uses terms such as "might," "merely," or "may" in suggesting an idea does not generally prevent anticipation.[119] Nevertheless, a suggestion to make something that the skilled artisan may not be able to make does not anticipate.[120] Furthermore, the fact that prior art reports obtaining an unfavorable result does not defeat anticipation if the reference discloses all of the claimed elements.[121] "It is well-settled that utility or efficacy need not be demonstrated for a reference to serve as anticipatory prior art under section 102."[122]

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of a named compound no matter how beneficial to mankind it might be.") (distinguished by *Gleave*, 560 F.3d at 1337).

119. Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc., 642 F.3d 1031, 1039 (Fed. Cir. 2011) (the fact that the prior art "discloses using the S65C mutation when diagnosing hemochromatosis, but qualifies that disclosure with the observation that the mutation '*may* only be a polymorphic variant'" does not negate anticipation); *Gleave*, 560 F.3d at 1335 (holding that an anticipatory reference need not "demonstrate the invention's *utility*"; "in the context of a claimed method for treating a disease, a prior art reference need not disclose 'proof of efficacy' to anticipate the claim"); Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp., 86 F. Supp. 2d 433, 441 (D.N.J. 2000) (rejecting argument that "mere 'suggestion' to premedicate cannot anticipate the '537 patent's premedication limitation"), *aff'd in part and vacated in part*, 246 F.3d 1368 (Fed. Cir. 2001); Ciba-Geigy Corp. v. Alza Corp., 864 F. Supp. 429, 437 (D.N.J. 1994) (rejecting argument that use of the word "might" fails to teach anything because the "tenor" of the disclosure "is not relevant" and all that matters is whether the reference identifies the invention), *aff'd in part, rev'd in part*, 68 F.3d 487 (Fed. Cir. 1995).

120. Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research, 304 F.3d 1221, 1229–30 (Fed. Cir. 2002) (prior art patent disclosing claimed "concept of creating a transgenic mouse with the mutated Swedish gene" did not anticipate that claim because the prior art inventor "did not make such a mouse and he did not tell (or know) which, if any, of the standard procedures from the scientific literature might be effective in achieving the complex series of transformations needed for a successful product").

121. *See Bristol-Myers*, 246 F.3d at 1378 (explaining that the scientist performing the experiment disclosed in a prior art reference "simply performed the claimed method on patients who did not show any antitumor effect. [The] performance of these same steps today would literally infringe the '803 claims; it is axiomatic that that which would literally infringe if later anticipates if earlier. Moreover, [the scientist] enabled the performance of those steps even though he did not achieve a favorable outcome, which was not a requirement of the claim.") (citation omitted).

122. Verizon Servs. Corp. v. Cox Fibernet Va., Inc., 602 F.3d 1325, 1337 (Fed. Cir. 2010).

A "reference is no less anticipatory if, after disclosing the invention, the reference then disparages it."[123]

[H] Art Need Not Be in Same Field As Invention to Anticipate

The concept of analogous art, which comes from the law of obviousness, does not apply to the law of anticipation. Anticipation generally cannot be defeated by arguing that the anticipatory reference comes from a field of art that is nonanalogous to the field of art relevant to the invention.[124]

[I] Device May Anticipate Claim to Method of Making

"[I]f a previously patented device, in its normal and usual operation, will perform the function which a [patentee] claims in a subsequent application for process patent, then such application for process patent will be considered to have been anticipated by the former patented device."[125]

§ 5:2.3 *Types of Prior Art*

[A] Printed Publications

No patent will be granted, and an existing patent will be rendered invalid under the pre-AIA statute, where the invention therein was "described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States . . . ."[126] "The 'printed publication' provision of § 102(b) was 'designed to prevent withdrawal by an inventor . . . of that which was already in the possession of the public.'"[127] Thus, "'public accessibility' has been called the touchstone in determining

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123. Celeritas Techs., Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361 (Fed. Cir. 1998).

124. *See* Revlon, Inc. v. Carson Prods. Co., 602 F. Supp. 1071, 1083 (S.D.N.Y. 1985) ("Unlike the doctrine of obviousness . . . anticipation does not require that the prior references be analogous or even relevant arts to the invention."), *aff'd*, 803 F.2d 676 (Fed. Cir. 1986); Twin Disc, Inc. v. United States, 231 U.S.P.Q. 417 (Ct. Cl. 1986) ("arguments that the alleged anticipatory prior art is 'nonanalogous art' or 'teaches away from the invention' or is not recognized as solving the problem solved by the claimed invention, is not . . . 'germane' to a rejection under section 102").

125. *In re* Ackenbach, 45 F.2d 437, 439 (C.C.P.A. 1930); *see also In re* King, 801 F.2d 1324, 1326–27 (Fed. Cir. 1986) (collecting cases on same point).

126. 35 U.S.C. § 102(b).

127. Bruckelmyer v. Ground Heaters, Inc., 445 F.3d 1374, 1378 (Fed. Cir. 2006) (quoting *In re* Wyer, 655 F.2d 221, 226 (C.C.P.A. 1981)).

whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)."[128]

The AIA provides that a "printed publication" prior to a patent's effective date is prior art unless it was disclosed less than one year before the effective filing date and it was derived from the inventor or is predated by a disclosure of the invention attributable to the inventor.[129]

[A][1] Accessibility of Publication

"A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it."[130] "If accessibility is proved, there is no requirement to show that particular members of the public actually received the information."[131]

Whether or not a publication has been cataloged or indexed is relevant to assessing accessibility; however, "a printed publication need not be easily searchable after publication if it was sufficiently disseminated at the time of its publication."[132] Furthermore, even if a reference was not distributed to the public but was merely presented

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128. *In re* Hall, 781 F.2d 897, 898–99 (Fed. Cir. 1986).

129. 35 U.S.C. § 102(a)(1), (b)(1) (AIA).

130. Suffolk Tech., LLC v. AOL Inc., 752 F.3d 1358, 1364–65 (Fed. Cir. 2014) (rejecting argument that newsgroup users for the newsgroup posting at issue were below the level of skill in the art because at the time "there were no courses or books concerning CGI," the poster himself "learned about CGI through self-study," the people with access to newsgroups were at universities or corporations, "a subset of people more likely to be skilled in the art," and defendant's own expert used newsgroups); *Bruckelmyer*, 445 F.3d at 1378; *see also* Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1568–69 (Fed. Cir. 1988) ("Accessibility goes to the issue of whether interested members of the relevant public could obtain the information if they wanted to."); *In re* Klopfenstein, 380 F.3d 1345, 1348 (Fed. Cir. 2004) ("the key inquiry is whether or not a reference has been made 'publicly accessible'").

131. *Constant*, 848 F.2d at 1569; *In re* Bayer, 568 F.2d 1357, 1361 (C.C.P.A. 1978) (a reference disclosed to only part of the public still qualifies as printed publication "so long as accessibility is sufficient 'to raise a presumption that the public concerned with the art would know of (the invention)'") (quoting Camp Bros. & Co. v. Portable Wagon Dump & Elevator Co., 251 F. 603, 607 (7th Cir. 1917)); Potter Instrument Co. v. Odec Comput. Sys., Inc., 499 F.2d 209, 210 n.2 (1st Cir. 1974) ("it is well established that limited circulation alone, does not disqualify a publication from contributing to the prior art").

132. *Suffolk Tech.*, 752 F.3d at 1365.

at a conference, it may qualify as a printed publication depending on a variety of factors.[133]

[A][2] Publication Date

A prior art reference is considered published upon the date that its copies reach the addressees, not when the publisher places them in the mail.[134] Furthermore, if accessibility of the reference must be demonstrated by relying on an index or database, inclusion in the index or database must be established before the critical date.[135]

[A][3] Examples

[A][3][a] Publication on FTP Site or Newsgroup

In *SRI International, Inc. v. Internet Security System, Inc.*, the Federal Circuit vacated and remanded the district court's grant of summary judgment of invalidity based on a paper located on an FTP site. The court held that the paper was not "intended for dissemination to the public" where awareness of the publication was limited to a peer-review committee and the FTP site was not organized in such a way as to allow for "meaningful research."[136] The court also noted the fact that the paper at issue was not "ready for public consumption," as it was "not a finished thesis" and was "still subject to pre-publication review."[137]

Unlike *SRI*, the Federal Circuit in *Suffolk Technology, LLC v. AOL Inc.* held that a Usenet newsgroup constituted a printed publication because while the FTP site in *SRI* was not publicized, the

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133. *See infra* section 5:2.3[A][3][b].

134. Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135 (Fed. Cir. 1986) (published only after the mailing); Carella v. Starlight Archery & Pro Line Co., 595 F. Supp. 613 (E.D. Mich. 1984) (not published if not received by addressee by the critical date); Protein Found., Inc. v. Brenner, 260 F. Supp. 519 (D.D.C. 1966) (not published if not received by addressee by the critical date); *Ex parte* Hudson, 18 U.S.P.Q.2d (BNA) 1322 (B.P.A.I. 1990) (not published if not delivered by the critical date); *Ex parte* Carnahan, 76 U.S.P.Q. (BNA) 335 (Pat. Off. Bd. App. 1947) (published when received by addressee); *see also* M.P.E.P. § 2128.02 ("A publication disseminated by mail is not prior art until it is received by at least one member of the public."); *cf. Ex parte* Albert, 18 U.S.P.Q.2d (BNA) 1325 (B.P.A.I. 1990) (published when received by addressee).

135. *In re* Lister, 583 F.3d 1307 (Fed. Cir. 2009).

136. SRI Int'l, Inc. v. Internet Sec. Sys., Inc., 511 F.3d 1186, 1196–98 (Fed. Cir. 2008); *see also* Pfizer, Inc. v. Teva Pharm. USA, Inc., 518 F.3d 1353, 1363 (Fed. Cir. 2008); Sun Pharm. Indus., Ltd. v. Eli Lilly & Co., 611 F.3d 1381, 1383 (Fed. Cir. 2010); Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 689 F.3d 1368, 1380 (Fed. Cir. 2012).

137. *SRI Int'l, Inc.*, 511 F.3d at 1197.

"entire purpose of the newsgroup postings" was "dialogue with the intended audience" and the particular post at issue "elicited at least six responses over the week following its publication" and "more people may have viewed the posts without posting anything themselves."[138] Furthermore, although the newsgroup posting was not searchable, the CGI-related post was "organized in a hierarchical manner, as evidenced by the name of the newsgroup at issue—comp.infosystems.www.authoring.cgi."[139]

[A][3][b] Presentation at a Conference

"[A]n entirely oral presentation at a scientific conference that includes neither slides nor copies of the presentation is without question not a 'printed publication' for the purposes of 35 U.S.C. § 102(b)."[140] Even "a presentation that includes a transient display of slides is likewise not necessarily a 'printed publication.'"[141] According to the Federal Circuit, the following factors are relevant to whether a temporarily displayed reference was made sufficiently accessible to the public to constitute a "printed publication" under section 102(b): "the length of time the display was exhibited, the expertise of the target audience, the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and the simplicity or ease with which the material displayed could have been copied."[142]

Thus, the Federal Circuit has held that an oral presentation of a paper at a congress "attended by 50 to 500 cell culturists" qualified as a printed publication because those in attendance "were actually told of the existence of the paper and informed of its contents by the oral presentation, and the document itself was actually disseminated without restriction to at least six persons."[143] Another court held that "photoprint display and description panels" presented during two Japanese trade shows qualified as a printed publication.[144] Slides displayed before the California Medical Association, however, did not qualify as a printed publication.[145]

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138. *Suffolk Tech.*, 752 F.3d at 1365.
139. *Id.* (emphasis added).
140. *Klopfenstein*, 380 F.3d at 1349 n.4.
141. *Id.*
142. *Id.* at 1350.
143. Mass. Inst. of Tech. v. Ab Fortia, 774 F.2d 1104, 1108–09 (Fed. Cir. 1985).
144. Tyler Refrigeration Corp. v. Kysor Indus. Corp., 601 F. Supp. 590, 603–04 (D. Del.), *aff'd on other grounds*, 777 F.2d 687 (Fed. Cir. 1985). Brochures distributed at the trade show describing the invention also qualified as a printed publication. *See* 601 F. Supp. at 604.
145. Regents of the Univ. of Cal. v. Howmedica, Inc., 530 F. Supp. 846, 860 (D.N.J. 1981) ("[T]he projection of the slides at the lecture was limited

[A][3][c] Nonconfidential but Limited Distribution

If a prior art reference is "one of an internal organizational character,"[146] a limited distribution of the reference is a publication if there is evidence of further dissemination;[147] but not if there is no evidence of further dissemination,[148] *or* if there is evidence of restrictions on further dissemination.[149]

More generally, distribution of the reference to a limited number of individuals or entities will not be held to be a printed publication where there is an expectation of confidential treatment by the recipients.[150] In *Kyocera Wireless Corp. v. International Trade Commission*, the Federal Circuit held that a "set of specifications for a second generation . . . mobile network" that was developed by "an independent standards organization comprised of telecommunications manufacturers and carriers" was a printed publication.[151] The specifications

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in duration and could not disclose the invention to the extent necessary to enable a person of ordinary skill in the art to make or use the invention."), *aff'd*, 676 F.2d 687 (3d Cir. 1982).

146. *Ex parte* Suozzi, 125 U.S.P.Q. (BNA) 445, 446 (Pat. & Trademark Office Bd. App. 1959).

147. Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc., 291 F.3d 1317 (Fed. Cir. 2002) (a genuine issue of material fact whether documents were publications where documents were released by a joint venture to "its three members and six participants").

148. Preemption Devices, Inc. v. Minn. Mining & Mfg. Co., 732 F.2d 903 (Fed. Cir. 1984) (mailing to one friend before the critical date "with a view to get some financial backing" failed to constitute a printed publication); *Suozzi*, 125 U.S.P.Q. (BNA) 445.

149. N. Telecomm., Inc. v. Datapoint Corp., 908 F.2d 931 (Fed. Cir. 1990) (no publication distributed to "approximately fifty persons or organizations involved in the AESOP-B project" before the critical date; the court emphasized the facts indicating restrictions on further dissemination: (1) one report "contained the legend 'reproduction or further dissemination is not authorized . . . not for public release'"; (2) other reports might also have contained such notices; and (3) the reports were housed in a library, access to which was restricted to authorized persons).

150. Cordis Corp. v. Bos. Sci. Corp., 561 F.3d 1319 (Fed. Cir. 2009); *but see* Garrett Corp. v. United States, 422 F.2d 874 (Ct. Cl. 1970) (publication when distributed to various governmental entities in England and the United States, and six commercial companies); Honeywell Inc. v. Sperry Rand Corp. & Ill. Sci. Devs., Inc. 180 U.S.P.Q. (BNA) 673 (D. Minn. 1973) (publication when distributed to persons representing various labs and companies).

151. Kyocera Wireless Corp. v. Int'l Trade Comm'n, 545 F.3d 1340 (Fed. Cir. 2008); Orion IP, LLC v. Hyundai Motor Am., 605 F.3d 967, 974 (Fed. Cir. 2010) (affirming denial of JMOL because evidence supported finding that reference qualified as prior art based on unrebutted testimony that catalog was used "by upwards of 150 to 200 salespersons").

"were drafted in smaller technical subcommittees," "U.S. companies took part in the ETSI work and had access to the GSM specifications through their European subsidiaries," the specifications were "visible to any member of the intended public without requesting them from an ETSI member," and "ETSI did not impose restrictions on ETSI members from disseminating information about the standard."[152]

[A][3][d] Thesis in University Library

In *In re Hall*, the Federal Circuit held that a thesis filed and indexed in a university library, where copies were freely available to the public, was a "printed publication."[153] However, in *In re Cronyn*,[154] the Federal Circuit held that college students' presentations of undergraduate theses to a defense committee of four faculty members that were not catalogued or indexed in a meaningful way were not printed publications.[155]

[A][3][e] Publicly Available Patent Prosecution Documents

Courts have found that publicly available patent applications that can be located through an indexing system qualify as "printed publications."[156] Similarly, a drawing in a patent application on file with a foreign patent office that was removed prior to patent issuance has been found to qualify as a "printed publication."[157] Patent

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152. *Kyocera*, 545 F.3d at 1350–51.
153. *In re* Hall, 781 F.2d 897, 899–900 (Fed. Cir. 1986).
154. *In re* Cronyn, 890 F.2d 1158 (Fed. Cir. 1989).
155. *Id*. at 1161. *See also* Ethicon, Inc. v. U.S. Surgical Corp., 762 F. Supp. 480, 500–01 (D. Conn. 1991), *aff'd*, 965 F.2d 1065 (Fed. Cir. 1992); Freeman v. Minn. Mining & Mfg. Co., 693 F. Supp. 134, 150 (D. Del. 1988), *aff'd in part and vacated in part on other grounds*, 884 F.2d 1398 (Fed. Cir. 1989); *In re* Bayer, 568 F.2d 1357, 1362 (C.C.P.A. 1978) ("[W]e are unconvinced that appellant's thesis defense before the graduate committee in its official capacity as arbiter of appellant's entitlement to a master's degree was somehow transmuted into a patent-defeating publication merely by depositing the thesis in the university library where it remained uncatalogued and unshelved as of the critical date in question.").
156. *In re* Wyer, 655 F.2d 221, 226 (C.C.P.A. 1981) (finding an Australian patent application that was classified, indexed and available for inspection more than two years before the filing date at issue along with a published abstract for the application qualified as a "printed publication").
157. Bruckelmyer v. Ground Heaters, Inc., 445 F.3d 1374, 1379 (Fed. Cir. 2006) (drawing in patent application cancelled prior to issuance qualified as a "printed publication" because "the '119 patent was classified and indexed [by the Canadian Patent Office] . . . further providing the

prosecution documents themselves need not be indexed to qualify as a "printed publication" if a published patent or patent application is properly indexed.[158]

[B] Known or Used by Others in This Country

Section 102(a) precludes patenting "inventions" that were already known to or used by others in this country because the "later inventor has not contributed to the store of knowledge."[159] Accordingly, under section 102(a), "in order to invalidate a patent based on prior knowledge or use, that knowledge or use must have been available to the public."[160] Thus, "notwithstanding abandonment of the prior use—which may preclude a challenge under section 102(g)—prior knowledge or use by others may invalidate a patent under section 102(a) if the prior knowledge or use was accessible to the public."[161]

[B][1] Known by Others

"For prior art to anticipate under 35 U.S.C. § 102(a) because it is 'known,' the knowledge must be publicly accessible."[162] "A presentation indicative of the state of knowledge and use in this country . . . qualifies as prior art."[163] On the other hand, drawings made "on a tablecloth" involving work by three individuals did not qualify as prior art.[164]

[B][2] Public Use

"The public use bar is triggered where, before the critical date, the invention is [(1)] in public use and [(2)] ready for patenting."[165] "The

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roadmap that would have allowed one skilled in the art to locate the '119 application").

158. *Id*. ("it does not matter whether the '119 application was catalogued or indexed 'in a meaningful way' because the '119 patent was indexed and could serve as a 'research aid'").
159. Woodland Tr. v. Flowertree Nursery, Inc., 148 F.3d 1368, 1370 (Fed. Cir. 1998).
160. *Id*.
161. *Id*.
162. Minn. Mining & Mfg. Co. v. Chemque, Inc., 303 F.3d 1294, 1306 (Fed. Cir. 2002); *Woodland Tr.*, 148 F.3d at 1370 (same); Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 139 (Fed. Cir. 1986) (same); *In re* Bass, 474 F.2d 1276, 1296 (C.C.P.A. 1973) (same).
163. Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1369 (Fed. Cir. 2000).
164. Nat'l Tractor Pullers Ass'n, Inc. v. Watkins, 205 U.S.P.Q. (BNA) 892 (N.D. Ill. 1980).
165. Minerva Surgical, Inc. v. Hologic, Inc., 59 F.4th 1371, 1377 (Fed. Cir. 2023).

'in public use' element of the bar is met if the invention was accessible to the public or was commercially exploited by the invention."[166] "Ready for patenting" may be shown by "proof of reduction to practice before the critical date" or "proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention."[167]

"Whether a patent is invalid due to a § 102(b) public use is a question of law based on underlying questions of fact."[168] When the asserted basis of invalidity is prior public use under section 102(b), "the party with the burden of proof must show that 'the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention.'"[169] "Section 102(b) may bar patentability by anticipation if the device used in public includes every limitation of the later claimed invention, or by obviousness if the differences between the claimed invention and the device used would have been obvious to one of ordinary skill in the art."[170]

A prior public use "need not be enabling" to anticipate.[171] It is sufficient to "determine whether the public use related to a device that embodied the invention."[172]

"The statutory phrase 'public use' does not necessarily mean open and visible in the ordinary sense; it includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor."[173] A prior use

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166. *Id*.
167. *Id*.
168. *Minn. Mining*, 303 F.3d at 1301.
169. Juicy Whip, Inc. v. Orange Bang, Inc., 292 F.3d 728, 737 (Fed. Cir. 2002) (quoting Scaltech Inc. v. Retec/Tetra LLC, 178 F.3d 1378, 1383 (Fed. Cir. 1999)).
170. Netscape Commc'ns Corp. v. Konrad, 295 F.3d 1315, 1321 (Fed. Cir. 2002).
171. Zenith Elecs. Corp. v. PDI Commc'ns Sys., Inc., 522 F.3d 1348, 1356 (Fed. Cir. 2008); *In re* Epstein, 32 F.3d 1559, 1568 (Fed. Cir. 1994) ("Beyond this 'in public use or on sale' finding, there is no requirement for an enablement-type inquiry.").
172. *Zenith*, 522 F.3d at 1356; J.A. LaPorte, Inc. v. Norfolk Dredging Co., 787 F.2d 1577, 1583 (Fed. Cir. 1986) ("[T]he question is not whether the sale, even a third party sale, 'discloses' the invention at the time of the sale, but whether the sale relates to that device that *embodies* the invention.").
173. New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1297 (Fed. Cir. 2002); *see also* Eolas Techs., Inc. v. Microsoft Corp., 399 F.3d 1325, 1334 (Fed. Cir. 2005) (vacating JMOL determination of no public use where inventor gave a "demonstration to two Sun Microsystems employees without confidentiality agreements"); Minerva Surgical, Inc. v. Hologic, Inc., 59 F.4th 1371 (Fed. Cir. 2023) (finding public use where

by a person other than the inventor "is not a bar when that prior use or knowledge is not available to the public."[174] On the other hand, "an inventor's own prior commercial use, albeit kept secret, may constitute a public use or sale . . . barring him from obtaining a patent."[175]

[B][2][a] Experimental Use Can Negate Prior Public Use

"The law recognizes that an inventor may test his invention in public without incurring the public use bar."[176] Known as the experimental use doctrine, it negates the application of the public use bar.[177] Thus, experimental uses, "even if apparently public in a colloquial sense, do not constitute a public use within the meaning of section 102."[178] The Supreme Court once stated that "[t]he use of an invention by the inventor himself, or of any other person under his direction, by way of experiment, and in order to bring the invention to perfection, has never been regarded as [a public] use."[179] "[E]xperimental use, which means perfecting or completing an invention to the point of determining that it will work for its intended purpose, ends with an actual reduction to practice."[180]

Experimental use is limited to testing "performed to perfect claimed features, or, in a few instances . . . to perfect features inherent to the claimed invention."[181] Objective evidence is required to demonstrate an experimental use.[182]

"there were no 'confidentiality obligations imposed upon' those who observed the Aurora device").

174. *Woodland Tr.*, 148 F.3d at 1371.

175. *Id*. at 1370.

176. *Netscape*, 295 F.3d at 1320.

177. *See* EZ Dock, Inc. v. Schafer Sys., Inc., 276 F.3d 1347, 1351 (Fed. Cir. 2002) ("This court has repeatedly stressed that evidence of experimental use does not give rise to a free-standing doctrinal exception to statutory bars, but instead operates to negate application of section 102(b)."). The experimental use doctrine, as a means to negate the effects of prior public use or sale, should not be confused with the experimental use defense to infringement. *See infra* section 10:5.11. The former is a means to negate a potential source of invalidity while the latter is a defense to infringement.

178. Baxter Int'l, Inc. v. Cobe Labs., Inc., 88 F.3d 1054, 1059 (Fed. Cir. 1996).

179. City of Elizabeth v. Am. Nicholson Pavement Co., 97 U.S. 126, 134 (1877).

180. RCA Corp. v. Data Gen. Corp., 887 F.2d 1056, 1061 (Fed. Cir. 1989).

181. *See* Electromotive Div. of Gen. Motors Corp. v. Transp. Sys. Div. of Gen. Elec. Co., 417 F.3d 1203, 1211 (Fed. Cir. 2005).

182. *Id*. at 1212 ("an inventor's subjective intent to experiment cannot establish that his activities are, in fact, experimental"); LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n, 958 F.2d 1066, 1072 (Fed. Cir. 1992)

Despite the long pedigree of the experimental use doctrine, "[f]ew decisions address how to determine if a pre-critical date public use or sale is experimental rather than a public use or sale under § 102(b)."[183]

[B][2][b] Burden of Proof

As with other invalidity defenses, the "accused infringer carries the burden of proving invalidity by clear and convincing evidence."[184] The patentee may rebut such evidence with "evidence showing that his public use or sale was primarily for purposes of experimentation, thus neutralizing the accused infringer's showing."[185] "[G]enerally, oral testimony of prior public use must be corroborated in order to invalidate a patent."[186]

[B][2][c] Evidentiary Factors

As explained above, courts look to "objective indicia . . . in determining whether the inventors engaged in experimentation." The Federal Circuit has provided a list of factors that may be considered:

(1) the necessity for public testing;

(2) the amount of control over the experiment retained by the inventor;

(3) the nature of the invention;

(4) the length of the test period;

(5) whether payment was made;

(6) whether there was a secrecy obligation;

("[A]n inventor's secretly held subjective intent to 'experiment,' even if true, is unavailing without objective evidence to support the contention.").

183. *See Electromotive*, 417 F.3d at 1212.

184. *See id*. at 1212 n.2; Schreiber Mfg. Co. v. Saft Am., Inc., 704 F. Supp. 759, 763 (E.D. Mich. 1989) ("When a sec. 102(b) bar is asserted, whether of the public use or on sale variety, the patent challenger has the burden to present sufficient facts to establish a prima facie case that the invention was either in 'public use' or 'on sale.'").

185. *See Electromotive*, 417 F.3d at 1212 n.2; *Schreiber*, 704 F. Supp. at 763 ("Once the patent challenger makes a proper prima facie showing of a sale in a summary judgment proceeding, it is incumbent on the patentee to come forward with some evidence showing that there is a genuine issue of material fact as to the sec. 102(b) bar.").

186. Juicy Whip, Inc. v. Orange Bang, Inc., 292 F.3d 728, 737–38 (Fed. Cir. 2002); Finnigan Corp. v. ITC, 180 F.3d 1354, 1367 n.10 (Fed. Cir. 1999) ("[O]ral testimony, unsupported by patents or exhibits, tending to show prior use of a device regularly patented is, in the nature of the case, open to grave suspicion.") (quoting Deering v. Winona Harvester Works, 155 U.S. 286, 300–01 (1894)).

(7) whether records of the experiment were kept;

(8) who conducted the experiment;

(9) the degree of commercial exploitation during testing;

(10) whether the invention reasonably requires evaluation under actual conditions of use;

(11) whether testing was systematically performed;

(12) whether the inventor continually monitored the invention during test; and

(13) the nature of the contacts made with potential customers.[187]

Not every factor carries equal weight, nor need every factor be applied in every case.[188] One factor, though, stands above all others in importance. The degree of control exercised by the inventor over the testing "is critically important"[189] as is "customer awareness" of the fact that the use is experimental.[190] Accordingly, "control and customer awareness ordinarily must be proven if experimentation is to be found."[191]

[B][2][d] When Do Clinical Trials Fall Within the Experimental Use Doctrine and Negate Public Use?

Whether a use is an experimental use depends on the scope of the claim. "Once an inventor realizes that the invention as later claimed indeed works for its intended purpose, further 'experimentation' may constitute a barring public use."[192] Consequently, "[t]he fact that a sale or use occurs under a regulatory testing procedure . . . does not make such uses or sales per se experimental for purposes of 35 U.S.C. § 102(b)."[193]

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187. *Electromotive*, 417 F.3d at 1213.
188. *See id*. ("This list is not exhaustive, and all of the experimentation factors may not apply in a particular case.").
189. *Id*. (quoting Lough v. Brunswick Corp., 86 F.3d 1113, 1120 (Fed. Cir. 1996)).
190. *Electromotive*, 417 F.3d at 1214 ("we hold not only that customer awareness is among the experimentation factors, but also that it is critical").
191. *Id*. at 1214–15.
192. New Railhead Mfg. L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1297 (Fed. Cir. 2002).
193. Pennwalt Corp. v. Akzona, Inc., 740 F.2d 1573, 1580 (Fed. Cir. 1984).

The claims at issue in the *Eli Lilly*[194] case were directed both to a particular compound, and to a method of treating schizophrenia with that compound.[195] The Southern District of Indiana held, and Federal Circuit affirmed, that the clinical trials were not a public use, as the studies "were conducted by Lilly personnel in the Lilly clinic" and there was "restricted access to the facility" and the studies were "fully controlled by Lilly."[196] Furthermore, the volunteers were all healthy and not suffering from schizophrenia, and were paid for their services.[197] In the alternative, the Southern District held that the clinical trials were experimental uses of the compound because "this type of atypical antipsychotic drug was highly unpredictable" and "the art was plagued with unpredicted side effects that rendered otherwise promising compounds useless in the clinical setting."[198] The product was conceived to replace a previous treatment for schizophrenia that had toxic effects in patients, and as a result, "testing olanzapine in actual schizophrenic patients was required to prove it would 'work for its intended purpose,' i.e. as a safe, atypical antipsychotic drug."[199] Consequently, the clinical trials were mere experimental uses.[200]

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194. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 364 F. Supp. 2d 820 (S.D. Ind. 2005), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).

195. *Eli Lilly & Co.*, 364 F. Supp. 2d at 851–52. The Federal Circuit also dealt with the experimental use doctrine and clinical trials in SmithKline Beecham Corp. v. Apotex Corp., 365 F.3d 1306 (Fed. Cir. 2004), but the opinion was vacated by 403 F.3d 1328 (Fed. Cir. 2005).

196. *Eli Lilly & Co.*, 364 F. Supp. 2d at 912; TP Labs., Inc. v. Prof'l Positioners, Inc., 724 F.2d 965 (Fed. Cir. 1984) (installation of orthodontic appliance in patients not public use because dentist-patient relationship involved a vow of secrecy).

197. *Eli Lilly & Co.*, 364 F. Supp. 2d at 912.

198. *Id*. at 914.

199. *Id*.

200. *Id*.; *see also Electromotive*, 417 F.3d at 1381 ("Lilly tailored its tests to their experimental drug safety and efficacy purpose, adequately monitored for results, and maintained confidentiality throughout the duration of the study. The trial court did not err in finding no public use."); Dey, L.P. v. Sunovion Pharm., Inc., 715 F.3d 1351 (Fed. Cir. 2013) (reversing and remanding summary judgment of invalidity based on prior use of claimed drug in defendant's clinical trials under section 102(b); finding fact question as to whether use was sufficiently "public" where investigators were subject to a written confidentiality obligation (though patients were not), patients were not informed of the identity of the drug or particular formulation and were informed that they could not provide the drug to others or keep unused supplies; noting "[m]any cases concern studies in which investigators sign strict confidentiality agreements but patients do not, and courts have routinely rejected the argument that such an arrangement necessarily strips the trial of confidentiality protection or renders it accessible to the public").

Finally, because, pursuant to section 102(b), an invalidating "public use" must occur in this country, clinical trials conducted in foreign countries do not raise "public use" issues under the statute.

[C] On-Sale Bar

The U.S. Supreme Court has held that the on-sale bar set forth in section 102(b) "applies when two conditions are satisfied before the critical date. First, the product must be the subject of a commercial offer for sale. . . . Second, the invention must be ready for patenting."[201] The elements of these two prongs are explained below in subsections [C][1] and [C][2].

"By phrasing the statutory bar in the passive voice, Congress indicated that it does not matter who places the invention 'on sale'; it only matters that someone—inventor, supplier or other third party—placed it on sale."[202]

As with prior public use of the invention, experimental use can negate what would otherwise be an invalidating prior sale of the invention. "If the sale was primarily for experimentation rather than commercial gain, then the sale is not invalidating under § 102(b)."[203] "[E]vidence of experimental use may negate either the 'ready for patenting' or 'public use' prong."[204]

The fact that the buyer or seller of a patented product is unaware of an inherent property claimed by the patentee is not relevant to determining applicability of the on-sale bar.[205]

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201. Pfaff v. Wells Elec., Inc., 525 U.S. 55, 67 (1998). On-sale bar cases decided under the totality of the circumstances test, which predates the Supreme Court's decision in *Pfaff*, should be considered in view of *Pfaff*. *See Electromotive*, 417 F.3d at 1209 ("Following *Pfaff*, we now apply the two-part test 'without balancing various polices [of the bar] according to the totality of the circumstances.'") (quoting Weatherchem Corp. v. J.L. Clark, Inc., 163 F.3d 1326, 1333 (Fed. Cir. 1998)).
202. Special Devices, Inc. v. OEA, Inc., 270 F.3d 1353, 1355 (Fed. Cir. 2001).
203. *Electromotive*, 417 F.3d at 1210. See *supra* section 5:2.3[B][2][d] for a discussion of experimental use.
204. Invitrogen Corp. v. Biocrest Mfg. L.P., 424 F.3d 1374, 1379–80 (Fed. Cir. 2005).
205. Abbott Labs. v. Geneva Pharm., Inc., 182 F.3d 1315, 1319 (Fed. Cir. 1999) ("[T]here is no requirement that a sales offer specifically identify all the characteristics of an invention offered for sale or that the parties recognize the significance of all of these characteristics at the time of the offer."). See also *supra* section 5:2.2[D] for a discussion of inherency.

[C][1] "Subject of a Commercial Sale"

[C][1][a] General Principles

As explained above, the first prong of *Pfaff* requires that "the product must be the subject of a commercial [sale] or offer for sale." "[T]wo elements are necessary" for determining if the first prong of *Pfaff* is satisfied.[206] A "court must find that (1) there was a 'commercial offer'; and (2) that offer was for the patented invention."[207]

[C][1][a][i] Commercial Offer or Sale

The first element requires "a determination of whether a commercial offer for sale [or sale] has occurred, applying traditional contract law principles."[208] A "single sale or offer for sale" satisfies the first prong.[209]

An offer for sale for purposes of the on-sale bar must be an offer that would, if accepted, result in a binding contract "under contract law principles."[210] Generally, courts "will look to the Uniform Commercial Code" to determine whether activity "rises to the level of a commercial offer for sale."[211]

"[T]he mere sale of manufacturing services by a contract manufacturer to an inventor to create embodiments of a patented product for the inventor does not constitute a 'commercial sale' of the invention."[212] "[A] commercial offer for sale made by a foreign entity that is directed to a United States customer at its place of business in the United States may serve as an invaliding [sic] activity."[213]

Offering its first interpretation of the on-sale bar in the AIA, the Federal Circuit found that where the existence of a sale was made known to the public, the sale constitutes prior art even if the public disclosure did not reveal the invention.[214]

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206. Sparton Corp. v. United States, 399 F.3d 1321, 1323 (Fed. Cir. 2005).
207. *Id*.
208. *Electromotive*, 417 F.3d at 1209 (quoting Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1352 (Fed. Cir. 2002)).
209. *Electromotive*, 417 F.3d at 1209.
210. Grp. One, Ltd. v. Hallmark Cards, Inc., 254 F.3d 1041, 1046–47 (Fed. Cir. 2001); Merck & CIE v. Watson Labs., Inc., 822 F.3d 1347 (Fed. Cir. 2016) (finding series of communications resulted in a commercial sale); Merck & CIE v. Watson Labs., Inc., 822 F.3d 1347 (Fed. Cir. 2016) (finding series of communications resulted in a commercial sale).
211. *Grp. One*, 254 F.3d at 1047.
212. Meds. Co. v. Hospira, Inc., 827 F.3d 1363, 1373 (Fed. Cir. 2016).
213. *Id*.
214. Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc., 855 F.3d 1356, 1371 (Fed. Cir. 2017).

[C][1][a][ii] Offer for the Patented Invention

As may be self-evident, the fact that an offer is not for the patented product at issue "is of utmost importance" in determining the applicability of the on-sale bar.[215]

[C][1][b] Research Agreements

Research agreements may, but do not necessarily, qualify as agreements for commercial sale sufficient to trigger a section 102(b) bar. One court, based on the following facts, concluded that an agreement was merely for research purposes and therefore not a basis for an on-sale bar:

- agreement for conducting R&D to achieve approval for a commercial plant in five years;
- disclosure of "technical information concerning claimed process";
- agreement could be terminated "at any time by giving sixty days notice" resulting in a non-exclusive license to practice claimed process; and
- if agreement not terminated when commercial phase reached, party "would receive an exclusive license" to make plants and "to sell the resultant products."[216]

On the other hand, another court, on different facts, found the combination of research and commercial purposes in an agreement triggered the on-sale bar:

- patentee "shall supply" purchaser at patentee's "fully allocated cost with all quantities of any Licensed Product reasonably required by [purchaser] for its own research, development, and test marketing, including that required to perform all preclinical and clinical studies"; and
- provision obligating patentee to supply purchaser's U.S. or worldwide "requirements of Active Ingredients . . . at prices and time schedules which are reasonably competitive with those of other sources."[217]

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215. *Sparton*, 399 F.3d at 1323.
216. *In re* Kollar, 286 F.3d 1326, 1330–31 (Fed. Cir. 2002).
217. Enzo Biochem, Inc. v. Gen-Probe, Inc., 424 F.3d 1276, 1279–82 (Fed. Cir. 2005). Meds. Co. v. Hospira, Inc., 791 F.3d 1368 (Fed. Cir. 2015) (reversing district court's finding of no commercial sale where only "manufacturing services" were sold "and title to the pharmaceutical batches did not change hands" because the batches (1) "met the already-approved

[C][1][c] Granting Licenses

"[M]erely granting a license to an invention, without more, does not trigger the on-sale bar of § 102(b)."[218] Even "[a]n offer to enter into a license under a patent" that includes future sales by the patentee to the licensee "of the invention covered by the patent when and if it has been developed . . . is not an offer to sell the patented invention that constitutes an on-sale bar."[219]

Nevertheless, a licensee cannot disguise "a sales price as a licensing fee" to avoid triggering the on-sale bar.[220] Courts will consider whether the communication constitutes "a definite offer to sell the product" based on general contract principles.[221] A license that contains a provision requiring the sale of a patented product does not avoid the on-sale bar by virtue of the fact that it also contains licensing provisions.[222]

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specifications for" the FDA-approved product; (2) were marked "with commercial product codes and customer lot numbers"; (3) were sent to the patentee "for commercial and clinical packaging"; and (4) had a value of $10 million each).

218. *Kollar*, 286 F.3d at 1331 (Fed. Cir. 2002); Mas-Hamilton Grp. v. LaGard, Inc., 156 F.3d 1206, 1217 (Fed. Cir. 1998) (granting "production rights in the invention" and "the exclusive right to market" it did not trigger on-sale bar); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1267 (Fed. Cir. 1986) ("[A]ssignment or sale of the rights in the invention and potential patent rights is not a sale of 'the invention' within the meaning of section 102(b).").

219. Elan Corp., PLC v. Andrx Pharm., Inc., 366 F.3d 1336, 1341 (Fed. Cir. 2004) (finding letter "not offering to sell naproxen tablets" to licensee, "but rather granting a license under the patent and offering [license] the opportunity to become its partner in the clinical testing and eventual marketing of such tablets at some indefinite point in the future"; noting that the letter "lacked any mention of quantities, time of delivery, place of delivery, or product specifications beyond the general statement that the potential product would be a 500 mg once-daily tablet containing naproxen").

220. *Id*.

221. *Id*.; *see also* Grp. One, Ltd. v. Hallmark Cards, Inc., 254 F.3d 1041, 1048 (Fed. Cir. 2001) ("Only an offer which rises to the level of a commercial offer for sale . . . constitutes an offer for sale under § 102(b).").

222. *Enzo Biochem*, 424 F.3d at 1282 (provision that "clearly imposes upon [licensor] the obligation to sell and on [licensee] the obligation to purchase a significant percentage of its U.S. and worldwide requirements" of the patented biological compound placed the invention "on-sale").

[C][1][d] Method Claims

The analysis of what constitutes a sale for purposes of method claims differs from claims to tangible objects.[223] "When money changes hands as a result of the transfer of title to the tangible item, a sale normally has occurred. A process, however, is a different kind of invention; it consists of acts, rather than a tangible item. It consists of doing something, and therefore has to be carried out or performed."[224] Of course, "sale by the patentee or a licensee of the patent of a product made by the claimed process would constitute such a sale because that party is commercializing the patented process in the same sense as would occur when the sale of a tangible patented item takes place."[225] "Actually performing the process itself for consideration would similarly trigger the application of § 102(b)."[226] Also selling the product with instructions to use the process can constitute a sale of the process.[227]

[C][2] "Ready for Patenting"

The ready for patenting condition "may be satisfied in at least two ways:

> by proof of reduction to practice before the critical date; or
>
> by proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention."[228]

One court found a DNA sequence was "ready for patenting" as a claim to a DNA probe for detecting *N. gonorrhoeae* because that sequence had been shown to be specific for *N. gonorrhoeae* and was recognized as being useful as a probe for *N. gonorrhoeae*, as well as

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223. *Kollar*, 286 F.3d at 1332 ("The Board also erred in failing to recognize the distinction between a claim to a product, device, or apparatus, all of which are tangible items, and a claim to a process, which consists of a series of acts" for purposes of its on-sale analysis.).
224. *Id*.
225. *Id*. at 1333.
226. *Id*.; Scaltech, Inc. v. Retec/Tetra, L.L.C., 269 F.3d 1321, 1328 (Fed. Cir. 2001).
227. *Enzo Biochem*, 424 F.3d at 1285 (sale of DNA probes for the detection of *N. gonorrhoeae* constituted an on-sale bar to claims covering the method of using the probes in a hybridization assay because the probes were sold with "accompanying instructions as to how to use the probe in the hybridization assay [and] . . . carrying out such a hybridization assay is inseparable from the compositions themselves").
228. Pfaff v. Wells Elec., Inc., 525 U.S. 55, 67–68 (1998).

the fact that the sequence "was shown to be the same as an ATCC deposit made for the purpose of supporting the patent application."[229]

[D] First Patented in a Foreign Country

Section 102(d) is designed "to encourage the filing of applications in the United States within a year of the foreign filing of a counterpart patent application."[230] This statute has three requirements that must be satisfied to invalidate a claim:

> First, the applicant must file an application on the invention in another country. Then, more than twelve months later, the applicant must file for a patent on the same invention in this country. Third, the foreign patent must issue before the applicant filed the U.S. patent application. If all three occur, then the U.S. patent is invalid under section 102(d).[231]

An invention is "patented" within the meaning of section 102(d) "[w]hen a foreign patent issues with claims directed to the same invention as the U.S. application"; the "validity of the foreign claims is irrelevant to the § 102(d) inquiry."[232] The section 102(d) bar applies as long as the foreign application fully discloses the invention, "regardless [of] whether the foreign patent contains claims to less than all aspects of the invention."[233]

[E] Admitted Prior Art

If a patentee states in the specification that something is in the prior art, then that constitutes a "binding" admission.[234]

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229. *Enzo Biochem*, 424 F.3d at 1279–85.
230. *In re* Kathawala, 9 F.3d 942, 947 (Fed. Cir. 1993).
231. Bayer AG v. Schein Pharm., Inc., 301 F.3d 1306, 1312 (Fed. Cir. 2002).
232. *Kathawala*, 9 F.3d at 945.
233. *Id*. at 947.
234. Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342 (Fed. Cir. 2007) (patentee's argument "that stem cells had not been proven to exist in cord blood prior to the experiments described in the patents" rejected because it was "contrary to the representation in the specification that the prior art disclosed stem cells in the cord blood"); Constant v. Advanced Micro Device, Inc., 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in the patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness."); *In re* Nomiya, 509 F.2d 566, 570–71 (C.C.P.A. 1975).

§ 5:3 Obviousness*

The mere fact that an invention is new does not merit a patent over the prior art. If an inventor's only contribution is an obvious modification or extension of prior teachings, no patent should be issued. The principle, however, can be stated more easily than applied.

§ 5:3.1 Statutory Provision: Section 103

[A] The Obviousness Standard: Section 103(a)

The requirement that a patent claim not be obvious in view of the prior art is codified in section 103(a) of the patent statute.[235] It states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.[236]

In other words, an invention is not patentable if it would have been obvious to someone of ordinary skill in the art as it existed when the invention was made.[237]

Nonobviousness, as the last sentence of section 103(a) makes clear, does not require a flash of genius; trial and error, or even luck can result in a nonobvious invention.[238] On the other hand, "the results

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* Written by Daniel L. Reisner.

235. *See* 35 U.S.C. § 103.

236. 35 U.S.C. § 103(a). As originally enacted by the 1952 Patent Act, section 103 was a single paragraph identical to the current section 103(a). *See* Pub. L. No. 82-593, § 103, 66 Stat. 792, 798 (1952).

237. Graham v. John Deere Co., 383 U.S. 1, 15 (1966); KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

238. Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000) (explaining that subjective motivations of inventors and actual path to invention is immaterial under hypothetical person of ordinary skill in the art standard); *see* Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) ("A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, *it makes no difference which*.") (emphasis added); *see also Graham*, 383 U.S. at 15 (rejecting a "flash of creative genius" as a condition of patentability).

of ordinary innovation are not the subject of exclusive rights under the patent laws."[239]

[B] Biotechnology Processes: Section 103(b)

Congress passed the Biotechnological Process Patent Act of 1995, adding subsection (b) to alleviate certain concerns of the biotechnology industry.[240] The AIA repealed section 103(b) for patents and applications that contained at any time a claim with an effective date on or after March 16, 2013, or a reference to any patent or application that contained such a claim at any time.[241]

In pertinent part, section 103(b) states:

> Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process[242] using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) of this section shall be considered nonobvious if—
>
> (A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and
>
> (B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.[243]

The amendment was a response to the Federal Circuit's decision in *In re Durden*,[244] which held that an otherwise obvious chemical process does not satisfy the nonobviousness requirement of section 103 simply because the specific starting material employed or the product obtained were novel and nonobvious.[245] By enacting subsection 103(b), Congress intended to limit the application of *In re Durden* because of its significant effect on the patentability of biotechnology processes, demonstrated by reports that the "PTO frequently cites this case in

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239. *KSR*, 127 S. Ct. at 1746.
240. Pub. L. No. 104-41, § 1, 109 Stat. 351 (1995).
241. 35 U.S.C. §§ 103, 146(n)(1) (AIA).
242. *See* 35 U.S.C. § 103(b)(3) (defining "biotechnological process" as used in this subsection). The legislative history defines "biotechnology" as "any technique that uses living organisms—or substances from those organisms—to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses." Biotechnology Process Patents, 141 CONG. REC. S15220 (Oct. 17, 1995).
243. 35 U.S.C. § 103(b)(1).
244. *In re* Durden, 763 F.2d 1406 (Fed. Cir. 1985).
245. *Id*. at 1408, 1410.

automatically rejecting applications for biotechnology processes."[246] According to Senator Hatch, co-author of the legislation, the subsection "resolves the *In re* Durden problem in our patent law by providing that a biotechnological process of making or using a product may be considered nonobvious if the starting material or resulting product is patentable."[247]

For an otherwise obvious biotechnological process to qualify for this exception to *In re Durden*, subsection (b) requires that any biotechnological process patent "shall also contain the claims to the composition of matter used in or made by that process, or shall, if such composition of matter is claimed in another patent, be set to expire on the same date as such other patent . . . ."[248]

Although section 103(b) is limited to biotechnology, the Federal Circuit's holding in *In re Ochiai*,[249] just one month after passage of section 103(b), undermined the *Durden* limitation for all processes, not merely biotechnological processes.[250]

[C] The Co-Ownership/Joint Venture Exception to Prior Art

[C][1] Pre-AIA Section 103(c)

Certain forms of nonpublic prior art can prevent one from obtaining patent rights. Prior patent applications that ultimately are issued (section 102(e)) or invention by another (sections 102(f) and (g)), for example, can prevent one from acquiring patent rights.[251] Prior to a

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246. Biotechnology Process Patents, 141 CONG. REC. S15220–02, S15221–22 (Oct. 17, 1995) (statement by Sen. Hatch) (explaining the inconsistent and erroneous application of *In re Durden* and its progeny to biotechnological process patenting and the vulnerability of inventors to foreign production based on their novel and nonobvious starting materials).

247. *Id*. at S15222.

248. 35 U.S.C. § 103(b)(2)(A)–(B). See *infra* section 7:7.2 for a discussion involving obviousness of processes to make antibodies.

249. *In re* Ochiai, 71 F.3d 1565, 1571–72 (Fed. Cir. 1995); *see also* M.P.E.P. § 2116.01.

250. *Ochiai*, 71 F.3d at 1571–72 ("[A]s we clearly indicated in *In re* Dillon . . . '[w]hen any applicant properly presents and argues suitable method claims, they should be examined in light of all . . . relevant factors, free from any presumed controlling effect of *Durden*' or any other precedent.").

251. OddzOn Prods., Inc. v. Just Toys, 122 F.3d 1396, 1401–02 (Fed. Cir. 1997) (citing *Bass*, 474 F.2d at 1290) (prior invention under subsections 102(e)–(g) by another who has not abandoned, suppressed, or concealed it constitutes prior art for purposes of the nonobviousness determination under section 103(a)); *see also In re* Zenitz, 333 F.2d 924, 926 (C.C.P.A.

series of amendments to section 103(c), this was a thorny problem for inventions arising from different research teams within a single institution or collaborations between different institutions. An institution's own non-public work or work with collaborators could prevent it from obtaining patent rights. This problem hampered research for many years until Congress changed the law.

First, Congress added subsection (c) by an amendment in 1984 to section 103[252] to limit a body of case law[253] that jeopardized the validity of patents for obviousness based on the prior, nonpublic work of fellow members of research teams working within a single organization.[254] The 1984 amendment excluded section 102(f) and (g) prior art from serving as obviousness prior art (but not as anticipatory prior art) if it was made, owned by the same person, or subject to an obligation of assignment to the same person when the invention was made.[255] As further amended in 1999,[256] section 103(c) stated:

> Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this

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1964) ("This court has held in a number of decisions that a United States patent speaks for all it discloses as of its filing date, even when used in combination with other references. . . . The question is not what prior art [applicant] was *aware of* at the time he made his invention, but whether his invention would be obvious in view of the *state of the art at the time it was made*.").

252. Patent Law Amendments Act of 1984, Pub. L. No. 98-622, Title 1, § 103, 98 Stat. 3384 (1984).

253. *See In re* Clemens, 622 F.2d 1029 (C.C.P.A. 1980); *In re* Bass, 474 F.2d 1276 (C.C.P.A. 1973).

254. *OddzOn*, 122 F.3d at 1401–03 (describing 1984 amendment to section 103); Kimberly-Clark Corp. v. Procter & Gamble Distrib. Co., 973 F.2d 911, 917 (Fed. Cir. 1992) (same); *see also* Section-by-Section Analysis: Patent Law Amendments of 1984, 130 CONG. REC. H10525 (1984), *reprinted in* 1984 U.S.C.C.A.N. 5827, 5833–34 (discussing the problems caused by *Bass* and *Clemens*).

255. *In re* Bartfeld, 925 F.2d 1450, 1452–53 (Fed. Cir. 1991) (stating that the 1984 amendment does not disqualify any section 102(e) prior art).

256. Congress amended section 103(c) to cover section 102(e) prior art within the safe harbor provision of section 103(c). *See* American Inventors Protection Act of 1999, Pub. L. No. 106-113, Title IV, § 4807(a), 113 Stat. 1501 (1999); *see also* Riverwood Int'l Corp. v. R.A. Jones & Co., 324 F.3d 1346, 1355 n.2 (Fed. Cir. 2003) ("Under a 1999 amendment to 35 U.S.C. § 103(c), subject matter which qualifies as prior art only under section 102(e) cannot preclude patentability under section 103 where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.").

> section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.[257]

Section 103(c) thus creates an exception to the rule for "prior art [that was] commonly owned with the claimed invention at the time the invention was made."[258]

Congress amended section 103(c) again in 2004 to include multiple organizations working together under a joint research agreement even if they had not agreed to assigning inventions to a single owner.[259] Under the statute, subject matter developed by another person and a claimed invention are deemed to be owned by the same person (even in the absence of such an assignment)[260] if the following criteria are met:

- "the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made"
- "the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement"
- the patent application discloses "the names of the parties to the joint research agreement."[261]

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257. The 1999 amendment is now codified at 35 U.S.C. § 103(c)(1).
258. *OddzOn*, 122 F.3d at 1403; *see Riverwood*, 324 F.3d at 1355 n.2.
259. Congress enacted the Cooperative Research and Technology Enhancement (CREATE) Act in 2004. *See* H.R. REP. NO. 108-425, at 1 (House Committee on the Judiciary describing the CREATE Act as designed "to promote research among universities, the public sector, and private enterprise").
260. *See* H.R. REP. NO. 108-425, at 6 ("The revised standard will permit one party to a joint research agreement who owns an invention to claim the benefit of 35 U.S.C. § 103(c) without requiring the potentially disqualifying subject matter and the invention be owned by a single entity or subject to an obligation of common assignment.").
261. 35 U.S.C. § 103(c)(2). *See* H.R. REP. NO. 108-425, at 9 ("In particular, § 103(c) is amended to add a new paragraph that permits reliance on the provisions of § 103(c) by parties that have not commonly assigned their rights to subject matter and the invention at the time a claimed invention was made. It does so by construing the phrase 'owned by the same person or subject to an obligation of assignment' in newly redesignated § 103(c)(1), to include circumstances in which the parties have entered into a qualifying joint research agreement before to making the invention.").

[C][2] AIA Section 102(b)(2)(C)

Pre-AIA section 103(c)(1) has been moved in the AIA to section 102(b)(2)(C). It provides that a disclosure is not prior art under subsection (a)(2) if "the subject matter disclosed and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person."

Similarly, pre-AIA section 103(c)(2), added to section 103 by the CREATE Act in 2004,[262] has been moved in the AIA to section 102(c).

[D] Incorporation of Section 102 Definition of Prior Art

[D][1] Pre-AIA

The provisions of section 102 define what is prior art for purposes of an obviousness determination (in addition to anticipation determinations).[263] Subsection 103(a) refers to prior art "disclosed or described as set forth in section 102,"[264] and subsection 103(c) specifically mentions "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102."[265] Subsection 103(c) also excludes subject matter that qualifies as prior art under subsections 102(e), (f), and (g) from qualifying as prior art for purposes of section 103 if certain requirements are satisfied concerning co-ownership of co-development.[266] The Federal Circuit has concluded that, at a minimum, invention under subsections 102(a), (b), (e), (f), and (g) qualify as prior art for determining obviousness.[267]

[D][2] AIA

The provisions of the AIA version of section 102 define what is prior art for purposes of an obviousness determination (in addition to anticipation determinations).[268] Under the AIA, section 103 provides:

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262. Pub. L. No. 108-453, 118 Stat. 3596 (2004).
263. See *supra* section 5:2.3 for a discussion of what qualifies as prior art under section 102.
264. 35 U.S.C. § 103(a).
265. 35 U.S.C. § 103(c).
266. See M.P.E.P. § 246 for a discussion of the effective dates of the various provisions of subsection 103(c).
267. *OddzOn Prods.*, 122 F.3d at 1402, 1403–04.
268. See *supra* section 5:2.3 for a discussion of what qualifies as prior art under section 102.

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

§ 5:3.2 *Overview of the Obviousness Question*

[A] The *Graham* Factors

If a single prior art reference teaches the invention, there is no need for courts to answer the question of what the prior art suggested to the skilled artisan and whether that would render an invention obvious because a claim to that invention is not valid and is anticipated by the prior art. On the other hand, when considering whether a combination of references renders a claim obvious, one must consider the four factors set forth by the Supreme Court in *Graham v. John Deere Co.*:[269]

(1) the scope and content of the prior art,

(2) the differences between the prior art and the claimed invention,

(3) the level of skill in the art, and

(4) the objective indicia of nonobviousness.[270]

The first three *Graham* factors, sometimes referred to as the primary considerations or the subjective evidence (because they were based on the mind of the hypothetical person of ordinary skill),[271] serve as the "foundational facts for the prima facie case of obviousness."[272] The fourth *Graham* factor is often referred to as the secondary consideration or, more accurately, the objective indicia of *nonobviousness*.[273] If a court or the PTO considers the *Graham* factors "and concludes

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269. Graham v. John Deere Co., 383 U.S. 1 (1966).
270. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing *Graham*, 383 U.S. at 15).
271. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379–80 (Fed. Cir. 1986).
272. *In re* Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997). For a further discussion of prima facie obviousness, see section 7:2.2[A].
273. *In re* Dembiczak, 175 F.3d 994, 998 (Fed. Cir. 1999); Para-Ordnance Mfg. v. SGS Imps. Int'l, Inc., 73 F.3d 1085, 1088 (Fed. Cir. 1995); *Hybritech*, 802 F.2d at 1379–80.

the claimed subject matter was obvious, the claim is invalid under § 103."[274]

The *Graham* factors may, in part, be considered as a means for determining whether multiple references can be combined to render a claim obvious.[275] For example,

> [w]here the level of skill is high, one may assume a keener appreciation of nuances taught by the prior art. Similarly, appreciation of the differences between the claims in suit and the scope of prior art references—a matter itself informed by the operative level of skill in the art—informs the question of whether to combine prior art references. At bottom, in each case the factual inquiry whether to combine references must be thorough and searching.[276]

Determination of whether references may be combined should also be based on "whether the elements exist in 'analogous art,' that is, art that is reasonably pertinent to the problem with which the inventor is concerned."[277]

[B] A Landmark Decision: *KSR v. Teleflex*

As described above, the Supreme Court, in *Graham v. John Deere*,[278] set forth several factors for courts to consider in determining obviousness. The Federal Circuit, however, concluded that the *Graham* factors by themselves merely provided "background" for an obviousness analysis, not a rule of decision.[279] After one has determined the content of the art, the differences between the art and the invention, and the level of skill in the art, one must still determine whether they point to obviousness or invention. As explained in the next section, the Federal

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274. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007). See *infra* sections 5:3.5 to 5:3.8 for discussion of each *Graham* factor.
275. McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351 (Fed. Cir. 2001) ("The assessment of whether to combine references in a given case has sometimes been viewed conceptually as a subset of the first *Graham* factor, the scope and content of the prior art. Although that view is not incorrect, accurate assessment of whether to combine references may require attention to other *Graham* factors.") (internal citations omitted). See *infra* section 5:3.3[A] for a discussion of when prior art can be combined.
276. *McGinley*, 262 F.3d at 1351.
277. *In re* Gorman, 933 F.2d 982, 986 (Fed. Cir. 1991).
278. Graham v. John Deere Co., 383 U.S. 1 (1966).
279. Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1289–90 (Fed. Cir. 2006) ("In *Graham*, the Court held that . . . the obviousness analysis begins with several basic factual inquiries . . . . After ascertaining these facts, the Court held that the obviousness *vel non* of the invention is then determined 'against th[e] *background*' of the *Graham* factors.").

Circuit developed standards to guide the evaluation of obviousness, requiring a *T*eaching, *S*uggestion or *M*otivation to combine elements from the prior art, subsequently referred to as "TSM."[280]

The Supreme Court, in *KSR International Co. v. Teleflex Inc.*,[281] criticized the Federal Circuit's use of the TSM test, "rejecting [its] rigid approach."[282] The Court reviewed its own prior precedents and concluded that an obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."[283] The Court did not entirely reject the reasoning behind the TSM test but rejected the Federal Circuit's requirement that TSM be required part of an obviousness determination.[284]

The *KSR* Court held that "a court must ask whether the improvement is more than the predictable use of prior art elements according to established functions."[285] A court must apply the *Graham* factors, "which continue to define the inquiry that controls" and determine whether "the claimed subject matter was obvious."[286] Accordingly, the entire body of case law prior to *KSR* applying the TSM test must be reevaluated in view of *KSR*.[287] Subsequent to *KSR*, the Federal Circuit has on certain facts found summary judgment appropriate[288] and on

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280. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007) ("the Federal Circuit has employed an approach referred to . . . as the 'teaching, suggestion, or motivation' test (TSM test)").

281. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

282. *Id*. at 1739.

283. *Id*. at 1741.

284. *Id*. ("[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. . . . Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents.").

285. *Id*. at 1740.

286. *Id*. at 1734.

287. *Id*.

288. *See, e.g.*, Hoffman-La Roche Inc. v. Apotex Inc., 748 F.3d 1326 (Fed. Cir. 2014); Ohio Willow Wood Co. v. Alps S., LLC, 735 F.3d 1333 (Fed. Cir. 2013); Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369 (Fed. Cir. 2013); Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356 (Fed. Cir. 2012); MySpace, Inc. v. GraphOn Corp., 672 F.3d 1250 (Fed. Cir. 2012); *In re* Katz Interactive Call Processing Patent Litig., 639 F.3d 1303 (Fed. Cir. 2011); Tokai Corp. v. Easton Enters., Inc., 632 F.3d 1358 (Fed. Cir. 2011); King Pharm., Inc. v. Eon Labs, Inc., 616 F.3d 1267 (Fed. Cir. 2010); Dow Jones & Co., Inc. v. Ablaise Ltd., 606 F.3d 1338 (Fed. Cir. 2010); Media Techs. Licensing, LLC v. Upper Deck Co., 596 F.3d 1334 (Fed. Cir. 2010); Perfect Web Techs., Inc. v. InfoUSA, Inc., 587 F.3d 1324 (Fed. Cir. 2009); Ball Aerosol & Specialty Container,

other facts has found summary judgment improper.[289]

§ 5:3.3 Criterion for Obviousness

The concept of "prima facie" obviousness is used to determine if an initial threshold showing of obviousness has been met.[290] It is frequently used as an evidentiary mechanism in Patent Office proceedings to determine if the examiner made a sufficient threshold showing of obviousness that shifts the burden to the applicant to present evidence of nonobviousness.[291] Prima facie obviousness is also used on occasion in patent infringement litigation when a court deems that a patent challenger has made a threshold showing of obviousness.[292] The failure to rebut a proper prima facie case of obviousness results in the unpatentability (in the PTO) or invalidity (in infringement litigation) of the claim at issue.[293] On the other hand, once sufficient rebuttal evidence has been presented, "the prime facie case dissolves, and the decision is made on the entirety of the evidence."[294]

Inc. v. Ltd. Brands, Inc., 555 F.3d 984 (Fed. Cir. 2009); Ricoh Co. v. Quanta Comput. Inc., 550 F.3d 1325 (Fed. Cir. 2008).

289. *See, e.g.*, Ivera Med. Corp. v. Hospira, Inc., 801 F.3d 1336 (Fed. Cir. 2015); Plantronics, Inc. v. Aliph, Inc., 724 F.3d 1343 (Fed. Cir. 2013); OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc., 701 F.3d 698 (Fed. Cir. 2012); Innovention Toys, LLC v. MGA Entm't, Inc., 637 F.3d 1314 (Fed. Cir. 2011); Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc., 617 F.3d 1296 (Fed. Cir. 2010); TriMed, Inc. v. Stryker Corp., 608 F.3d 1333 (Fed. Cir. 2010); Source Search Techs., LLC v. LendingTree, LLC, 588 F.3d 1063 (Fed. Cir. 2009); SüdChemie, Inc. v. Multisorb Techs., Inc., 554 F.3d 1001 (Fed. Cir. 2009).

290. See *infra* section 7:2.2[A] for a further discussion of prima facie obviousness.

291. *In re* Piasecki, 745 F.2d 1468, 1472 (Fed. Cir. 1984) ("The concept of *prima facie* obviousness in *ex parte* patent examination is but a procedural mechanism to allocate in an orderly way the burdens of going forward and of persuasion as between the examiner and the applicant.").

292. *See* Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1375–76 (Fed. Cir. 2000); Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000); Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006).

293. *See In re* Dillon, 919 F.2d 688, 693 (Fed. Cir. 1990) (claim to compound held unpatentable because Patent Office established prima facie case of obviousness unrebutted by applicant). "Patentability" is used to refer to the determination of whether the PTO should grant a patent. "Patent validity" is used to refer to a determination made in an infringement litigation when the validity of a granted patent is at issue.

294. *In re* Kumar, 418 F.3d 1361, 1366 (Fed. Cir. 2005); *see also In re* Oetiker, 977 F.2d 1443, 1445–46 (Fed. Cir. 1992); M.P.E.P. § 2142.

According to the Federal Circuit, prior to *KSR*, a prima facie obviousness determination ultimately requires consideration of:

(A) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and

(B) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.[295]

Given the Supreme Court's rejection of TSM as a requirement for finding obviousness, courts may reformulate the concept of prime facie obviousness. *KSR* held that the Federal Circuit's TSM test, which serves as a foundation for the prima facie obviousness test, cannot be applied as a requirement for determining obviousness, although it does serve as a "[h]elpful insight[ ]."[296] Several Federal Circuit decisions, even before *KSR*, noted that TSM need not be found in the prior art.[297] These courts held there is no requirement that "an actual teaching to combine" exists before finding obviousness based on multiple references.[298] This body of case law may serve as the foundation

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295. Noelle v. Lederman, 355 F.3d 1343, 1351–52 (Fed. Cir. 2004) (quoting *In re* Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991)). The obviousness analysis, like anticipation, requires that the prior art disclose each element of the claimed invention. Obviousness analysis often involves identification of a primary reference that is normally the closest prior art and secondary references that supply the teaching missing in the primary reference. *See In re* Merchant, 575 F.2d 865, 868 (C.C.P.A. 1978) ("A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference.").

296. *KSR*, 127 S. Ct. at 1741.

297. DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1364–70 (Fed. Cir. 2006) ("There is flexibility in our obviousness jurisprudence because a motivation may be found implicitly in the prior art."); Alza Corp. v. Mylan Labs., Inc., 484 F.3d 1286, 1291 (Fed. Cir. 2006).

298. *Id.*; *see also In re* Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) ("knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested [the invention] to those of ordinary skill in the art"); Cross Med. Prods. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1322 (Fed. Cir. 2005) ("the motivation to combine need not be found in prior art references, but equally can be found in the knowledge generally available to one of ordinary skill in the art," including knowledge of the problem to be solved).

for a post-*KSR* obviousness jurisprudence.[299]

[A] Combination of References/Prior Art Suggestion of the Invention

If a single prior art reference teaches the invention, there is no need for obviousness because normally the invention would be anticipated by that reference. Obviousness analysis, therefore, frequently involves combining multiple references. The mere fact, however, that multiple references exist that, if combined, reveal the invention, does not render it obvious. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."[300] "Broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence.'"[301] Nevertheless, there is a "need for caution in granting a patent based on the combination of elements found in the prior art."[302] The following sections describe various issues relevant to combining elements from the prior art.

[A][1] Problem Solved by Invention

Even prior to *KSR*, the courts held that evidence that prior art may be combined can be based on ordinary skill in the art, the nature of the problem to be solved, or, in the majority of cases, on the prior art.[303] A known problem may provide a basis to combine prior art,

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299. *See KSR*, 127 S. Ct. at 1743 ("We note that the Court of Appeals has since elaborated a broader conception of the TSM test than was applied in the instant matter. [citing *DyStar* and *Alza*]. . . . The extent to which they may describe an analysis more consistent with our earlier precedents and our decision here is a matter for the Court of Appeals to consider in its future cases.").

300. *KSR*, 127 S. Ct. at 1741 ("This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed obviousness almost of necessity will be combinations of what, in some sense, is already known.").

301. *Id*. (citing *In re* Dembiczak, 175 F.3d 994, 1000 (Fed. Cir. 1999), *abrogated on other grounds by In re* Gartside, 203 F.3d 1305 (Fed. Cir. 2000)); DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1366–67 (Fed. Cir. 2006); *Alza*, 464 F.3d at 1291.

302. *KSR*, 127 S. Ct. at 1739; Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp., 340 U.S. 147, 152 (1950) (a "patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men").

303. Brown & Williamson Tobacco Corp. v. Philip Morris, Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000) (citing Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573 (Fed. Cir. 1996)); *see In re* Rouffet, 149

however, this should be distinguished from the situation where the nature of the problem is not understood. In that case "a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified."[304]

The Supreme Court, in *KSR*, reiterated the importance of considering the impact of known problems rendering obvious a claimed solution. If a patent claim covers an obvious solution to a known problem the claim is obvious.[305] This is true even if its invention provides a nonobvious solution to another problem.[306] Thus, courts "are not limited to the same motivation that may have motivated the inventors."[307]

[A][2] Hindsight

"A fact finder should be aware . . . of the distortion raised by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."[308] Evidence of motivation to combine cannot come from hindsight.[309] "[R]ejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner [or accused infringer] to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of

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F.3d 1350, 1359 (Fed. Cir. 1998) (explaining that the suggestion usually comes from the teachings of the prior art references).

304. *In re* Namiya, 509 F.2d 566, 571 (C.C.P.A. 1975) (quoting *In re* Sponnoble, 405 F.2d 578, 585 (C.C.P.A. 1969)).

305. *KSR*, 127 S. Ct. at 1741 ("One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.").

306. *Id*. ("Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.").

307. Par Pharm., Inc. v. Twi Pharm., Inc., 773 F.3d 1186, 1197 (Fed. Cir. 2014); Alcon Research, Ltd. v. Apotex Inc., 687 F.3d 1362, 1369 (Fed. Cir. 2012) ("We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had.").

308. *KSR*, 127 S. Ct. at 1742 (2007); Graham v. John Deere Co., 383 U.S. 1, 36 (1966) (warning against a "temptation to read into the prior art the teachings of the invention in issue" and "against slipping into the use of hindsight").

309. Tex. Instruments v. U.S. Int'l Trade Comm'n, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("respondents can do no more than piece the invention together using the patented invention as a template. Such hindsight reasoning is impermissible").

the claimed invention."[310] Nevertheless, "the law does not require that the references be combined for the reasons contemplated by the inventor."[311] Moreover, the risk of hindsight cannot be used to justify, as the Federal Circuit has done prior to *KSR*, a requirement that suggestion, teaching, or motivation be found in the prior art to show obviousness.[312]

[A][3] Number of References by Itself Does Not Determine Obviousness

The criterion for determining obviousness "is not the number of references, but what they would have meant to a person of ordinary skill in the field of the invention."[313] The Federal Circuit has found that a "large number of cited references does not negate the obviousness of the combination [where] the prior art uses the various elements for the same purposes as they are used by" the patent applicant.[314]

[A][4] Uncorroborated Expert Testimony Not Evidence of Obviousness

Prior to *KSR*, many courts held that expert testimony that an invention is obvious unsupported by prior art references does not constitute evidence of obviousness.[315]

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310. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting *Rouffet*, 149 F.3d at 1357–58).

311. *In re* Beattie, 974 F.2d 1309, 1312 (Fed. Cir. 1992); *KSR*, 127 S. Ct. at 1741 ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls.").

312. *KSR*, 127 S. Ct. at 1734.

313. *In re* Gorman, 933 F.2d 982, 986 (Fed. Cir. 1991) (affirming rejection "in view of thirteen references"); Kan. Jack, Inc. v. Kuhn, 719 F.2d 1144, 1149 (Fed. Cir. 1983) (fact that teachings repeated in numerous references strengthened obviousness determination); *In re* Miller, 159 F.2d 756, 758–59 (C.C.P.A. 1947) (rejecting argument that need for eight references to support claim rejection indicates patentability); *but see* Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1383 (Fed. Cir. 1986) (combination of about twenty references that "skirt[ed] all around" the invention did not render it obvious).

314. *Gorman*, 933 F.2d at 987.

315. Upjohn Co. v. Mova Pharm. Corp., 225 F.3d 1306, 1311 (Fed. Cir. 2000); ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546 (Fed. Cir. 1998) ("Lydell points to no evidence supporting the obviousness determination, other than the conclusory opinion of its expert witness."); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination."); *In re* Fine, 837 F.2d 1071, 1074 (Fed. Cir.

Subsequent to *KSR*, one court rejected an "unsupported statement" by an expert, finding that it "cannot refute the detailed testimony" of the defendant's obviousness expert.[316]

Expert testimony, however, corroborated or not, may not be needed to substantiate the motivation to combine when the rationale is simple enough. "[W]e have recognized that some cases involve technologies and prior art that are simple enough that no expert testimony is needed."[317]

[A][5] Art That Teaches Away from Invention

Art that teaches away from the invention tends to show nonobviousness.[318] A reference teaches away when the skilled artisan "would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken

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1988) (references combined by examiner, using hindsight reconstruction, without evidence to support the combination and in the face of contrary teachings in the prior art, do not establish a prima facie case of obviousness); RCA Corp. v. Data Gen. Corp., 701 F. Supp. 456, 470–77 (D. Del. 1988) (conclusory statements of expert witness that combination of elements would have been within the skill of the art "contribute little to an obviousness analysis"), *aff'd*, 887 F.2d 1056 (Fed. Cir. 1989); *cf.* Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1322 (Fed. Cir. 2005) (reversing nonobviousness ruling because "the motivation to combine need not be found in prior art references, but equally can be found in the knowledge generally available to one of ordinary skill in the art" including knowing the problem to be solved).

316. Daiichi Sankyo Co. v. Apotex, Inc., 501 F.3d 1254 (Fed. Cir. 2007) (nonprecedential).

317. Intercontinental Great Brands v. Kellogg N. Am. Co., Nos. 2015-2082 and 2015-2084, 2017 WL 3906853, at *9, 869 F.3d 1336, 1348 (Fed. Cir. 2017) (citing Wyers v. Master Lock Co., 616 F.3d 1231, 1239 (Fed. Cir. 2010) ("KSR and our later cases establish that the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony."); Perfect Web Techs. v. InfoUSA, Inc., 587 F.3d 1324, 1329 (Fed. Cir. 2009); Sundance, Inc. v. DeMonte Fabricating Ltd., 550 F.3d 1356, 1365 (Fed. Cir. 2008)).

318. *See, e.g.*, *KSR*, 127 S. Ct. at 1740 ("[W]hen the prior art teaches away from combining certain elements, discovery of a successful means of combining them is more likely to be nonobvious."); Micro Chem., Inc. v. Great Plains Chem. Co., 103 F.3d 1538, 1546–47 (Fed. Cir. 1997) (even though all claimed elements were known, prior art "led away" from combination); Hiedelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072 (Fed. Cir. 1994) (prior art "encumbered by limitations [ ] that had not previously been overcome"); *Fine*, 837 F.2d at 1074 ("error to find obviousness where references 'diverge from and teach away from the invention at hand'") (quoting W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1550 (Fed. Cir. 1983)).

by the applicant."[319] Known disadvantages of old devices may also be considered in determining obviousness.[320] Furthermore, references may implicitly teach away if the combination of references yields a "seemingly inoperative device"[321] or if a reference appears to teach that the product would not have the desired property.[322] A reference that merely teaches an alternative to the invention does not necessarily teach away from it.[323] However, prior art may implicitly teach away from one solution if every reference teaches a different solution.[324] Well-known teachings may not be negated by a warning from a single reference.[325] Merely expressing some doubt also does not constitute teaching away.[326] "A reference does not teach away . . . if it merely expresses a general preference for an alternative invention but

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319. *In re* Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994) ("The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.").

320. United States v. Adams, 383 U.S. 39, 52 (1966) ("[K]nown disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness."); *but see In re* Mouttet, 686 F.3d 1322 (Fed. Cir. 2012) (holding patent invalid as obvious where it replaced prior art optical circuitry with electrical circuitry despite prior art suggestion that electrical circuitry would be inferior for some purposes, because there was no suggestion in prior art that the combination "should not" or "cannot" be implemented).

321. *In re* Sponnoble, 405 F.2d 578, 587 (C.C.P.A. 1969).

322. *In re* Caldwell, 319 F.2d 254, 257 (C.C.P.A. 1963).

323. Para-Ordnance Mfg. v. SGS Imps. Int'l, Inc., 73 F.3d 1085, 1090 (Fed. Cir. 1995); *see also* Pozen Inc. v. Par Pharma., Inc., 696 F.3d 1151 (Fed. Cir. 2012) (claim terms added during prosecution—"therapeutic package," "finished pharmaceutical container," and "said container further containing or comprising labeling directing the use of said package in the treatment of migraine"—supported by disclosure of "several dosage forms, including an oral unit dosage, to teach treating migraines" because the skilled artisan "would know these pharmaceutical dosages are administered to a patient in containers or packages with labeling and inserts with dosage instructions.").

324. Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1343 (Fed. Cir. 2011).

325. *In re* Gorman, 933 F.2d 982, 987 (Fed. Cir. 1991) ("admonition that lollipops on sticks are dangerous to children" does not teach away because "candy on a stick is too well known").

326. *In re* Kubin, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("Mathew's quasi-agnostic stance toward the existence of a human homologue of the 2B4 gene cannot fairly be seen as dissuading one of ordinary skill in the art from combining Mathew's teachings with those of Valiante.").

does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed."[327]

[A][6] Prior Art Must Be Read As a Whole

The prior art must be read as a whole, not just selected portions.[328]

[A][7] Inherency

An obviousness determination includes consideration of "what the prior art teaches explicitly and inherently."[329] Accordingly, the Federal Circuit has "recognized that inherency may supply a missing claim limitation in an obviousness analysis."[330] "It is long settled that in the context of obviousness, the 'mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a thing drawn to those things from the prior art.'"[331]

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327. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009) (quoting *In re* Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004)); *accord* Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738–39 (Fed. Cir. 2013) (references merely showing "increased side effects" from increasing adapalene concentration from 0.03% to 0.1% fail to teach away from 0.3% because nothing in the references "indicate[s] that increasing the concentration to 0.3%" would increase the side effects "enough to dissuade the development of a 0.3% adapalene product" and in fact they did not prevent the prior art development of a commercial 0.1% product).

328. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 448 (Fed. Cir. 1988) ("'It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.'") (quoting *In re* Wesslau, 353 F.2d 238, 241 (C.C.P.A. 1965)).

329. *In re* Zurko, 258 F.3d 1379, 1383 (Fed. Cir. 2001); *In re* Grasselli, 713 F.2d 731, 739 (Fed. Cir. 1983) (considering affidavits because they could potentially support "*inferences of inherency* which underlie the PTO's § 103 rejections").

330. Par Pharm., Inc. v. Twi Pharm., Inc., 773 F.3d 1186, 1194–95 (Fed. Cir. 2014). Applying this principle, the Federal Circuit affirmed rejection of claims over multiple references even if they did not expressly teach the claimed element of redirecting noise by refraction because the evidence supported finding that the prior art teaching of reducing noise by mixing "inherently discloses redirection of noise." *In re* Napier, 55 F.3d 610, 613 (Fed. Cir. 1995).

331. Persion Pharm. LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184, 1190 (Fed. Cir. 2019) (quoting *In re* Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981)); *see also* Gen. Elec. Co. v. Jewel Incandescent Lamp Co., 326

The Federal Circuit has, however, also warned that that "the use of inherency in the context of obviousness must be carefully circumscribed because '[t]hat which may be inherent is not necessarily known' and that which is unknown cannot be obvious."[332] Even if inherency does not apply because the "necessarily" present requirement is not satisfied, a court may find a claim obvious if the prior art discloses the claimed method steps for the same purpose even regardless of whether the prior art discloses the claimed result.[333]

[B] Predictability/Reasonable Expectation of Success

[B][1] The Standard

The Supreme Court mentioned predictability five times in its *KSR* decision on obviousness, stressing its importance in determining patentability over combinations of known elements. "The combination of familiar elements according to known methods is likely to be obvious when it yields no more than predictable results."[334] Combinations of known elements may not be predictable if the prior art teaches away from the combination,[335] if the elements are not combined "according to their established functions,"[336] or if the combination

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U.S. 242, 249, 66 S. Ct. 81, 90 L. Ed. 43 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect.").

332. Southwire Co. v. Cerro Wire LLC, No. 2016–2287, 2017 WL 3927195, at *3, 870 F.3d 1306, 1310–11 (Fed. Cir. Sept. 8, 2017) (quoting Honeywell Int'l v. Mexichem Amanco Holding S.A., 865 F.3d 1348, 1354 (Fed. Cir. 2017) (quoting *In re* Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993))).

333. *Id.*, 2017 WL 3927195, at *4, 870 F.3d at 1311 ("Our predecessor court has held that where '*all process limitations . . . are expressly disclosed* by [the prior art reference], except for the *functionally expressed* [limitation at issue],' the PTO can require an applicant 'to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.' *In re* Best, 562 F.2d 1252, 1254–55 (CCPA 1977).").

334. *KSR*, 127 S. Ct. at 1739.

335. *Id.*; see also *supra* section 5:3.3[A][5] for a further discussion of art that teaches away.

336. *KSR*, 127 S. Ct. at 1740; Anderson's-Black Rock Inc. v. Pavement Salvage Co., 396 U.S. 57, 60–62 (1969) (combination of radiant heat burner and paving machine "performed a useful function" but found obvious because "it added nothing to nature and quality of the radiant-heat burner already patented"); Sakraida v. AG Pro, Inc., 425 U.S. 273, 282 (1976) (arranging "old elements with each performing the same function it had been known to perform" is obvious); Asyst Tech., Inc. v. Emtrak, Inc., 544 F.3d 1310, 1315 (Fed. Cir. 2008) ("two alternative means of connecting the transducer stations [known in the art] are buses and multiplexers"; affirming

creates some "new synergy."[337] Prior to *KSR*, the Federal Circuit held that obviousness requires that the prior art provides one of ordinary skill with a reasonable expectation of success.[338] On the other hand, the Federal Circuit also acknowledged that "[o]bviousness does not require absolute predictability of success."[339] Subsequent to *KSR*, the Federal Circuit reaffirmed its reasonable expectation of success requirement.[340]

Challenges faced when developing a commercial embodiment of the invention that extend beyond satisfying the limitations of the claim have little relevance in evaluating whether there was a reasonable expectation of success.[341]

The following examples illustrate the "reasonable expectation of success" test:

JMOL of obviousness because the patentee "has not suggested that the [claimed] multiplexer in its system operates in any way other than its conventional manner or that replacing a bus with a multiplexer would be an operation that would not be familiar to anyone of skill in the art" and the "evidence showed that the choice between the two devices was a familiar one that was based on well-known considerations").

337. *KSR*, 127 S. Ct. at 1740.

338. *In re* Vaeck, 947 F.2d 488, 492 (Fed. Cir. 1991).

339. *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) ("Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious.").

340. Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1432 (Fed. Cir. 2007) (when relying on a "combination" of references, "the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition, device, or carry out the claimed process, and would have a reasonable expectation of success in doing so").

341. Allergan, Inc. v. Sandoz Inc., 726 F.3d 1286 (Fed. Cir. 2013) (reversing in part summary judgment of nonobviousness of claims to combination eye care products with two different active ingredients because the difficulty in formulating a branded commercial embodiment of the claimed formulation is not particularly probative where commercial embodiment contains many elements in addition to those claimed: "There is no requirement that one of ordinary skill have a reasonable expectation of success in developing [the particular commercial embodiment]. Rather, the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention.").

In re Kubin[342]

Claim: "An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48."

Prior Art: Prior reference disclosing the protein encoded by the claimed sequence, a monoclonal antibody specific to that protein and "a five-step protocol for cloning nucleic acid molecules encoding" this protein using the antibody.

Holding: "These references, which together teach a protein identical to NAIL, a commercially available monoclonal antibody specific for NAIL, and explicit instruction for obtaining the DNA sequence for NAIL, are not analogous to prior art that gives 'no direction as to which of many possible choices is likely to be successful' or 'only general guidance as to the particular form of the claimed invention or how to achieve it.' *O'Farrell*, 853 F.2d at 903. . . . Thus, this court affirms the Board's conclusion as to obviousness."

Alza Corp. v. Mylan Laboratories, Inc.[343]

Claim: Sustained-release oxybutynin formulation for oral administration.

Prior Art: Expert testimony and prior art showed that a person of ordinary skill "would have expected a general, albeit imperfect, correlation between a drug's lipophilicity and its colonic absorptivity."

Holding: "Accordingly, we cannot perceive clear error in the district court's factual findings that while colonic absorption was not guaranteed, the evidence, viewed as a whole, is clear and convincing that a person of ordinary skill in the art would nonetheless have perceived a reasonable likelihood of success."

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342. *In re* Kubin, 561 F.3d 1351 (Fed. Cir. 2009).
343. Alza Corp. v. Mylan Labs., Inc., 484 F.3d 1286, 1295 (Fed. Cir. 2006); *see also Pharmastem*, 491 F.3d 1342; Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367–69 (Fed. Cir. 2007).

In re O'Farrell[344]

Claim: Method for making "a predetermined protein" using a heterologous DNA in a bacteria.

Prior Art: Prior art used a gene for ribosomal RNA as the heterologous gene and predicted that substituting a gene for a predetermined protein in its place should also result in the production of a protein.

Holding: Prior art provided a reasonable expectation of success by explicitly suggesting the substitution that is the difference between the claimed invention and the prior art, and presenting preliminary evidence suggesting that the method could be used to make proteins.

Merck & Co. v. Biocraft Laboratories, Inc.[345]

Claim: Claimed combination of two known compounds.

Prior Art: Patent teaching 1,200 different combinations, including the claimed combination, for the same purpose as in the claim at issue.

Holding: Combination in claimed 10 to 1 ratio was "reached by means of routine procedures, and produced only predictable results."

Ex parte Erlich[346]

Claim: Hybridomas producing monoclonal antibodies specific for human fibroblast interferon.

Prior Art: Published references documenting success researchers had in adapting and extending fundamental technique of Kohler and Milstein to other antigens to produce monoclonol antibodies specific to those antigens.

Holding: "Person of ordinary skill in the art at the time of present invention . . . would have . . . entered this venture with a reasonable expectation of success given the large number of successes other researchers had at that point in adapting hybridoma technology to other antigens."

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344. *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).
345. Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804 (Fed. Cir. 1989).
346. *Ex parte* Erlich, 22 U.S.P.Q.2d (BNA) 1463 (B.P.A.I. 1992).

[B][2] "Obvious to Try"

Prior to *KSR*, the Federal Circuit often stated that obvious to try is not the standard to determine obviousness under section 103.[347] The Federal Circuit, however, warned that "the meaning of this maxim is sometimes lost."[348] Pre-*KSR* courts explained that an effort "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" is only obvious to try.[349]

The Supreme Court, however, in *KSR*, criticized the Federal Circuit's statement that "obvious to try" does not mean that something is obvious when applied to a limited universe of possibles with predictable outcomes.[350] "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."[351] After *KSR*, the Federal Circuit, applying *KSR* and *O'Farrell*, held that claims to a specified nucleic acid sequence were invalid over a prior reference disclosing the protein encoded by that sequence, a monoclonal antibody specific to that protein and "a five-step protocol for cloning

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347. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986).

348. *O'Farrell*, 853 F.2d at 903 ("Any invention that would in fact have been obvious under § 103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?").

349. *Id*. (an effort "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it" is also only obvious to try); Novo Industri A/S v. Travenol Labs., Inc., 677 F.2d 1202, 1208 (7th Cir. 1982); *In re* Yates, 663 F.2d 1054, 1057 (C.C.P.A. 1981); *In re* Antonie, 559 F.2d 618, 621 (C.C.P.A. 1977)); *Hybritech*, 802 F.2d at 1380 ("At *most*, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished."); *In re* Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966).

350. *KSR*, 127 S. Ct. at 1739, 1742 ("The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'").

351. *Id*. at 1742; Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1363, 1367 (Fed. Cir. 2007) (holding obvious claims to besylate salt of amlodipine over reference providing "ample motivation to narrow the genus of 53 pharmaceutically-acceptable unions . . . to a few, including benzene sulphonate").

nucleic acid molecules encoding" this protein using the antibody.[352] On the other hand, obvious to try was not sufficient when, instead of identifying "predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds anyone of which could have been selected as a lead compound for further investigation."[353] Obvious to try was also not sufficient when defendants' expert failed to explain "why a skilled artisan would have chosen a bioequivalent PK profile in the absence of a known PK/PD relationship."[354]

The Federal Circuit summarized the post-*KSR* obvious-to-try law:

> We have previously identified two categories of impermissible "obvious to try" analyses that run afoul of KSR and § 103: when what was "obvious to try" was (a) to vary all parameters or try every available option until one succeeds, where the prior art gave no indication of critical parameters and no direction as to which of many possibilities is likely to be successful; or (b) to explore a new technology or general approach in a seemingly promising field of experimentation, where the prior art gave only general guidance as to the particular form or method of achieving the claimed invention.[355]

[C] Enablement of Obvious Teaching Required

An applicant or patentee may rebut a prima facie case of obviousness by showing that the prior art did not enable one skilled in the art to produce the now-claimed invention.[356]

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352. *In re* Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009); *cf. In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995) (holding (pre-*KSR*) that DNA encoding HBGFs not rendered obvious by partial amino acid sequence for HBGF).
353. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007).
354. *In re* Cyclobenzaprine Hydrochloride, 676 F.3d 1063, 1073 (Fed. Cir. 2012) ("[T]he absence of such testimony suggests that skilled artisans would not have encountered finite, small, or easily traversed options in developing a therapeutically effective, extended-release formulation.").
355. *In re* Copaxone Consol. Cases, 906 F.3d 1013, 1025 (Fed. Cir. 2018).
356. *In re* Payne, 606 F.2d 303, 314–15 (C.C.P.A. 1979) ("the presumption of obviousness based on close structural similarity is overcome where the prior art does not disclose or render obvious a method for making the claimed compound"); *In re* Hoeksema, 399 F.2d 269, 274 (C.C.P.A. 1968) ("the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds").

[D] Ranges

"A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the art."[357] For example, the Federal Circuit found a claimed composition prima facie obvious because it required "about 1 to 3 percent" rhenium and the prior art "taught compositions with 0 to 7 percent rhenium."[358]

The same principle—that overlapping claimed and prior ranges support a finding of prima facie obviousness—applies even where the prior art merely discloses overlapping ranges of "structurally and functionally similar compounds."[359] Because the art teaches (1) "stable formulations of naloxone, naltrexone, and methylanaltrexone," (2) that all three "are well-known opioid antagonists," (3) that each has "remarkably similar structures," and (4) that pH ranges for the first two that overlap with the claimed range for methylanaltrexone, the Federal Circuit held that claims to formulations of methylanaltrexone at a pH of 3.0 to 4.0 were prima facie obvious.[360]

[E] Unexpected Results

[E][1] General Rule

A finding of "unexpected results" is "tantamount to a finding of nonobviousness."[361] Thus, evidence of unexpected results "must be considered in evaluating the obviousness of a claimed invention."[362] Such evidence includes "comparative data in the specification," factual evidence submitted by the patentee, and evidence of "synergy."[363] Evidence of unexpected results may rebut a prima facie case of obviousness.[364] Both unexpected differences in properties and difference

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357. Valeant Pharm. Int'l, Inc. v. Mylan Pharm. Inc., 955 F.3d 25, 31 (Fed. Cir. 2020) (quoting *In re* Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (citing *In re* Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997)); *In re* Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *In re* Malagari, 499 F.2d 1297, 1303 (C.C.P.A. 1974)]).
358. *See Peterson*, 315 F.3d at 1329–30.
359. *See Valeant*, 955 F.3d at 32.
360. *See id*. at 33.
361. Hoganas AB v. Dresser Indus., 9 F.3d 948, 954 n.28 (Fed. Cir. 1993); *see also KSR*, 127 S. Ct. at 1740 (combinations of known elements not obvious if they create a "new synergy"). *See generally infra* section 7:2.2[B].
362. Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1483 (Fed. Cir. 1997); *In re* Dillon, 919 F.2d 688, 692–93 (Fed. Cir. 1990) (en banc) ("[e]ach situation must be considered on its own facts").
363. *Richardson-Vicks*, 122 F.3d at 1482–83.
364. *In re* Merck & Co., 800 F.2d 1091, 1098 (Fed. Cir. 1986); *In re* De Blauwe, 736 F.2d 699, 706 n.8 (Fed. Cir. 1984) ("proper showing of unexpected results will rebut a prima facie case of obviousness"); *see also* Kao

in degree can establish nonobviousness,[365] but, "[m]ere improvement in property does not always suffice to show unexpected results."[366] To establish unexpected results the applicant must demonstrate substantially improved results and state that the results were unexpected.[367] Unexpected results must be demonstrated through factual evidence; conclusory statements in the specification will not suffice.[368] To overcome a rejection during prosecution, the applicant may make the assertion in the application or through other evidentiary submissions such as an affidavit or declaration under Rule 132 of the Rules of Practice in Patent Cases.[369] Naked attorney argument is insufficient to establish unexpected results.[370]

[E][2] Application to Pharmaceutical Patents

A prima facie case of obviousness for a compound claim can be established by "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed composition[ ]."[371] To overcome such prima facie case of obviousness, the patentee must show that the patented compound possesses "unexpected properties" over the prior art compounds.[372]

The principle that unexpected results support a finding of nonobviousness "may apply especially often when dealing with medicinal chemistry. The biological effects of a new compound will often be too

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Corp. v. Unilever U.S., Inc., 441 F.3d 963, 970 (Fed. Cir. 2006) (rejecting argument that unexpected results evidence cannot overcome the "overwhelming" evidence based on the combination of prior art references because this evidence "is little more than the very evidence used to establish the prima facie case"; "If the evidence used to establish the prima facie case were necessarily sufficient to overcome rebuttal of that case, rebuttal would be impossible.").

365. *In re* Wagner, 371 F.2d 877, 885 (C.C.P.A. 1967).

366. *In re* Soni, 54 F.3d 746, 751 (Fed. Cir. 1995); Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004) (unexpected results are "'different in kind and not merely in degree from the results of the prior art'") (quoting *In re* Aller, 220 F.2d 454, 456 (C.C.P.A. 1955)); *see infra* section 7:2.2[B][4].

367. *In re Soni*, 54 F.3d at 750.

368. *Id*. (applicant must offer more than "mere argument or conclusory statements" of unexpected results to overcome prima facie obviousness); *see In re* De Blauwe, 736 F.2d 699 (Fed. Cir. 1984).

369. 37 C.F.R. § 1.132; *In re* Orfeo, 440 F.2d 439, 441 (C.C.P.A. 1971).

370. *Soni*, 54 F.2d at 750; *see In re* Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

371. *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990). See section 7:2.2[B] for a more in-depth discussion of unexpected results.

372. *In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986).

complex to predict with any accuracy."[373] Courts also consider evidence, or lack thereof, that a combination of known drugs produces an unexpected "synergy."[374]

Unexpected advantages have also been found in diagnostic tests where doctors previously used different types of tests (competitive assays with radioactive tracers) prior to the introduction of the patented antibody tests and detected hormone growth deficiencies undetectable by prior art tests.[375]

§ 5:3.4 Questions of Law and Fact

The conclusion on obviousness is a "question of law" but the "underlying findings" are questions of fact.[376] For example, "[w]hat a reference teaches is a question of fact."[377] Appellate courts review determinations of the *Graham* factors under the substantial evidence or clear error standard.[378] The courts apply the substantial evidence standard if the appeal is from the PTO Board or if reviewing a jury's

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373. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 2001 U.S. Dist. LEXIS 18361, at *38 (S.D. Ind. Oct. 12, 2001); *see also* Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000); Ortho Pharm. Corp. v. Johnson & Johnson Corp., 959 F.2d 936, 943 (Fed. Cir. 1992) ("one could not predict the effect of small structural changes on the biological activity of steroid hormones"); *but see* Abbott Labs. v. Andrx Pharm., Inc., 452 F.3d 1331 (Fed. Cir. 2006) (reversing grant of preliminary injunction based on rejection of unexpected improvement in taste perversion profile of claimed formulation).

374. *E.g.*, Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1484 (Fed. Cir. 2000) (trial court erred in discounting evidences of "synergy" between the ibuprofen and pseudoephedrine, but these evidences "do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious"); McNeil-PPC, Inc. v. L. Perrigo Co., 207 F. Supp. 2d 356, 365 (E.D. Pa. 2002) (clinical studies did not show synergy between loperamide with simethicone, but "largely confirm[ed] what one would expect"), *aff'd in relevant part*, 337 F.3d 1362 (Fed. Cir. 2003).

375. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1382–83 (Fed. Cir. 1986).

376. *Yamanouchi*, 231 F.3d at 1343; *see also* Dennison Mfg. Co. v. Panduit Corp., 475 U.S. 809, 810–11 (1986) ("While the ultimate question of patent validity is one of law, . . . the § 103 condition [that is, nonobviousness] . . . lends itself to several basic factual inquires.") (quoting Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966)); Sjolund v. Musland, 847 F.2d 1573, 1580 (Fed. Cir. 1988).

377. *In re* Beattie, 974 F.2d 1309, 1311 (Fed. Cir. 1992).

378. *See* Mendenhall v. Cedarapids, Inc., 5 F.3d 1557, 1561 n.3 (Fed. Cir. 1993); Miles Labs., Inc. v. Shandon, Inc., 997 F.2d 870, 877 (Fed. Cir. 1993).

conclusions.[379] In contrast, the clear error standard is used if the case is on review from a bench trial.[380] In applying the substantial evidence standard, the reviewing court must ask "whether a reasonable fact finder could have arrived at the agency's [or jury's] decision."[381] The possibility of drawing two inconsistent conclusions from the evidence does not prevent a finding that a decision was supported by substantial evidence.[382] On the other hand, "a finding is clearly erroneous when, despite some supporting evidence, 'the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'"[383]

Each of the following is a determination of fact:

- what the prior art teaches
- the scope and content of the prior art
- differences between the prior art and the claimed invention
- level of ordinary skill in the art
- objective evidence of secondary considerations of patentability
- whether the prior art teaches toward or away from the claimed invention.[384]

An appellate court may reverse a finding of obviousness if a court fails to examine the underlying references to determine whether an expert's opinion is supported by the evidence.[385]

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379. Noelle v. Lederman, 355 F.3d 1343, 1348 (Fed. Cir. 2004); *In re* Gartside, 203 F.3d 1305, 1315 (Fed. Cir. 2000); Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1323 (Fed. Cir. 2002) (citing LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc., 275 F.3d 1347, 1353 (Fed. Cir. 2001)).
380. Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1369 (Fed. Cir. 2005); Golden Blount, Inc. v. Robert H. Peterson Co. *(Golden Blount I)*, 365 F.3d 1054, 1058 (Fed. Cir. 2004).
381. *Noelle*, 355 F.3d at 1348 (quoting *Gartside*, 203 F.3d at 1312).
382. *Id*.
383. *Merck*, 395 F.3d at 1369 (quoting United States v. U.S. Gypsum Co., 333 U.S. 364, 395 (1948)).
384. *Para-Ordnance*, 73 F.3d at 1088.
385. *See* Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1473 (Fed. Cir. 1997) (denial of judgment as matter of law reversed because expert "read into the prior art reference teachings that are not there"); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination.").

Whether prior art suggests the claimed combination (a pre-*KSR* requirement) is a question of law reviewed de novo by the appellate court.[386] If there is a genuine dispute over a material fact concerning any *Graham* factor, summary judgment is inappropriate.[387]

§ 5:3.5 Scope and Content of the Prior Art

The obviousness test of patentability requires determining the parameters of the pertinent art. In responding to the question, "What is the prior art?," courts have developed the doctrine of analogous and nonanalogous art.

[A] Analogous Art

Only analogous art is relevant to obviousness.[388] If the art is nonanalogous it is "too remote" to be treated as prior art for section 103 purposes.[389] However, some courts have recognized that nonanalogous art may be cited as "illustrative of the adaption of well known principles to practical uses."[390] Art is analogous if the reference is either "within the field of the inventor's endeavor," or in a field that is "reasonably pertinent to the particular problem" the inventor tried to solve.[391] In other words, prior art includes references in the art in question and references in fields that a person with ordinary skill in the art would look to in solving a particular problem.[392]

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386. *See* Mendenhall v. Cedarapids, Inc., 5 F.3d 1557, 1561 n.3 (Fed. Cir. 1993); *Ashland Oil*, 776 F.2d at 297 n.24.
387. *See* Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 763 (Fed. Cir. 1988); *but see* Ryco Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 719–20 (Fed. Cir. 1991) (granting summary judgment finding the patent obvious even though commercial success was in patentee's favor).
388. A.J. Deer Co. v. U.S. Slicing Mach. Co., 21 F.2d 812 (7th Cir. 1927) (holding that references in remote and non-analogous arts are not to be considered in determining obviousness); *see* Graham v. John Deere Co., 383 U.S. 1, 35 (1966) (warning that a restrictive view of applicable prior art is not justifiable).
389. *In re* Clay, 966 F.2d 656, 658 (Fed. Cir. 1992) (quoting *In re* Sovish, 769 F.2d 738, 741 (Fed. Cir. 1985)); *In re* Wood, 599 F.2d 1032, 1036 (Fed. Cir. 1979) ("The rationale behind this rule precluding rejections based on combination of teachings of references from nonanalogous arts is the realization that an inventor could not possibly be aware of every teaching in every art. . . . [W]e attempt to more closely approximate the reality of the circumstances surrounding the making of the invention by only presuming knowledge by the inventor of prior art in the field of his endeavor and in analogous arts.").
390. *In re* Mariani, 177 F.2d 293, 295 (C.C.P.A. 1949).
391. *Id.*; *In re* Deminiski, 796 F.2d 436 (Fed. Cir. 1986).
392. *See Clay*, 966 F.2d at 658; Liposome Co. v. Vestar, Inc., 36 U.S.P.Q.2d (BNA) 1295, 1313 (D. Del. 1994).

The following examples of analogous art serve to illustrate the concept:

- For a patent for human hair treatment, prior art animal hair treatment is analogous.[393]
- For a patent on surgical stapling, prior art on paper stapling is not analogous.[394]
- For a patent on automobile luggage rack, prior art patent on artist easel not analogous.[395]
- Patent on RLG aircraft guidance systems; prior art on aeronautic propulsion system not analogous even though both describe ion beams. "These fields are, at best, distant cousins."[396]

[B] Defining the Problem

The Federal Circuit, prior to *KSR*, stated that "[t]he scope of the prior art has been defined as that 'reasonably pertinent to the *particular problem* with which the inventor was involved.'"[397] The *KSR* Court, however, stated that *any* problem solved by the invention is relevant, not just the problem relevant to the inventor.[398]

Accurately defining the problem is a critical step that can alter the outcome of the section 103 determination.[399] Overbroad definitions of the problem can misdirect the obviousness analysis.[400] In *Ryko Manufacturing Co. v. Nu-Star, Inc.*,[401] the Federal Circuit found the lower court's definition of the pertinent art to be too broad and "imprecise to illuminate the obviousness inquiry."[402] The inventor sought to discover the most convenient and efficient activation device to permit select people to activate an automatic car wash system. The

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393. Revlon v. Carson Prod. Co., 803 F.2d 676, 678 (Fed. Cir. 1986).
394. U.S. Surgical v. Hosp. Prods., 701 F. Supp. 314, 334 (D. Conn. 1988).
395. Bott v. Four Star Corp., 218 U.S.P.Q. (BNA) 358, 368 (E.D. Mich. 1983).
396. Litton Sys., Inc. v. Honeywell, Inc., 87 F.3d 1559, 1567–68 (Fed. Cir. 1996), *vacated by* 520 U.S. 1111 (1997).
397. Lindemann Maschinfabrik GmbH v. Am. Hoist, 730 F.2d 1452, 1460 (Fed. Cir. 1984) (emphasis added).
398. *See supra* section 5:3.3[A][1].
399. Oscar Mayer Foods Corp. v. Conagra, Inc., 1994 WL 712488, at *4 (Fed. Cir. Dec. 22, 1994) ("The nature of the problem solved affects all of the four factual inquiries underlying obviousness.").
400. Ryco Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 716 (Fed. Cir. 1991); *see* Linderman v. Am. Hoist, 730 F.2d 1452, 1460 (Fed. Cir. 1984) (holding that court erroneously defined problem as "compressing waste material," where the actual problem was "crushing massive scrapmetal," which none of the prior art involved).
401. Ryco Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714 (Fed. Cir. 1991).
402. *Id*. at 716.

court found that the "relevant art did not encompass automatic car washing systems, but rather activation devices for such systems."[403]

§ 5:3.6 "Ordinary Skill in the Art" Under Section 103

[A] Six Factors

Obviousness is determined "not from the viewpoint of the inventor, but from the viewpoint of a person of ordinary skill in the field of the invention."[404] "A person of ordinary skill is also a person of ordinary creativity, not an automaton."[405] The Federal Circuit considers six factors in determining the level of skill in the art:[406]

- "educational level of the inventor";
- "type of problems encountered in the art";
- "prior art solutions";
- "rapidity of innovation";
- "sophistication of technology"; and
- "educational level of active workers in the field."

Expert testimony can be rejected if it is "without regard to viewing the appropriate 'skill in the art.'"[407] One court found an expert lacked experience relevant to a patent covering a diuretic for treating cardiovascular and renal diseases because he lacked experience "in the design of medicinal compositions, their structural activity, mechanics of uses or the inductive testing of chemical, pharmacological and/or biological hypotheses created within that process."[408] Courts can

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403. *Id*.
404. Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 956 (Fed. Cir. 1997); *see also* Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) ("A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights.").
405. *KSR*, 127 S. Ct. at 1742.
406. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 449–50 (Fed. Cir. 1986); *see also* Ruiz v. A.B. Chance Co., 234 F.3d 654, 666–67 (Fed. Cir. 2000).
407. Merck & Co. v. Biocraft Labs., Inc., 690 F. Supp. 1376, 1383 (D.N.J. 1988), *rev'd on other grounds*, 874 F.2d 804 (Fed. Cir. 1989).
408. *Merck*, 690 F. Supp. at 1383 n.3 ("[A] person of ordinary skill in the art would have had either a Ph.D degree in Chemistry or Pharmacology, or an M.D. degree with concentration in medicinal chemistry and renal physiology . . . several years of hands-on work experience in the design and evaluation of novel diuretic agents and would have been part of a

also reject expert testimony if the expert offers an opinion based on the vantage point of one of extraordinary skill in the art.[409]

[B] Skill in the Pharmaceutical Arts

In the field of pharmaceuticals and medicinal chemistry, courts find varying degrees of skill, depending on the patent, including advanced degrees and years of specialized training, and can be based on entire teams of scientists with diverse skills:

Daiichi Sankyo Co. v. Apotex, Inc.[410]

Claim: [M]ethod for treating bacterial ear infections by topically administering the antibiotics ofloxacin into the ear.

Skill: "[A] person engaged in developing pharmaceutical formulations and treatments for the ear or a specialist in ear treatments such as an otologist, otolaryngologist, or otorhinolaryngologist who also has training in pharmaceutical formulations."

Imperial Chemical Industries, PLC v. Danbury Pharmacal, Inc.[411]

Claim: Method of use of the compound atenolol in treatment of hypertension.

Skill: "[A] PhD degree in organic chemistry, with an emphasis in medicinal chemistry (*i.e.* products), who would have some experience with the development of beta-blockers, and would be thoroughly familiar with the prior art which discusses the structure-activity relationships of the existing beta-blockers and have knowledge of the methodologies of drug development."

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research team that monitored the diuretic activities of novel agents . . . [a]lso would have had personal exposure to structure/activity relationships in a class of potential diuretic compounds.").

409. Studiengesellschaft Kohle mbH v. Dart Indus., 549 F. Supp. 716, 732 (D. Del. 1982) (rejecting expert testimony on obviousness by Nobel Laureate Ziegler because opinion represented view of "world's leading authority on organo-aluminums"; rejecting view of laureate's graduate student because although not "extraordinarily accomplished . . . his close association with Ziegler and intimate familiarity with [Ziegler's] work . . . did make him especially likely to find alkyl aluminums in the" prior art), *aff'd*, 726 F.2d 724 (Fed. Cir. 1984).

410. Daiichi Sankyo Co. v. Apotex, Inc., 501 F.3d 1254 (Fed. Cir. 2007).

411. Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 352 (D. Del. 1991), *aff'd*, 972 F.2d 1354 (Fed. Cir. 1992).

Merck & Co. v. Danbury Pharmacal, Inc.[412]

Claim: "Method of use of cyclobenzaprine to treat certain types of skeletal muscle disorders."

Skill: "[A] doctoral degree in pharmacology and special training or experience in the area of neuropharmacology, including the 'design, execution, implementation and interpretation' of clinical tests or experiments."

Mead Johnson & Co. v. Premo Pharmaceutical Labs.[413]

Claim: Method for preparing compound isoxsuprine.

Skill: Had skill "in the medicinal chemistry art . . . had a Ph.D degree in organic chemistry with a deep interest in biochemistry and medicinal chemistry . . . (and fully aware of the techniques of drug design including molecular modification utilizing bioisosterism, Dr. Burger's treatise on medicinal chemistry, and much of the literature at the time in the medicinal chemistry field)."

Eli Lilly & Co. v. Teva Pharmaceuticals USA, Inc.[414]

Claim: Use of fenfluramine and fluoxetine to treat Premenstrual Dysphoric Disorder, a severe form of Premenstrual Syndrome.

Skill: "A hypothetical medical doctor (an OB/GYN, a family practice physician, or a psychiatrist) who: (1) regularly sees and treats patients suffering from PMS, and (2) is familiar with the relevant prior art."[415]

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412. Merck & Co. v. Danbury Pharmacal, Inc., 694 F. Supp. 1, 30 (D. Del. 1988), *aff'd*, 873 F.2d 1418 (Fed. Cir. 1989).
413. Mead Johnson & Co. v. Premo Pharm. Labs., 207 U.S.P.Q. (BNA) 820, 841 (D.N.J. 1980).
414. Eli Lilly & Co. v. Teva Pharm. USA, Inc., 2004 U.S. Dist. LEXIS 14724, at *104 (S.D. Ind. July 29, 2004), *aff'd*, 2005 U.S. App. LEXIS 14583 (Fed. Cir. July 13, 2005).
415. *Eli Lilly & Co.*, 2004 U.S. Dist. LEXIS 14724, at *102.

Alza Corp. v. Mylan Laboratories, Inc.[416]

Claim: Sustained-release oxybutynin formulation for oral administration.

Skill: "An advanced degree in pharmacy, biology, chemistry or chemical engineering and at least two years of experience with controlled-release technology; or a bachelor's degree in one (or more) of those fields plus five years of experience with such technology."[417]

Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.[418]

Claim: The chemical compound pioglitazone.

Skill: "[A] person with ordinary skill in the art would have a graduate degree in chemistry or a relevant branch of chemistry and practical experience applying that education by working at or consulting with a pharmaceutical company in the development of pharmaceutical compounds. It is unnecessary to refine further the minimum qualifications of a person with ordinary skill in the art, since nothing that follows in this analysis turns on the presence of a more precisely drawn definition."

In pharmaceutical patent cases, courts sometimes find that "ordinary skill in the art" covers several members of a research team.[419] Some courts find that a high level of skill in the art depends on the financial resources of the researchers.[420] One court found that "[t]he subtlety

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416. Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1293 (Fed. Cir. 2006).
417. *Id.* (noting district court's finding).
418. Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 341, 373 (S.D.N.Y. 2006), *aff'd*, 492 F.3d 1350 (Fed. Cir. 2007).
419. Merck & Co. v. Biocraft Labs., Inc., 690 F. Supp. 1376, 1382 (D.N.J. 1988) (skilled artisan "would have been part of a research team"); Ind. Gen. Corp. v. Krystinel Corp., 421 F.2d 1023, 1031 (2d Cir. 1970) (skilled artisan "must be highly educated, sophisticated persons who generally have at their disposal laboratory facilities and staffs of competent assistants"); *but see* Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 352 n.41 (D. Del. 1991) ("There are smaller institutions of research than [the plaintiff] that may not have the resources to devote such a team to this type of work [in medicinal chemistry] and would still be able to achieve the desired results.").
420. *See* Mattel, Inc. v. Hyatt, 206 U.S.P.Q. (BNA) 499 (C.D. Cal. 1979) ("The level of ordinary skill in the pertinent art of computers and computer

of the teachings of the various patents in this field indicate the high level of sophistication . . . prevalent in the art."[421]

[C] Relevance of the Inventor in Determining "Ordinary Skill in the Art"

The Federal Circuit clearly distinguishes the inventor from one of ordinary skill in the art.[422] The inventor's skill can still be considered as one of six factors in determining the appropriate level of skill in the art, although "the actual inventor's skill is not determinative."[423] The Federal Circuit in *Markman* recognized that inventor testimony may be relevant in determining ordinary skill in the art.[424]

The field in which the inventor is skilled is also relevant to determining ordinary skill in the art.[425]

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controlled displays at the time of the alleged invention was high because of the technical expertise demanded as a minimum prerequisite to be skilled in the art, the specialized nature of the art, the preponderance of persons engaged in the art with advanced degrees, and the use of well funded, organized research endeavors in the art."), *aff'd*, 664 F.2d 757 (9th Cir. 1981); Columbia Broad. Sys. v. Sylvania Elec. Prods. Inc., 415 F.2d 719, 727 (1st Cir. 1969) ("In view of the fact that millions of dollars were expended and in view of the scale of the organized application of technical intelligence to color television, it would be a classic understatement to say that the level of skill in the art was high.").

421. H.H. Robertson Co. v. Barger Metal Fabricating Co., 225 U.S.P.Q. (BNA) 1191, 1202 (N.D. Ohio 1984).

422. *See, e.g.*, Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1454 (Fed. Cir. 1984) ("It should be clear that that hypothetical person is not the inventor, but an imaginary being possessing 'ordinary skill in the art' created by Congress to provide a *standard of patentability*."); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 956 (Fed. Cir. 1997) ("The decision of obviousness vel non is made not from the viewpoint of the inventor, but from the viewpoint of a person of ordinary skill in the field of the invention.").

423. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986).

424. *See* Markman v. Westview Instruments, Inc., 52 F.3d 967, 983 (Fed. Cir. 1995) ("Markman testified as an inventor of the patent in suit and as one of ordinary skill in the art (or, perhaps more accurately, one of 'extraordinary' skill in the art) that 'inventory' did not need to include articles of clothing."); *but see* Air-Vend, Inc. v. Thorne Indus. Inc., 625 F. Supp. 1123, 1137 (D. Minn. 1985) ("Particularly helpful in determining what prior art references would have suggested to a person of ordinary skill was the testimony of Scholta, the inventor . . . ."), *aff'd*, 831 F.2d 306 (Fed. Cir. 1987).

425. Daiichi Sankyo Co. v. Apotex, Inc., 501 F.3d 1254 (Fed. Cir. 2007) (considering fact that inventors had expertise in "new drug development" in rejecting argument that level of skill for method of treatment claim should be limited to a medical doctor).

§ 5:3.7 Practical Evidence of Nonobviousness: The Secondary Considerations

In addition to determining obviousness based on comparing the claimed invention to prior art, courts can consider certain objective secondary considerations of nonobviousness. The "objective evidence of nonobviousness must be commensurate in scope with the claims."[426] The Supreme Court explained, in *Graham v. John Deere Co.*,[427] that secondary considerations "focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible of judicial treatment than are the highly technical facts often present in patent litigation."[428] The secondary considerations include the following first three factors referred to explicitly by *Graham*,[429] *Adams*,[430] and several other factors elaborated by lower courts:[431]

(1) long-felt but unsolved need

(2) commercial success

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426. *In re* Kulling, 897 F.2d 1147, 1149 (Fed. Cir. 1990); *see also* Therasense, Inc. v. Becton, Dickinson & Co., 593 F.3d 1325 (Fed. Cir. 2010) ("Because the claims are broad enough to cover devices that either do or do not solve the 'short fill' problem, Abbott's objective evidence of non-obviousness fails because it is not 'commensurate in scope with the claims which the evidence is offered to support.'"); *In re* Tiffin, 448 F.2d 791, 792 (C.C.P.A. 1971) (objective evidence of nonobviousness "with respect to 'cups'" found "not commensurate with scope of claims" more broadly reciting "containers").

427. Graham v. John Deere Co., 383 U.S. 1 (1966).

428. *Id*. at 35–36.

429. *Graham*, 383 U.S. 1. The *Graham* Court referred to secondary considerations such "as commercial success, long felt but unsolved needs, failure of others, etc." *Id*. at 17–18. While the Federal Circuit recognized that the *Graham* decision specifically mentioned three secondary considerations, courts have considered additional factors "under *Graham*'s 'etc.' clause." Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1380 (Fed. Cir. 2000).

430. United States v. Adams, 383 U.S. 39, 51–52 (1966) ("[T]he operating characteristics of [defendant's patent] . . . have been unexpected . . . . [K]nown disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness.").

431. *In re* Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *Ecolochem*, 227 F.3d at 1376–80; Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998); Advanced Display Sys. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 1988); Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd., 254 F. Supp. 2d 527, 570 (E.D. Pa. 2003), *rev'd on other grounds*, 357 F.3d 1319 (Fed. Cir. 2004); Scimed Life Sys., Inc. v. Johnson & Johnson, 225 F. Supp. 2d 422, 440 (D. Del. 2002).

(3) failed efforts of others

(4) copying by others

(5) praise for the invention

(6) unexpected results[432]

(7) licenses

(8) industry acclamation

(9) disbelief of experts

(10) general skepticism of those in the art before the invention

(11) commercial acquiescence

(12) simultaneous development

The courts and the Patent Office "must" weigh secondary considerations "in determining obviousness."[433] Courts may give the first three factors stated above greater weight because they were specifically mentioned in *Graham*.[434] The precise role of secondary considerations in an obviousness analysis, however, can be hard to define.

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432. Unexpected results (also known as unexpected properties) are sometimes treated as a secondary consideration and at other times have been treated as part of the primary obviousness determination. See *supra* section 5:3.3[D] and section 7:2.2[B], *infra*, for a further discussion of unexpected results.

433. Ruiz v. A.B. Chance Co., 234 F.3d 654, 667 (Fed. Cir. 2000); Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1483 (Fed. Cir. 1997) (reiterating "the well-established rule that all evidence of nonobviousness must be considered when assessing patentability" by the Patent Office and the courts) (quoting *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995)); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986) ("Objective evidence . . . must be considered before a conclusion on obviousness is reached and is not merely 'icing on the cake,' as the district court stated at trial."); Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1572 (Fed. Cir. 1996) (reversing summary judgment because district court failed to consider secondary considerations even though prior art suggested invention); *In re* Sernaker, 702 F.2d 989, 996 (Fed. Cir. 1983); *but see* Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1131 (Fed. Cir. 2000) (failure of district court to consider certain secondary considerations was harmless error because indicators of non-obviousness could not "overcome the strong evidence of obviousness").

434. *Ecolochem*, 227 F.3d at 1380 ("The factors specifically mentioned in *Graham*, and those that we give the most weight to in the instant case, are the commercial success of the invention, long-felt but unsolved needs, and failure of others to invent.").

Evidence of secondary considerations is sometimes "the most probative of obviousness."[435] On the other hand, "the existence of such evidence . . . does not control the obviousness determination."[436] If the teaching of the prior art establishes a strong case of obviousness, secondary consideration need not be given much weight.[437] "Secondary considerations are not secondary in importance . . . a court is entitled to weigh all the considerations, primary and secondary, and then render its decision."[438] Absence of secondary considerations evidence has a neutral impact on obviousness.[439] "[A] fact finder in district court litigation may not defer examination of the objective considerations until after the fact finder makes an obviousness finding."[440] A court may, however, first conclude that the challenger "made a strong prima facie showing of obviousness" before considering the secondary considerations.[441]

[A] Long-Felt Need/Failure of Others

"[A]lthough long-felt need is closely related to failure of others, these considerations are distinct and we treat each separately."[442]

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435. *Richardson-Vicks*, 122 F.3d at 1483; *see also Pro-Mold*, 75 F.3d at 1573 ("It is secondary considerations that are often most probative and determinative of the ultimate conclusion of obviousness or non-obviousness."); W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1555 (Fed. Cir. 1983) (secondary considerations "may be the most pertinent, probative, and revealing evidence available to aid in reaching a conclusion on the obvious/non-obvious issue").
436. *Richardson-Vicks*, 122 F.3d at 1483; *see also W.L. Gore & Assocs.*, 721 F.2d at 1555 (secondary considerations "may in a given case be entitled to more weight or less, depending on its nature and its relationship to the merits of the invention").
437. SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349, 1358 (Fed. Cir. 2000); Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 719 (Fed. Cir. 1991) (secondary considerations may be of insufficient weight to override a determination of obviousness based on primary considerations); Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 768 (Fed. Cir. 1988) (secondary considerations "must be considered, [but] they do not control the obviousness conclusion").
438. *Ryko*, 950 F.2d at 719.
439. Miles Labs., Inc. v. Shandon Inc., 997 F.2d 870, 878 (Fed. Cir. 1993) ("lack of objective indicia of non-obviousness does not weigh in favor of obviousness").
440. *In re* Cyclobenzaprine Hydrochloride, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (citing Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)).
441. Intercontinental Great Brands v. Kellogg N. Am. Co., 869 F.3d 1336, 1345 (Fed. Cir. 2017).
442. Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356, 1369 n.5 (Fed. Cir. 2017).

"[E]vidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand"; however, long-felt need may be established "without presenting evidence of failure of others."[443]

[A][1] General Rule

If a skilled artisan recognizes that a solution was needed to solve a particular problem in the prior art for a long time, an invention that fulfills such a long-felt need may not be obvious, particularly if other people have tried and failed to find such a solution.[444] In fact, "there can be little better evidence negating an expectation of success than actual reports of failure."[445] "If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence—the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of knowledge. . . . If [the patented] device were obvious, other persons skilled in the art would have made it."[446] Granting of "fast track" status under 21 U.S.C. § 356(b)(1) by the FDA of the commercial embodiment of the patent claims provides one way to demonstrate a long-felt and unmet need.[447]

The long-felt need is measured from the date the problem is recognized and efforts are made to solve the problem, not from the date of the most pertinent prior art.[448] The solution to a long-felt need must have a relationship to the patent claim, not merely to the product covered by the claim.[449] "Evidence of the existence of a long-felt need may be found, among other places, in the prior art . . . or in the patent itself."[450]

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443. *Id*. at 1369.
444. *In re* Mahurkar Patent Litig., 831 F. Supp. 1354, 1377–78 (N.D. Ill. 1993).
445. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir. 2003).
446. *Mahurkar*, 831 F. Supp. at 1378.
447. Ferring B.V. v. Watson Labs., Inc.-Fla., 764 F.3d 1401, 1404 (Fed. Cir. 2014).
448. Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("long-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem" not the date of the most pertinent reference).
449. Sjolund v. Musland, 847 F.2d 1573, 1582 (Fed. Cir. 1988).
450. Alza Corp. v. Mylan Labs., 388 F. Supp. 2d 717, 741 (N.D. W. Va. 2005), *aff'd*, 464 F.3d 1286 (Fed. Cir. 2006).

[A][2] Application to Pharmaceutical Patents

Several cases have considered long-felt need and failure of others in evaluating obviousness of pharmaceutical patents:

Eli Lilly & Co. v. Teva Pharmaceuticals USA, Inc.[451]

Problem:	Relying primarily on expert witness testimony, the court found that "as of October 1987, the etiology of PMS was unknown," and "many hypotheses existed as to the etiology of PMS, but no known treatments had been devised or developed that provide relief to both the physical and emotional symptoms of PMS."[452]
Prior Treatments:	At the time of the invention, existing treatments were only directed to the emotional symptoms of PMS.[453]
Solution:	The patentee's drug, fluoxetine, "was the first drug to provide relief for both [the physical and emotional] symptoms, and the '988 patent was the first indication that fluoxetine was effective for PMS."[454]
Conclusion:	The court found there was a "specific need to treat PMS,"[455] and apparently accepted patentee Lilly's assertion that "there was a widespread failure of others to develop a safe and effective treatment for patients suffering from PMS."[456]

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451. Eli Lilly & Co. v. Teva Pharm. USA, Inc., 2004 U.S. Dist. LEXIS 14724 (S.D. Ind. July 29, 2004), *aff'd*, 2005 U.S. App. LEXIS 14583 (Fed. Cir. July 13, 2005).
452. *Eli Lilly & Co.*, 2004 U.S. Dist. LEXIS 14724, at *45–47.
453. *Id.* at *54–55.
454. *Id.* at *116. The court also found the development of fluoxetine in the form of Prozac to treat depression does not satisfy this need because it failed to "account for the specific need to treat PMS." *Id.* at *117.
455. *Id.* at *117.
456. *Id.* at *116.

Ortho-McNeil Pharmaceuticals, Inc. v. Mylan Laboratories, Inc.[457]

Problem: The problem was to find "a broad-spectrum quinolone that safely and effectively treated respiratory infections."[458] Citing a leading treatise, the court noted that "the effectiveness of the current available agents against gram-positive respiratory pathogens, particularly S. pneumoniae, is less than optimal."[459]

Prior Treatments: Prior art quinolones had "shortcomings . . . [in] treat[ing] respiratory infections effectively."[460]

Solution: The patentee developed levofloxacin, an isomer of the prior art compound ofloxacin. Levofloxacin is twice as active as ofloxacin, less toxic and unexpectedly more effective against S. pneunomiae than ofloxacin.[461]

In re Cyclobenzaprine Hydrochloride[462]

Problem: The problem was "making a therapeutically effective product" containing a muscle relaxant.[463] "The immediate-release formulation existed for decades, but that formulation's regimen of multiple daily doses led to poor patient compliance."[464] The Federal Circuit ruled that the district court erred by disregarding the evidence of failure of others because the district court relied on the fact that the prior failure was in an attempt to solve "the additional goal of reducing side effects."[465] "The district court was not required to disregard Cephalon and ALZA's common goal simply because ALZA had an *additional* goal not encompassed by the patents in suit."[466]

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457. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W. Va. 2004).
458. *Id.* at 758.
459. *Id.*
460. *Id.*
461. *Id.* at 755–56.
462. *In re* Cyclobenzaprine Hydrochloride, 676 F.3d 1063 (Fed. Cir. 2012).
463. *Id.* at 1081.
464. *Id.* at 1083.
465. *Id.* at 1082.
466. *Id.*

Prior Treatments:	"The evidence of ALZA's failure to develop an extended-release formulation strongly supports a nonobviousness finding. . . . Clinical trials, however, revealed that ALZA's product was not therapeutically effective. ALZA lost $10 million in its unsuccessful attempt to develop an extended-release formulation."[467]
Solution:	"At trial, Cephalon called a former ALZA vice president, Dr. Samuel Saks . . . expressed surprise that Cephalon succeeded, because he believed a lower C_{min} would be less effective. Thus, where ALZA failed to develop a therapeutically effective product, Cephalon took a materially different approach and succeeded."[468]

No court has articulated a precise standard for the length of time that must pass in order to create an inference of nonobviousness. One court, however, stated that six years was not enough time to qualify as a long-felt need given the "time consuming" process of making a vaccine.[469]

One court reversed a summary judgment grant of invalidity for "failing to view the evidence" in the light most favorable to the patentee. The district court improperly concluded on a summary judgment motion that evidence of "several other opioid-NSAID compositions available on the market" negated patentee's evidence that two pharmaceutical companies failed to obtain FDA approval for their opioid-NSAID combinations.[470]

[B] Commercial Success

[B][1] General Rule

"Commercial success is an indication of nonobviousness that must be considered in a patentability analysis."[471] One court held that where commercial success was "the only" indication of nonobviousness and the evidence of obviousness was sufficient, the evidence of commercial success did not render the claimed invention nonobvious.[472] The Federal Circuit has held that a patentee's evidence of commercial success may not be discounted merely because the owner possessed other patents which may have precluded its competitors from

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467. *Id.* at 1081.
468. *Id.* at 1081–82.
469. Boehringer Ingelheim Animal Health, Inc. v. Schering-Plough Corp., 984 F. Supp. 239, 258 (D.N.J. 1997).
470. Knoll Pharm. v. Teva Pharm. USA, 367 F.3d 1381, 1385 (Fed. Cir. 2004).
471. Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989).
472. *Id*.

entering the market.[473] Generally, commercial success can be shown by the substantial sale of the patented articles.[474] Evidence limited solely to sales volume, however, "provides a very weak showing of commercial success, if any."[475] Evidence of limited or no profitability undermines showing of commercial success.[476] Other relevant evidence includes "market share, growth in market share, and replacing

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473. Merck Sharp & Dohme Corp. v. Hospira, Inc., 874 F.3d 724, 731 (Fed. Cir. 2017) ("[M]ultiple patents do not necessarily detract from evidence of commercial success of a product or process . . . . Commercial success is thus a fact-specific inquiry that may be relevant to an inference of nonobviousness, even given the existence of other relevant patents.").

474. Tec Air, Inc. v. Denso Mfg. Mich. Inc., 192 F.3d 1353, 1360–61 (Fed. Cir. 1999).

475. *In re* Huang, 100 F.3d 135, 137–40 (Fed. Cir. 1996) (affirming Board of Patent Appeals determination that applicant failed to prove that evidence of commercial success overcame prima facie case of obviousness, where assertions of commercial success were neither supported by an evidentiary showing nor placed in a meaningful context, *e.g.*, market share or profitability); *In re* Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[I]nformation solely on numbers of units sold is insufficient to establish commercial success."); Kan. Jack, Inc. v. Kuhn, 719 F.2d 1144, 1151 (Fed. Cir. 1983); *see also* Cable Elec. Prods., Inc. v. Genmark, Inc., 770 F.2d 1015, 1026–27 (Fed. Cir. 1985) (district court correctly determined to accord no weight to declaration stating that product had realized profits of not less than fifty cents per unit in considering evidence of commercial success; without further economic evidence, it would be improper to infer that the reported sales represent a substantial share of any definable market or whether the profitability per unit is anything out of the ordinary in the industry involved).

476. Medpointe Healthcare, Inc. v. Hi-Tech Pharmacal Co., 115 F. App'x 76, 80–81 (Fed. Cir. 2004) (unpublished) (weak evidence of commercial success inadequate to demonstrate nonobviousness; purported commercial success somewhat tenuous given that product has so far only broken even in the amount of money made, with the product's long-term profitability yet to be established); Gates Formed-Fibre Prods., Inc. v. Del. Valley Corp., 1999 U.S. App. LEXIS 7273, at *6 (Fed. Cir. Apr. 13, 1999) (unpublished) (secondary considerations did not rebut a holding of obviousness where there was evidence showing a small market share with little to no profits); *cf.* Hildebrand v. Steck Mfg. Co., 395 F. Supp. 2d 1036, 1047–48 (D. Colo. 2005) (affidavit presenting a gross profits estimation of $416,000 for product's first ten months of sale created a genuine issue of commercial success so as to preclude summary judgment on the issue); Alza Corp. v. Mylan Labs., 388 F. Supp. 2d 717, 741 (N.D. W. Va. 2005) (finding product was "at least a moderate commercial success," where despite yielding a relatively disappointing profit margin, product sales met or exceeded third-party analysis projections; holding nevertheless that patent was obviousness), *aff'd*, 464 F.3d 1286 (Fed. Cir. 2006).

earlier units sold by others."[477] "There is no requirement that the invention be the only successful product in its market niche or the most successful."[478]

The patentee must also establish a nexus between commercial success and the claimed invention. "A prima facie case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent."[479]

Once the patentee presents a prima facie case of nexus, the burden of coming forward with evidence to rebut the nexus shifts to the accused infringer. "It is thus the task of the challenger to adduce evidence to show that the commercial success was due to extraneous factors other than the patented invention, such as advertising, superior workmanship, etc."[480] The amount of spending on marketing and advertising in comparison with similar products or companies is relevant to determining whether the nexus exists. Where commercial success "is the only such indication" of nonobviousness, "it is insufficient to render [the patentee's] claimed invention nonobvious."[481]

Evidence of commercial success based on patented features of the commercial embodiment is not generally defeated by evidence that unpatented features also contributed to the product's success.[482]

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477. Ferag AG v. Grapha-Holding AG, 935 F. Supp. 1238, 1247 (D.D.C. 1996).
478. Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 2d 341, 386 (S.D.N.Y. 2006), *aff'd*, 492 F.3d 1350 (Fed. Cir. 2007).
479. Demaco Corp. v. F. Von Langsdorff Licensing, Ltd., 851 F.2d 1387, 1392 (Fed. Cir. 1988); *see also* Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356 (Fed. Cir. 2012) (holding that patentee had not demonstrated a "sufficient nexus" between patented cooling agents and market success or copying for purpose of demonstrating indicia of nonobviousness, because evidence showed that marketing, packaging, sweetness, and higher-quality ingredients contributed to commercial success and competitor sought to copy those elements as well as the patented feature); *Takeda*, 417 F. Supp. 2d at 386 ("ACTOS® is the embodiment of pioglitazone, the invention disclosed in the '777 Patent, and therefore this commercial success can presumptively be attributed to the invention itself."), *aff'd*, 492 F.3d 1350 (Fed. Cir. 2007); *but see* Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1580 (Fed. Cir. 1983) (finding obviousness despite evidence of commercial success because evidence did not show such "success as its marketed system enjoyed was due to anything disclosed in the patent in suit which was not readily available in the prior art").
480. *Demaco*, 851 F.2d at 1393.
481. Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989).
482. Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1378 (Fed. Cir. 2000) (finding clear error because the "success was due to both the mobility, undisputably not covered by the claims, and to the improved filtration

[B][2] Application to Pharmaceutical Patents

A prima facie case of commercial success can be made out based on factors such as market share and gross sales.[483]

"Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention."[484] A patentee may not rely solely on the fact that its commercial drug product is the first of its kind on the market when the prior art disclosed other similar drugs that have not been marketed.[485]

When evaluating the commercial success of a prescription drug, courts consider the drug's "clinical properties"[486] in addition to other factors such as marketing and advertising campaigns. The existence of evidence "that marketing and financing played a role in the success of [the patented product] as they do with any product" is not outcome determinative where the totality of the evidence demonstrates "that the commercial success . . . was due to the merits of the claimed invention."[487]

In *Hybritech v. Monoclonal Antibodies*,[488] the Federal Circuit found that the nexus between commercial success and the patented invention existed where the patentee spent "25–30% of income" on marketing.[489]

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process, undisputedly covered by the claims"; defendant "had the burden of disproving that the improved filtration process contributed to the success of the invention").

483. *Takeda*, 417 F. Supp. 2d at 386 (finding ACTOS® "a huge commercial success" based on its achieving "47% of the TZD market" within four years of launch and "9.9% of the total" oral anti-diabetic market, and gross 2003 sales in excess of $1.7 billion), *aff'd*, 492 F.3d 1350 (Fed. Cir. 2007).

484. *In re* Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

485. Novartis AG v. Torrent Pharm. Ltd., 853 F.3d 1316, 1331 (Fed. Cir. 2017) (fact that Gilenya was "the first commercially-available solid oral multiple sclerosis treatment" does not establish commercial success because "treatment of multiple sclerosis with a solid oral composition . . . was indisputably known in the prior art").

486. Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc., 348 F. Supp. 2d 713, 757 (N.D. W. Va. 2004); *see also* Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1382 (Fed. Cir. 1986) ("the record shows that advertising makes those in the industry—hospitals, doctors, and clinical laboratories—aware of the diagnostic kits but does not make these potential users buy them; the products have to work"); *Takeda*, 417 F. Supp. 2d at 386 (finding "strong evidence from medical practitioners about the benefits and perceived benefits of ACTOS®" overcame evidence that "success is more attributable to [pharmaceutical company's] marketing efforts"), *aff'd*, 492 F.3d 1350 (Fed. Cir. 2007).

487. *Hybritech*, 802 F.2d at 1383.

488. *Hybritech*, 802 F.2d 1367.

489. *Id*. at 1382.

The court found such spending was not unusual given that "expenditures of *mature* companies in this field are between 17 and 32%."[490] The court further noted that the patentee was a newcomer to the diagnostic kits market: "Competing with products from industry giants such as Abbott Labs, Hoffman LaRoche, Becton-Dickinson, and Baxter-Travenol, Hybritech's HCG kit became the market leader with roughly twenty-five percent of the market at the expense of market shares of the other companies."[491]

Another court found that a nexus existed despite evidence that "80 percent of the $75.4 million Lilly spent developing Sarafem consisted of marketing expenditures."[492] The active ingredient in Sarafem is fluoxetine, a drug which Lilly obtained FDA approval to market under the Prozac label to treat depression. Subsequently, Lilly obtained FDA approval to market fluoxetine under the Sarafem label to treat PMS. Thus, "much of Sarafem's product development would have been coincident with the development of Prozac."[493] In light of this, the court held that "spending 80 percent of development costs on marketing may not have been out of line."[494] Furthermore, the court did not find Teva's expert testimony persuasive because the witness did not "identify a drug comparable to Sarafem so that we may understand these numbers in context."[495]

One court found that a nexus existed where patentee "did not devote an unusual amount of resources to marketing" and "maintained a relatively low ratio of total sales to promotional expenditures as compared to competing respiratory anti-infectives."[496] Aggressive

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490. *Id*.

491. *Id*.; *see also* Ortho Pharm. Corp. v. Smith, 1990 WL 121353 (E.D. Pa. Aug. 17, 1990) (commercial success found where market share for patented product increased from 2.5% to over 20% in four year period "in the face of stiff competition from established" competing products), *aff'd*, 959 F.2d 936, 942 (Fed. Cir. 1992).

492. Eli Lilly & Co. v. Teva Pharm. USA, Inc., 2004 U.S. Dist. LEXIS 14724, at *68 (S.D. Ind. July 29, 2004).

493. *Id*.

494. *Id*.

495. *Id*.

496. Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc., 348 F. Supp. 2d 713, 757 (N.D. W. Va. 2004); *see also* Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 2d 341, 386–87 (S.D.N.Y. 2006) (patentee "GlaxoSmithKline invest[s] roughly the same amount of money in their efforts to market their two TZD products, and both drugs have found success"), *aff'd*, 491 F.3d 1350 (Fed. Cir. 2007); Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 2001 U.S. Dist. LEXIS 18361, at *37 (S.D. Ind. Oct. 12, 2001) ("Lilly's marketing and advertising budgets for AXID (nizatidine) have been relatively modest by industry standards."); Merck & Co. v. Danbury Pharmacal, Inc., 694 F. Supp. 1, 31 (D. Del. 1988)

marketing and high advertising costs relative to revenue, however, can destroy any nexus between the patent and the patented product's success.[497] The court found that the "probative value of the commercial success of Imodium Advanced is significantly mitigated by the fact that Imodium Advanced's sales are the calculated result of an aggressive marketing campaign of unprecedented scope in the antidiarrheal market."[498] Around the time McNeil obtained FDA approval to sell Imodium Advanced in 1997, it waged a "massive $45 million marketing and advertising campaign."[499] It is not clear how long this campaign lasted, but the $45 million figure appears to be quite substantial when compared to Imodium Advanced's modest sales.[500] In addition, the court relied on a sales publication prepared by McNeil, which stated: "With this heavy media-spending plan, Imodium will significantly out-spend all other competitors and remain the category share-of-voice leader."[501]

There are other factors that can negate the nexus between the patented invention and commercial success. The Federal Circuit held that "[f]inancial success is not significantly probative" because "others were legally barred from commercially testing" prior art ideas due to Merck's other patent and exclusive rights in this field.[502] Merck owned another patent in the relevant field, and had marketing exclusivity to "offer Fosamax at any dosage for the next five years."[503]

[C] Licensing

[C][1] General Rule

Acceptance of a license is perceived to be commercial acquiescence illustrating the validity of the patent. The rationale underlying this principle is that people would not act against their economic interests

("Merck spends less on advertising per total amount of purchases than any of its competitors."), *aff'd*, 873 F.2d 1418 (Fed. Cir. 1989).

497. McNeil-PPC, Inc. v. L. Perrigo Co., 207 F. Supp. 2d 356, 365, 375 (E.D. Pa. 2002), *aff'd*, 337 F.3d 1362 (Fed. Cir. 2003).

498. *McNeil-PPC, Inc.*, 207 F. Supp. 2d at 372.

499. *Id*. at 364.

500. *Id*. at 365 ("In 1997, sales of Imodium Advanced neared $10 million, and approached $27.7 million in 1998, the product's first full year of sales. . . . McNeil's projections indicate that the total sales of all Imodium Advanced products will approach $200 million by the end of 2002.").

501. *Id*.

502. Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005).

503. *Id*.; *cf. Takeda*, 417 F. Supp. 2d at 387 n.77 (distinguishing *Merck*, where patentee owned a method claim for using a particular compound and a prior patent on the compound itself, from *Takeda*, where the patentee merely owned a prior art patent), *aff'd*, 491 F.3d 1350 (Fed. Cir. 2007).

unless convinced of the patent's validity. In a case where the patentee's and infringer's major competitor took a license from the patentee, the Federal Circuit noted "such real world considerations provide a colorful picture of the state of the art, what was known by those in the art, and a solid evidentiary foundation on which to rest a nonobviousness determination."[504] However, although "[l]icenses taken under the patent in suit may constitute evidence of nonobviousness," it should be noted that "only little weight can be attributed to such evidence if the patentee does not demonstrate 'a nexus between the merits of the invention and the licenses of record.'"[505] When evidence suggests that a license was acquired for reasons other than a belief in the validity of the patent, the license loses its significance in the obviousness determination.[506]

[C][2] Application to Pharmaceutical Patents

Courts sometimes discount the importance of licensing in cases against generic drug makers. One court held that a brand name drug company's licensing of a patent to cover an FDA approved drug is "not evidence of nonobviousness."[507] An expert witness testified that "there are two reasons a company may take a license: (1) for defensive purposes to prevent it from being sued as an infringer by the patentee; or (2) for offensive purposes to prevent others from entering the marketplace."[508] The court held that the license had considerable value to Lilly, even if the patent was not valid. It explained that

> Lilly could use the license offensively whether or not it believed the license to be valid. Once Lilly licensed the '998 patent, Lilly could list it in the Orange Book with respect to Sarafem. Lilly then would have standing to bring suit for infringement against a

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504. Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1575 (Fed. Cir. 1992).

505. *In re* GPAC Inc., 57 F.3d 1573, 1580 (Fed. Cir. 1995) (citing Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983)).

506. EWP Corp. v. Reliance Universal Inc., 755 F.2d 898, 907–08 (Fed. Cir. 1985) (licensing programs "are not infallible guides to patentability . . . sometimes [they] succeed because they are mutually beneficial to the licensee group or because of business judgments that it is cheaper to take licenses than to defend infringement suits, or for other reasons unrelated to the unobviousness of the license's subject matter").

507. Eli Lilly & Co. v. Teva Pharm., 2004 U.S. Dist. LEXIS 14724, at *63 n.15 (S.D. Ind. July 29, 2004); *see also* Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc., 348 F. Supp. 2d 713, 760 (N.D. W. Va. 2004) (patentee failed to show that "the licenses were sought because of the merits of" the patent where the generic offered evidence suggesting that three pharmaceutical companies took licenses for the drug due to "its extended patent life").

508. *Eli Lilly*, 2004 U.S. Dist. LEXIS 14724, at *63–64.

> generic drug manufacturer and keep the generic manufacturer off the market for up to 30 months.[509]

Evidence that a "substantial number of large pharmaceutical companies were doing research" in the field relevant to the patent and numerous resulting interferences with the patent at issue, combined with evidence that none of the competitors introduced a product within the claims is evidence of nonobviousness because, like licensing, it demonstrates respect for the patent.[510]

[D] Copying

[D][1] General Rule

"The copying of an invention may constitute evidence that the invention is not an obvious one. . . . This would be particularly true where the copyist had itself attempted for a substantial length of time to design a similar device, and had failed."[511] Evidence of copying, however, "is only equivocal evidence of non-obviousness in the absence of more compelling objective indicia of other secondary considerations."[512]

[D][2] Application to Pharmaceutical Patents

Some courts take into account the fact that a generic drug maker must copy a brand name drug to obtain FDA approval and give copying little weight in obviousness analysis.[513] However, evidence that a

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509. *Id*. at *64.

510. Ortho Pharm. Corp. v. Smith, 1990 WL 121353, at *7 (E.D. Pa. 1990), *aff'd*, 959 F.2d 936, 942 (Fed. Cir. 1992).

511. Vandenberg v. Dairy Equip. Co., 740 F.2d 1560, 1567 (Fed. Cir. 1984).

512. Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1380 (Fed. Cir. 2000); *see also In re* GPAC, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("[M]ore than the mere fact of copying by an accused infringer is needed to make that action significant to a determination of the obviousness issue."); Cable Elec. Prods. v. Genmark, Inc., 770 F.2d 1015, 1028 (Fed. Cir. 1985) (evidence needed in addition to fact of copying because the copying "could have occurred out of a general lack of concern for patent property"), *overruled on other grounds by* Midwest Indus., Inc. v. Karavan Trailers, Inc., 175 F.3d 1356, 1358–61 (Fed. Cir. 1999) (en banc).

513. *Eli Lilly*, 2004 U.S. Dist. LEXIS 14724, at *116 n.21 ("because the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects, Teva's demonstration of equivalency of Sarafem to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention"); Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 2001 U.S. Dist. LEXIS 18361, at *41–42 (S.D. Ind. Oct. 12, 2001) (recognizing on the one hand that Hatch-Waxman requires copying approved drug and on the other hand that "the very need

generic company decided to copy one brand name drug over another can be significant in an obviousness analysis.[514]

[E] Near-Simultaneous Invention

[E][1] General Rule

Evidence that others arrived at the same or similar solutions under the same state of prior art is a secondary consideration tending to show the claim was obvious.[515] "The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art."[516] However, the Federal Circuit also noted that "the possibility of near simultaneous invention by two or more equally talented inventors working independently, . . . may or may not be an indication of obviousness when considered in light of all the circumstances."[517] Near simultaneous development may have occurred after the patentee's

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for copying results from and emphasizes the unpredictability of medicinal chemistry," and concluding that courts cannot "ignore the copying as evidence of non-obviousness, even though it may be entitled to relatively little weight").

514. *Ortho-McNeil Pharm.*, 348 F. Supp. 2d at 759 (explaining that "Mylan's decision to copy LEVAQUIN instead of FLOXIN is significant evidence of non-obviousness," and rejecting Mylan's argument that it "would produce a generic drug without heavily weighing its respective properties"); Forest Labs., Inc. v. Ivax Pharm., Inc., 438 F. Supp. 2d 479, 496 (D. Del. 2006) ("The success of Lexapro® and its benefits compared with other SSRIs is also supported by the efforts of generic drug manufacturers, including Defendants, to copy the claimed invention. In the Court's view, the copying of others is particularly telling in this case, because citalopram is currently available as a generic drug. Indeed, citalopram is sold generically by Defendants, yet Defendants seek to copy and sell Lexapro®. Further, five generic drug manufacturers have sought approval to market generic escitalopram products despite the fact that they are already making or can make generic citalopram.").

515. Concrete Appliance Co. v. Gomery, 269 U.S. 177, 184–85 (1925); *Ecolochem*, 227 F.3d at 1379.

516. *Ecolochem*, 227 F.3d at 1379 (citation omitted).

517. Lindemann Maschinenfabrik GmbH v. Am. Hoist & Derrick Co., 730 F.2d 1452, 1460 (Fed. Cir. 1984); *see also In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986) ("evidence of contemporaneous invention is probative of 'the level of knowledge in the art at the time the invention was made'"); Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877 (Fed. Cir. 1998); *Hybritech*, 802 F.2d at 1380 n.4 (Fed. Cir. 1986) (evidence of development "more than a year after the . . . filing date here and roughly two years after conception" is of "little probative value").

date of invention, but would have little probative value if it occurred well after the invention date.[518]

[E][2] Application to Pharmaceutical Patents

A court may discount evidence of near simultaneous invention when countered with evidence that the other inventions were by those of extraordinary skill.[519] The existence of several groups working independently and contemporaneously employing similar reasoning to obtain similar results can be probative of obviousness.[520]

§ 5:3.8 Prior Art Disclosure of Genus Containing Claimed Species

A reference that discloses a broad genus may teach away from a species by focusing on subgroups that do not include that particular species.[521] In addition, disclosure of a broad genus without more does not render obvious a particular species within that genus.[522] "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."[523] Of course, if the prior art generic formula also discloses the species as one of the examples, it will anticipate the claimed species. However, disclosure of a broad genus, without reciting or suggesting the claimed species, does not generally render the species obvious.[524]

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518. *See Hybritech*, 802 F.2d at 1380 n.4 (holding that near-simultaneous development "two years after conception occurred" was "of little probative value").
519. *Eli Lilly*, 2004 U.S. Dist. LEXIS 14724, at *121.
520. *Merck*, 800 F.2d at 1098 n.11 (citing *Ex parte* Edward L. Engelhardt, Reissue Application No. 776,464, Appeal No. 424-40 (PTO Bd. Pat. App. Apr. 23, 1980), JA at 22(*l*)–22(m)) ("Board indicated that evidence before it revealed that four other groups of inventors independently and contemporaneously discovered amitriptyline's antidepressant properties using reasoning based on a thorough knowledge of investigative techniques, which included the concept of isosterism, used in the medicinal art area.").
521. *In re* Baird, 16 F.3d 380, 382 (Fed. Cir. 1994) ("Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols.").
522. *Id*. at 383 ("A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds."); *see also* Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1321 (Fed. Cir. 2004) ("Thus simply because an invention falls within a range disclosed by the prior art does not necessarily make it per se obvious. Both the genus and species may be patentable.").
523. *Baird*, 16 F.3d at 382.
524. *Id*. at 383; *In re* Bell, 991 F.2d 781 (Fed. Cir. 1993) (DNA sequence not obvious over prior art suggesting near infinite number of sequences

§ 5:4 Written Description*

§ 5:4.1 Statutory Provision: Section 112

[A] Written Description Is a Separate Requirement

Section 112 of the patent statute requires that the patent specification "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]"[525] This portion of section 112, according to the Federal Circuit, "mandates satisfaction of two separate and independent requirements: an applicant must both describe the claimed invention adequately and enable its reproduction and use."[526] Hence, the "written description requirement" is a requirement "separate and independent" of the "enablement requirement."[527]

[B] Controversy over Status of Written Description Requirement

That section 112 establishes a written description requirement independent of the enablement requirement, is a position not without disagreement.[528] Several members of the Federal Circuit—constituting a minority—do not interpret section 112 as creating a written description requirement separate and independent of the enablement requirement. When the Federal Circuit declined to hear *University of Rochester v. G.D. Searle & Co.*[529] en banc, Judge Linn, joined by Judges Rader and Gajarsa, issued a dissent expressing that view:

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without suggesting claimed sequence); *In re* Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) (reversing obviousness rejection of claim to a specific compound over prior art disclosure of a "potentially infinite genus" that included the species because there was no disclosure or suggestion of that species).

* Written by Aaron Stiefel and Daniel L. Reisner.

525. 35 U.S.C. § 112 (1975).

526. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1330 (Fed. Cir. 2003).

527. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 921–22 (Fed. Cir. 2004).

528. Much of the controversy centers on inventions involving nucleic acid sequences. See section 7:6.4 for a more complete discussion of this topic.

529. Univ. of Rochester v. G.D. Searle & Co., 375 F.3d 1303, 1304 (Fed. Cir. 2004).

> Section 112 . . . requires a written description of the invention, but the measure of the sufficiency of that written description in meeting the conditions of patentability in paragraph 1 of that statute depends solely on whether it enables any person skilled in the art . . . to make and use the claimed invention and sets forth the best mode of carrying out the invention.
>
> Reading into paragraph 1 of section 112 an independent written description requirement, divorced from enablement, sets up an inevitable clash between the claims and the written description as the focus of the scope of coverage.[530]

Judge Rader also wrote a dissent from the same Federal Circuit decision, joined by Judges Garaja and Linn, that further refined the opposing point of view:

> In 1997, this court for the first time applied the written description language of 35 U.S.C. § 112, ¶ 1 as a general disclosure requirement in place of enablement, rather than in its traditional role as a doctrine to prevent applicants from adding new inventions to an older disclosure. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). In simple terms, contrary to logic and the statute itself, *Eli Lilly* requires one part of the specification (the written description) to provide 'adequate support' for another part of the specification (the claims). Neither *Eli Lilly* nor this case has explained the legal basis for this new validity requirement or the standard for 'adequate support.' Because this new judge-made doctrine has created enormous confusion which this court declines to resolve, I respectfully dissent.[531]

In contrast, Judge Lourie's opinion, concurring with the denial of the rehearing *en banc*, takes a very different position on the written description requirement:

> [T]here is and always has been a separate written description requirement in the patent law. The requirement to describe one's invention is basic to the patent law, and every patent draftsman knows that he or she must describe a client's invention independent of the need to enable one skilled in the relevant art to make and use the invention. The specification then must also describe how to make and use the invention (*i.e.*, enable it), but that is a different task.

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530. *Id.* at 1325.
531. *Id.* at 1307–08.

> The requirements of the statute cannot be swept away by claiming that it relates only to priority issues or that the prohibition on introduction of new matter takes care of the need for a written description.[532]

[C] Written Description Requirement Applies to Priority Determinations and to Adequacy of Original Disclosure

The written description requirement imposes consequences in two situations.

[C][1] Later Claims and Later Applications

Claims may be amended for a variety of reasons, including the discovery of prior art that forces the surrender of some claim scope.[533] Claims may also be added in later applications, such as divisionals, continuations, and continuations-in-part, that claim priority to earlier applications. The mere fact, however, that the patentee changes what he or she claims as the invention by amending claims does not offend the written description requirement. Nor does this change the burden of proof.[534] If the new claims cover less than the disclosed subject matter, the written description requirement will not invalidate the patent.[535] However, when a patentee is trying to claim the benefit of an earlier filing date or add a claim by amendment, the patentee must be able to show the claimed invention is adequately supported by the original disclosure.[536] An applicant may not rely on the filling

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532. *Id*. at 1305.

533. *In re* Wertheim, 541 F.2d 257, 263 (C.C.P.A. 1976) ("Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable.").

534. Monsanto Co. v. Scruggs, 459 F.3d 1328, 1337 (Fed. Cir. 2006) ("Nothing about a continuation or divisional makes it inherently more likely to fail the written description requirement or changes the burden of proof.").

535. *Wertheim*, 541 F.2d at 263; *In re* Johnson, 558 F.2d 1008, 1019 (C.C.P.A. 1977) ("The notion that one who fully discloses . . . a genus and numerous species therewithin, has somehow failed to disclose . . . that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.").

536. *See, e.g.*, Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1255 (Fed. Cir. 2004); Dynamic Drinkware, LLC v. Nat'l Graphics, Inc., No. 2015–1214, 2015 WL 5166366, at *6 (Fed. Cir. Sept. 4, 2015) ("A reference patent is only entitled to claim the benefit of the filing date of its provisional application if the disclosure of the provisional application provides support for the claims in the reference patent in compliance with § 112, ¶ 1."); Amgen Inc. v. Sanofi, 872 F.3d 1367, 1380 (Fed. Cir. 2017)

date of a parent application for content that appears only in the grandparent but not in the parent application and was not incorporated by reference.[537]

[C][2] Unsupported Original Claims

Even claims originally filed with the initial patent application can fail to satisfy the written description requirement. This is despite the fact that the originally filed claim is itself considered part of the specification.[538]

§ 5:4.2 The Requirement

[A] The Purpose of the Requirement

"The 'written description' requirement serves a teaching function, as a 'quid pro quo' in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'"[539] Another "purpose of the written description

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("We have previously stated that 'for the non-provisional utility application to be afforded the priority date of the provisional application, . . . the written description of the provisional must adequately support the claims of the non-provisional application.'") (citing New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1294 (Fed. Cir. 2002)).

537. Application of Seversky, 474 F.2d 671, 673–74 (C.C.P.A. 1973).

538. *See, e.g.*, LizardTech, Inc. v. Earth Res. Mapping, Inc., 424 F.3d 1336, 1346 (Fed. Cir. 2005) ("an originally filed claim can provide the requisite written description to satisfy section 112"; however, "nothing in claim 21 or the specification constitutes an adequate and enabling description" despite the fact that "claim 21 is part of the original disclosure"); *Rochester*, 358 F.3d at 922; *see also* Ariad Pharm., Inc. v. Mass. Inst. of Tech., 560 F.3d 1366 (Fed. Cir. 2009); *Enzo*, 323 F.3d at 968 (written description requirement not satisfied by "[t]he appearance of mere indistinct words in a specification or a claim, even an original claim.").

539. *Rochester*, 358 F.3d at 922; *see also* Gilead Scis., Inc. v. Natco Pharma Ltd., 753 F.3d 1208, 1212 (Fed. Cir. 2014) (obviousness-type double patenting "is based on the core principle that, in exchange for a patent, an inventor must fully disclose his invention and promise to permit free use of it at the end of his patent term. . . . The bar against double patenting was created to preserve that bargained-for right held by the public."). Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 150–51 (1989) (patent system "embodies a carefully crafted bargain" to encourage "the creation and disclosure of new" inventions and "consequent benefit to the community"); Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 484 (1974) (disclosure is "the quid pro quo" of the right to exclude); Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005) ("The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.").

requirement . . . [is] to ensure that the applicant had possession of the invention as of the filing date."[540] Additionally, another purpose of the requirement is to establish conception and that the applicant "actually invented the subject matter it claimed."[541]

The written description requirement also serves to "prevent[ ] applicants from using the amendment process to update their disclosures (claims or specifications) during their pendency before the patent office. Otherwise, applicants could add new matter to their disclosures and date them back to their original filing date, thus defeating an accurate accounting of the priority of invention."[542]

[B] The Standard Set Forth by the Federal Circuit

[B][1] Basic Test

The Federal Circuit has stated that the written description requirement obligates the applicant to "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*."[543] The written description requires that "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims."[544] A disclosure satisfies this requirement if it "allow[s]

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540. Enzo Biochem. Inc. v. Gen-Probe, Inc., 323 F.3d 946, 969 (Fed. Cir. 2002).

541. *Rochester*, 358 F.3d at 930 n.10; *see also* Amgen Inc. v. Sanofi, 872 F.3d 1367, 1373 (Fed. Cir. 2017) (the written description "requirement ensures 'that the inventor actually invented the invention claimed'") (quoting Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010)).

542. *Chiron*, 363 F.3d at 1255; Schriber-Schroth Co. v. Cleveland Tr. Co., 305 U.S. 47, 57 (1938) ("the application for a patent cannot be broadened by amendment so as to embrace an invention not described in the application as filed"); Turbocare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co., 264 F.3d 1111, 1118 (Fed. Cir. 2001) ("When the applicant adds a claim or otherwise amends his specification after the original filing date . . . the new claims or other added material must find support in the original specification."); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed. Cir. 1991) (the written description requirement applies "whether the case factually arises out of an assertion of entitlement to the filing date of a previously filed application under § 120 . . . or arises in the interference context wherein the issue is support for a count in the specification of one or more of the parties . . . or arises in an ex parte case involving a single application, but where the claim at issue was filed subsequent to the filing of the application.").

543. *Vas-Cath*, 935 F.2d at 1563–64.

544. Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323 (Fed. Cir. 2000).

one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described."[545]

There is a relationship between the scope of the claim as construed by the court and the difficulty of satisfying the written description requirement.[546] If a claim limitation does not relate to one of the operative steps of a claim and merely defines a composition that is used in a claimed method, the disclosure need only be "substantially equivalent" to that limitation.[547]

[B][2] Predictability, Criticality, and Other Factors

The "descriptive text" needed to meet the written description requirement "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence."[548] "A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention

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545. Koito Mfg. Co. v. Turn-Key-Tech., LLC, 381 F.3d 1142, 1154 (Fed. Cir. 2004); *Rochester*, 358 F.3d at 923; *Enzo*, 323 F.3d at 967; Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997).

546. *Ariad*, 560 F.3d at 1376–77 (invalidating claims for lack of written description while noting that "Ariad maintained the breadth of these claims through claim construction and into trial. . . . Ariad chose to assert claims that are broad far beyond the scope of the disclosure provided in the specification."); *see also* Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1380 (Fed. Cir. 2007) (invalidating claims for lack of enablement based on broad claim constructing while noting "[t]he motto, 'beware of what one asks for,' might be applicable here."); Idenix Pharm. LLC v. Gilead Scis. Inc., 941 F.3d 1149, 1156 n.3 (Fed. Cir. 2019) (observing that "under a narrower construction, the claims of the '597 patent might well be enabled, and the accused product would not infringe"); Trs. of Bos. Univ. v. Everlight Elec. Co., 896 F.3d 1357, 1365 (Fed. Cir. 2018) ("Having obtained a claim construction that included a purely amorphous layer within the scope of the claim, BU then needed to successfully defend against an enablement challenge as to the claim's full scope.").

547. Nalpropion Pharm., Inc. v. Actavis Labs. FL, Inc., 934 F.3d 1344, 1348 (Fed. Cir. 2019) (claim to method of treatment using a mixture of bupropion and sustained-release naltrexone as determined by "dissolution test of USP Apparatus 2 Paddle Method" supported by disclosure of data using "USP Apparatus 1 Basket Method" because the two were found to be "substantially equivalent").

548. *Capon*, 418 F.3d at 1357; *see also* Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006) (affirming judgment finding written description requirement satisfied because "based upon the sequence of events described in the specification," the inferential step required "'is so straight forward that a detailed description in the specification is not necessary'").

without describing all species that claim encompasses."[549] Whether a claim limitation is supported, for purposes of the written description requirement, by a narrower disclosure, may turn on the predictability of the particular art.[550] Where the art is predictable, a narrow disclosure may demonstrate that a person of skill in the art has possession of an invention that is broader in scope; when the art is unpredictable, a narrow disclosure may not support a broader claim.[551]

For biological subject matter, a "variety of factors" determine whether a specification supports "generic claims to biological subject matter . . . ."[552] These factors include:

- "the existing knowledge in the particular field";
- "the extent and content of the prior art";
- "the maturity of the science or technology"; and
- "the predictability of the aspect at issue."[553]

"In addition to predictability," courts "have held that the criticality or importance of an unclaimed limitation to the invention can be

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549. Utter v. Hiraga, 845 F.2d 993, 998 (Fed. Cir. 1988) (disclosure of device with preferred embodiment having an internal pivot supported generic claim that encompassed embodiments with internal pivot or external pivot); *see also In re* Cavallito, 282 F.2d 357, 361 (C.C.P.A. 1960) ("The mere fact that a claim covers a large, or even an unlimited number of products, does not necessarily establish that it is too broad.").

550. *In re* Smythe, 480 F.2d 1376, 1382–83 (C.C.P.A. 1973) ("We cannot agree with the broad proposition . . . that in every case where the description of the invention in the specification is narrower than that in the claim there has been a failure to fulfill the description requirement in section 112. Each case must be decided on its own facts."); *Capon*, 418 F.3d at 1357 ("Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.").

551. *Smythe*, 480 F.2d at 1383 ("This is not a case where there is any unpredictability such that appellants' description of air or inert gas would not convey to one skilled in the art knowledge that appellants invented an analysis system with a fluid segmentizing medium. In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application.").

552. *Capon*, 418 F.3d at 1359.

553. *Id.*; Ariad Pharm., Inc. v. Mass. Inst. of Tech., 560 F.3d 1366, 1372 (Fed. Cir. 2009) ("Lilly offered the undisputed expert testimony of David Latchman that the field of the invention was particularly unpredictable.").

relevant to the written description inquiry."[554] The Federal Circuit permitted issuance of a reissue application seeking to broaden claims so they no longer required having a metal tip with a tapered shape because the shape was not critical to overcoming prior art and "one skilled in the art would readily understand that in practicing the invention it is unimportant whether the tips are tapered."[555] On the other hand, when the patentee relies on a distinction over the prior art, the specification will be read as limited to what was actually disclosed.[556]

[B][3] Acceptable Forms of Description

The patent applicant may satisfy the written description requirement "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention."[557] The written description requirement may also be satisfied by a functional description "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure."[558] Only "[t]he original claims as filed," as opposed to the amended claims, "are part of the patent specification" and considered when evaluating the adequacy of the written description.[559]

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554. *In re* Glob. IP Holdings LLC, 927 F.3d 1373, 1377 (Fed. Cir. 2019).
555. *In re* Peters, 723 F.2d 891, 893–94 (Fed. Cir. 1983).
556. *See* Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998) ("Instead of suggesting that the '589 patent encompasses additional shapes, the specification specifically distinguishes the prior art as inferior and touts the advantages of the conical shape of the '589 cup. . . . Such statements make clear that the '589 patent discloses only conical shaped cups and nothing broader."); *In re* Sus, 306 F.2d 494, 505 (C.C.P.A. 1962) (affirming rejection for lack of written description: "It is sufficient to say that [the claims] cannot be read with the inclusiveness required by their broad language without eliminating therefrom the distinctions over the prior art which are here asserted by appellants as their invention.").
557. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see also* Koito Mfg. Co. v. Turn-Key-Tech., LLC, 381 F.3d 1142 (Fed. Cir. 2004) (holding that patent figure that showed that the flow channel was significantly thicker and wider than the adjacent mold cavity provided written description support for a claim limitation to a "flow channel" defined "as a portion of a mold cavity which is significantly thicker and wider than the adjacent mold cavity thickness"); Martin v. Johnson, 454 F.2d 746, 774, 751 (C.C.P.A. 1972) ("the omission of the structural formula . . . is of no consequence" because the specification discloses the "chemical name which reveals the chemical structure of the compound").
558. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) (discussing Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002)); *see Enzo*, 323 F.3d at 964.
559. N. Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 938 (Fed. Cir. 1990).

A very brief description, if otherwise adequate, can satisfy the written description requirement.[560] "An excess of description," furthermore, "does not injure the patent, unless the addition be fraudulent."[561] In addition, a specification need not "specifically mention a limitation that later appears in the claims . . . when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented."[562] A description, however, which merely "renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention."[563] Nor does a description of the hoped-for result of an invention suffice as a description of that invention.[564] The sufficiency of the written description must be "determined claim by claim."[565]

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560. Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365–66 (Fed. Cir. 2006) ("No length requirement exists for a disclosure to adequately describe an invention."); *In re* Hayes Microcomputer Prods., Inc. Patent Litig., 982 F.2d 1527, 1534 (Fed. Cir. 1992) (adequacy of the description evaluated "on its content in relation to the particular invention, not its length").

561. Sewall v. Jones, 91 U.S. 171, 186 (1875).

562. All Dental Prodx, LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 779 (Fed. Cir. 2002) ("Here, the invention involves heating a mass of thermoplastic material that lacks an identifiable form. That invention is described in the specification, albeit not *in haec verba*. It is also clear what the invention is not. It does not involve heating a thermoplastic mass having an identifiable form or shape. We therefore conclude that there are no genuine issues of material fact that the specification describes the claimed invention within the meaning of the statute.").

563. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1567 (Fed. Cir. 1997); *see also* TurboCare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co., 264 F.3d 1111, 1119 (Fed. Cir. 2001) (claims should be invalidated even if the claimed "embodiment may have been obvious from [the patent's] vague reference to a 'spring located . . . adjacent to said rings'"); Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997).

564. Ariad Pharm., Inc. v. Mass. Inst. of Tech., 560 F.3d 1366, 1374 (Fed. Cir. 2009) ("In the context of this invention, a vague functional description and an invitation for further research does not constitute written disclosure of a specific inhibitor."); Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004) (claim to method of using COX-2 selective compound to treat inflammation not supported by disclosure that failed to identify such a compound and where there was no evidence skilled artisans knew of such compounds); *In re* Wilder, 736 F.2d 1516, 1520–21 (Fed. Cir. 1984) (disclosing that "an object of the present invention to provide improved indicating apparatus for indicating the location of particular information on a record medium" insufficient to claim such apparatus because this was "little more than outlining goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate. . . . [T]he invention that achieves these general objectives must still be described.").

565. Capon v. Eshhar, 418 F.3d 1349, 1360 (Fed. Cir. 2005).

[B][4] Fact Determination

Satisfaction of the written description requirement is a question of fact, measured by the understanding of the ordinarily skilled artisan.[566] Several examples of inadequate written descriptions illustrate the application of the requirement.[567] In appropriate cases, however, the lack of an adequate written description can be decided as a matter of law.[568] Conclusory expert declarations do not create fact issues

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566. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) (specification's description of producing claimed EPO in two species of vertebrate or mammalian cells adequately supported claims covering EPO made using genus vertebrate or mammalian cells given that "the words 'vertebrate' and 'mammalian' readily 'convey[ ] distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identity of the members of the genus'").

567. *See, e.g.*, PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1307 (Fed. Cir. 2008) (invalidating claim where "Original Application described a vending machine with a 'display' or user interface' as part of the vending machine, rather than a vending machine with a 'customer interface' located on a customer's electronic device" as per the claim in the patent issuing on the CIP); PIN/NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235, 1247 (Fed. Cir. 2002) (invalidating claim that covers "separate application of the ingredients" because "nothing in the specification indicates that the invention is anything other than a mixture of two chemicals"); Augustine Med., Inc. v. Gaymar Indus., Inc., 181 F.3d 1291, 1303 (Fed. Cir. 1999) (claiming a "blanket which covers only a portion of a patient's body" not supported by disclosing "blanket 'up to the chin area'"); Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998) (claims that are "generic" as to the shape of a cup implant not supported by disclosure of "only conical shaped cups and nothing broader"); Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479–80 (Fed. Cir. 1998); *Lockwood*, 107 F.3d at 1572 (claiming any terminal containing a videodisc player not supported by disclosing TV with a keypad connected to central computer with videodisc player); *Wilder*, 736 F.2d at 1517–18, 1521 (claiming a "genus of indicating mechanisms" that do not require synchronous scanning not supported by disclosing a "species" of an indicating mechanism that requires synchronous scanning).

568. ICU Med., Inc. v. Alaris Med. Sys., Inc., 558 F.3d 1368, 1378–79 (Fed. Cir. 2009) ("We affirm the district court's grant of summary judgment of invalidity with respect to the asserted spikeless claims under the written description requirement of § 112."); *Ariad*, 560 F.3d at 1376 ("[T]he jury lacked substantial evidence for its verdict that the asserted claims were supported by adequate written description, and [we] thus hold the asserted claims invalid."), *aff'd en banc*, 598 F.3d 1366 (Fed. Cir. 2010); *PowerOasis*, 522 F.3d at 1301 (affirming summary judgment); Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004) (affirming summary judgment); *PIN/NIP*, 304 F.3d 1235 (reversing district court denial of JMOL that claim failed to meet written description requirement); Turbocare Div. of Demag Delaval Turbomachinery Corp. v.

sufficient to defeat summary judgment.[569]

[C] Conception and Written Description

"Conception is the touchstone of inventorship," which is "the completion of the mental part of invention."[570] Accordingly, the Federal Circuit has required the same particularity for proof of written description as for conception.[571] Conception—and therefore description—requires the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice."[572]

The courts have applied the conception standard to the written description requirement for chemical compounds. Courts have ruled that one has not conceived of a chemical compound if one has only identified hoped-for biological properties that are not associated with any known or disclosed compounds.[573]

Gen. Elec. Co., 264 F.3d 1111, 1119–20 (Fed. Cir. 2001) (affirming summary judgment); Augustine Med., Inc. v. Gaymar Indus., Inc., 181 F.3d 1291, 1303 (affirming summary judgment that the "application does not disclose the subject matter claimed in" the broadened claims); *Tronzo*, 156 F.3d at 1160 (reversing judgment that broad claims were supported by narrow disclosure and invalidating them as a matter of law); Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479–80 (Fed. Cir. 1998) (reversing a judgment that several claims were not invalid and invalidating claims broadened by amendment); *Lockwood*, 107 F.3d at 1571–72 (affirming summary judgment of invalidity because later-filed claim not supported by original disclosure).

569. *Ariad*, 560 F.3d at 1376 n.3 ("Dr. Kadesch certainly offered a general conclusion that he thought the inventors were in possession of the claimed invention in 1989. This conclusory testimony . . . is devoid of any factual content upon which the jury could have relied when considering the specification of the '516 patent."), *aff'd en banc*, 598 F.3d 1366 (Fed. Cir. 2010); *TurboCare*, 264 F.3d at 1119 (rejecting patentee's argument and "conclusory statements" of its expert); *PowerOasis*, 522 F.3d at 1306–10 (rejecting "conclusory expert declaration").

570. Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1227–28 (Fed. Cir. 1994).

571. Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993) ("If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. . . . [O]ne cannot describe what one has not conceived."); *see also Burroughs Wellcome*, 40 F.3d at 1228 ("The conception analysis necessarily turns on the inventor's ability to describe his invention with particularity.").

572. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991); Coleman v. Dines, 754 F.2d 353, 359 (Fed. Cir. 1985).

573. *Amgen*, 927 F.2d at 1206 ("Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or

Conception should not be confused with reduction to practice which is not required for written description.[574]

§ 5:4.3 *Genus and Species*

[A] Claimed Genus That Ignores Essential Element of the Invention

The Federal Circuit in *Gentry Gallery, Inc. v. Berkline Corp.*[575] found a claim to a sectional sofa with reclining controls invalid because it did not require the controls to be on the console even though "one skilled in the art would clearly understand that it was . . . essential to [the] invention, for the controls to be on the console."[576] The court based its decision on the language of specification:

> In this case, the original disclosure clearly identifies the console as the only possible location for the controls. It provides for only the most minor variation in the location of the controls, noting that the control "may be mounted on top or side surfaces of the console rather than on the front wall . . . without departing from this invention." . . . No similar variation beyond the console is even suggested. Additionally, the only discernible purpose from the console is to house the controls. As the disclosure states, identifying the only purpose relevant in the console, "[a]nother object of the present invention is to provide . . . a console positioned between [the reclining seats] that accommodates the controls for both of the reclining seats." Thus, locating the controls anywhere but on the console is outside the stated purpose of the invention.[577]

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whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property . . . because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property."); Oka v. Youssefyeh, 849 F.2d 581, 583 (Fed. Cir. 1988) (conception of a compound "requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it"); *Burroughs Wellcome*, 40 F.3d at 1229 ("Conception of a chemical substance includes knowledge of both the specific chemical structure of the compound and an operative method of making it.").

574. Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("[T]he written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent[.]"); *Rochester*, 358 F.3d at 926 ("We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an actual reduction to practice. Constructive reduction to practice is an established method of disclosure . . . .").

575. Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473 (Fed. Cir. 1998).

576. *Id*. at 1480.

577. *Id*. at 1479.

Claims that are construed more broadly may have greater difficulty satisfying the written description requirement.[578]

[A][1] Limiting Gentry

Several cases subsequent to *Gentry* have cautioned against applying it too broadly.[579]

The accused infringer in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*[580] argued, based on *Gentry*, that the claims should be invalidated if construed to cover use of endogenous erythropoietin because the disclosure was limited to use of exogenous DNA and the specification stated that the invention is "uniquely characterized" by exogenous expression of DNA.[581] The court rejected this argument because there was an indication in the background section of the patent that the invention broadly related to the use of "recombinant procedures" to make polypeptides possessing the "biological properties of naturally occurring erythropoietin."[582] In addition, the patentee could not "have described the other method, as it was not developed until 10 years later."[583]

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578. *Ariad*, 560 F.3d at 1376–77 (invalidating claims for lack of written description while noting that "Ariad maintained the breadth of these claims through claim construction and into trial. . . . Ariad chose to assert claims that are broad far beyond the scope of the disclosure provided in the specification."), *aff'd*, 598 F.3d 1336 (Fed. Cir. 2010); *see also* Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1380 (Fed. Cir. 2007) (invalidating claims for lack of enablement based on broad claim constructing while noting "[t]he motto, 'beware of what one asks for,' might be applicable here"). *See supra* note 546.

579. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1333 (Fed. Cir. 2003) (referring to statements in *Gentry* "that one of ordinary skill in the art would clearly understand that the location of the reclining controls on the claimed sectional sofa 'was not only important, but essential to [the] invention'" as "probably only dicta"); Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc., 291 F.3d 1317, 1323 (Fed. Cir. 2002) ("we did not announce [in *Gentry*] a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements."); Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 993 (Fed. Cir. 1999) ("*Gentry Gallery*, then, considers the situation where the patent's disclosure makes crystal clear that a particular (*i.e.*, narrow) understanding of a claim term is an 'essential element' of [the inventor's] invention.").

580. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003).

581. *Id*. at 1334.

582. *Id*.

583. *Id*.

The Federal Circuit, in another case, held that "the district court erroneously found the claims invalid under *Gentry Gallery*," although the claims were properly invalid under *Eli Lilly*.[584] The district court found that "lethality was an essential feature of the invention" but the claims were not limited to that feature. The Federal Circuit explained that *Gentry* does not establish a new "essential element" test and "that even if such a test existed, lethality was only a reason for the claimed invention, and not an element of it that needed to be defined in the claims."[585]

[A][2] Applying Gentry

Despite the warning to limit the application of *Gentry*, claims will still be invalidated when they claim more broadly than the disclosure.[586]

[B] Species Based on a Disclosed Genus

A patent which discloses a genus and claims a particular species within that genus does not satisfy the written description requirement without some disclosure directing one towards that species.[587]

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584. Carnegie Mellon Univ. v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1127 (Fed. Cir. 2008) (citing *Gentry*, 134 F.3d 1473; Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997)).

585. *Id*.

586. PIN/NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235, 1238–39, 1247 (Fed. Cir. 2002) (invalidating claim to "method of inhibiting sprout formation on tubers during storage" by applying two compounds to the tubers without requiring they be applied together because "nothing in the specification indicates that the invention is anything other than a mixture of two chemicals"); *see also In re* Wilder, 736 F.2d 1516, 1517–18, 1520 (Fed. Cir. 1984) (affirming rejection of claims "directed to the genus of indicating mechanisms that visually identify positions on a recording medium when the recording medium is scanned" because the patentee admitted "that the synchronous scanning equipment is the only embodiment of the invention disclosed in the original patent").

587. Purdue Pharma L.P. v. Collegium Pharm., Inc., __ F.4th __ (Fed. Cir. 2023); Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336 (Fed. Cir. 2013) (finding no written description for claimed enzyme species where the specification discussed genus of enzymes and disclosed in various places the individual limitations of the claimed enzymes but did not disclose those limitations together to indicate inventor actually possessed an enzyme with all of those limitations); *In re* Ruschig, 379 F.2d 990, 994 (C.C.P.A. 1967) ("Specific claims to single compounds require reasonably specific supporting disclosure and while . . . naming is not essential, something more than the disclosure of a class of 1,000 or 100, or even 48, compounds is required."); *see also* Fujikawa v. Wattanasin, 93 F.3d 1559, 1570–71 (Fed. Cir. 1996) (in the absence of disclosure that singles out the claimed "tree" in the forest, "simply describing a large

Likewise, disclosure of a range may not support a claim to one of the range's endpoints.[588]

[C] Genus Based on Disclosed Species or Examples

A genus can be supported by "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."[589]

Mere disclosure of a limited number of species not sufficiently representative of the genus fails to satisfy the written description requirement.[590] Accordingly, in some cases courts have found the species disclosure to be insufficient to support the genus claim.[591] Other

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genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses"); Fields v. Conover, 443 F.2d 1386, 1391–92 (C.C.P.A. 1971) (broad genus and examples did not support sub-genus). *But see In re* Edwards, 568 F.2d 1349 (C.C.P.A. 1978); *In re* Driscoll, 562 F.2d 1245, 1250 (C.C.P.A. 1977) ("Any seeming similarity between *Ruschig* and the present case is illusory, however, because the structural formula there relied on could have described, at best, only a subgenus including the specific compound claimed, and not the compound itself. In this respect, *Ruschig* is readily distinguishable from the present case where the exact subgenus claimed is clearly discernible in the generalized formula of the thiadiazole urea set forth in the earlier filed application.").

588. Biogen Int'l GmbH v. Mylan Pharm. Inc., 18 F.4th 1333, 1343 (Fed. Cir. 2021) ("The DMF480 dose is listed only once in the entire specification . . . . [and] appears at the end of one range among a series of ranges," supporting the court's finding of insufficient written description).

589. Ariad Pharm., Inc. v. Eli Lily & Co., 598 F.3d 1366, 1350 (Fed. Cir. 2010) (en banc).

590. See *infra* section 5:4.5[B][3] for a further description of cases concerning nucleic acid genus claims.

591. Ajinomoto Co. v. ITC, 932 F.3d 1342, 1359 (Fed. Cir. 2019) (substantial evidence supports upholding written description for claim to method of making an aromatic L-amino acid with an expression bacterium using a disclosed gene sequence for the amino acid with enhanced promoters because the patent provided "four examples of 'potent promoters'" and "the genus of more potent promoters was already well explored in the relevant art"); AbbVie Deutschland Gmbh & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1290, 1299–1302 (Fed. Cir. 2014) (upholding jury verdict that structurally similar antibodies supporting the full range of claimed binding affinities were not sufficient to claim the entire genus because they contained antibodies that differed structurally from the disclosed antibodies); Synthes USA, LLC v. Spinal Kinetics, Inc., 734 F.3d 1332, 1342 (Fed. Cir. 2013) (affirmed jury verdict that disclosure of "grooves" did not support claim to "any sort of opening located

cases, on different facts, reached the opposite conclusion.[592]

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anywhere on the cover plates to anchor the fiber system"); ICU Med., Inc. v. Alaris Med. Sys., Inc., 558 F.3d 1368, 1378–79 (Fed. Cir. 2009) (claims to medical valves that did not require a spike held invalid because "the specification describes only medical valves with spikes"); *Ariad*, 560 F.3d at 1376 ("Whatever thin thread of support a jury might find in the decoy-molecule hypothetical simply cannot bear the weight of the vast scope of these generic claims" to any method of reducing NF-KB activity); *In re* Alonso, 545 F.3d 1015, 1018, 1021 (Fed. Cir. 2008) ("the one compound disclosed by Alonso cannot be said to be representative of a densely populated genus" of "monoclonal antibodies idiotypic to the neurofibrosarcoma"—a class of antibodies that target malignant nerve sheath tumor); Carnegie Mellon Univ. v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1125 (Fed. Cir. 2008) ("generic claims . . . not limited to a single bacterial species, but broadly encompass[ing] coding sequences from *any* bacterial species" not support by disclosure of "the *poIA* gene coding sequence from one bacterial source" when "at the time of the invention, only three bacterial *poIA* genes . . . out of thousands of bacterial species had been cloned"); *In re* Lew, 257 F. App'x 281, 285 (Fed. Cir. 2007) (unpublished) ("ball bearing" not support for "curved member"); Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997) (a genus of compounds or DNA sequences was not described where a representative number of the compounds or DNA sequences were not recited); *Wilder*, 736 F.2d at 1518, 1520 ("synchronous scanning equipment" species did not support claim to "genus of indicating mechanisms that visually identify positions on a recording medium when" scanned); *see also In re* Gosteli, 872 F.2d 1008 (Fed. Cir. 1989); *In re* Smith, 458 F.2d 1389, 1395–96 (C.C.P.A. 1972) (rejecting argument that "disclosure of a genus and a species of a subgenus is a sufficient description of the subgenus" where "claimed subgenus of coating compounds with at least 8 carbon atoms was not adequately described in the earlier application which disclosed compounds with at least 12 carbons"); *In re* Sus, 306 F.2d 494 (C.C.P.A. 1962); *In re* Cavallito, 306 F.2d 505 (C.C.P.A. 1962); *In re* Shokal, 242 F.2d 771, 776 (C.C.P.A. 1957) ("[N]either the broad language relied on by appellants nor the specific examples given by them are sufficient to identify or point out the particular genus recited . . . .").

592. Tobinick v. Olmarker, 753 F.3d 1220, 1227 (Fed. Cir. 2014) ("administered locally" limitation supported by disclosure "of *at least one* embodiment," that is, "epidural injection"); *In re* Wallach, 378 F.3d 1330, 1333 (Fed. Cir. 2004) ("[T]he complete amino acid sequence of a protein [may] put one in possession of the genus of the DNA sequences encoding it."); Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 967 (Fed. Cir. 2002) ("If those sequences are representative of the scope of the genus claims; *i.e.*, if they indicate that the patentee has invented species sufficient to constitute the genera, they may be representative of the scope of those claims."); *In re* Herschler, 591 F.2d 693, 700 (C.C.P.A. 1979) (using DMSO to enhance penetration across the skin of any steroid supported by example of using DMSO with one specified steroid); *In re* Surrey, 370 F.2d 349, 353 (C.C.P.A. 1966) ("specific examples . . . along with" statement in "specification that those aromatic radicals can be substituted

Furthermore, one cannot claim a genus that is only supported by choosing an unmentioned characteristic of particular examples.[593]

[D] Functional Genus

The risk of inadequate written description is "especially acute with genus claims that use functional language to define the boundaries of a claimed genus."[594] A genus claim may be adequately described when a patentee has disclosed "[1] a representative number of species falling within the scope of the genus or [2] structural features common to the members of the genus"—but only if that permits the skilled artisan to "'visualize or recognize' the members of the genus."[595]

If a patentee identifies a genus of compounds that might possess the claimed functional properties, the patent must provide "blaze marks which single out particular" compounds in the genus.[596] If a skilled artisan reading the patent "would not 'visualize or recognize' the members of the genus" as including all of the claimed embodiments, the specification could not demonstrate the inventor had possession of those embodiments at the time of filing.[597] If a challenger introduces even a modicum of evidence demonstrating that success of a single example covered by a functionally defined genus claim does not automatically mean success for other claimed embodiments to which the patentee fails to respond, the claims can be invalidated as a matter of law for lack of written description.[598]

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with the same substituents exemplified for the phenyl radical" adequately supports chemical genus claim); *Cavallito*, 282 F.2d at 361; *In re* Grimme, 274 F.2d 949, 952 (C.C.P.A. 1960).

593. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1327 (Fed. Cir. 2000) ("[P]ick[ing] a characteristic possessed by two of their [disclosed] formulations, a characteristic that is not discussed even in passing in the disclosure, and then make it the basis of claims that cover not just those two formulations, but any formulation that has that characteristic . . . is exactly the type of overreaching the written description requirement was designed to guard against.").

594. *Ariad*, 598 F.3d at 1349.

595. *Amgen*, 872 F.3d at 1373 (quoting *Ariad*, 598 F.3d at 1350).

596. Idenix Pharm. LLC v. Gilead Scis. Inc., 941 F.3d 1149, 1164 (Fed. Cir. 2019).

597. *Id*. at 1164–65 (the "working examples, formulas synthesis routes and the target" disclosed by the patent all "suffer from the same flaw" because none of them provide "any meaningful guidance into what compounds beyond the examples and formulas, if any, provide the same result").

598. BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Res. Org., ___ F.3d ___ (Fed. Cir. 2022) ("jury had no reasonable basis to reject [challenger's] evidence, thin as it was, of inadequate written-description support" where the patentee "has not meaningfully disputed BASF's general point"—based on "hardly any but some [evidence]"—"that success in *Arabidopsis*

[D][1] Representative Species

In *Carnegie Mellon*, the court noted that "the narrow disclosure of the *E. coli polA* gene is not representative of and fails to adequately support the entire claimed genus" "of recombinant plasmids that contain coding sequences for DNA polymerase or nick-translation activity from any bacterial source."[599]

In *Eli Lilly*, "the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin."[600] Subsequently, the Federal Circuit distinguished *Eli Lilly* because "at the time of the invention, the sequences of RT genes were known [in the art] and members of the RT gene family shared significant homologies from one species of RT to another."[601]

In *Juno*, the court held that "two example scFvs for binding two targets did 'not provide information sufficient to establish that a skilled artisan would understand *how to identify* the species of scFvs capable of binding to the limitless number of targets as the claims require. . . . Without more in the disclosure, such as the characteristics of the exemplary scFvs that allow them to bind to particular targets or nucleotide sequences, the mere fact that scFvs in general bind' is not sufficient."[602]

[D][2] Common Structural Features

Claims have rarely been supported by common structural features.[603] Merely explaining that "scFvs have the same general, common

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did not automatically mean success (or possession of the invention) in *all* plant cells").

599. Carnegie Mellon Univ. v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1125, 1126 (Fed. Cir. 2008).

600. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997).

601. Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052, 1073 (Fed. Cir. 2005).

602. Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2022).

603. *Idenix*, 941 F.3d at 1164 (no common structural features because the specification "provides no method of distinguishing effective from ineffective compounds for the compounds reaching beyond the formulas disclosed in the '597 patent"); AbbVie Deutschland Gmbh & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1290, 1301 (Fed. Cir. 2014) ("the '128 and '485 patents do not describe any common structural features of the claimed antibodies"); *Eli Lilly*, 119 F.3d at 1568 ("[A] generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more . . . does not define any structural features commonly possessed by members of the genus that distinguish them from others.").

structure" is insufficient to support claims to scFvs with specific functional properties because they fail "to disclose a way to distinguish those scFvs capable of binding from scFvs incapable of binding those targets."[604]

One example of a claim that was supported by disclosure of common structural features is a genus claim requiring use of more potent promoters.[605] The Federal Circuit upheld a finding of common structural features based on substantial evidence that "promoters having fewer departures from a 'consensus sequence' in a promoter are generally stronger than promoters with more departures from such a sequence."[606] The court was not dissuaded despite evidence that "similarity to the consensus sequence is 'still not enough to predict the site and strength of promoter from a given sequence'" and that "the strongest promoters in *E. coli* do not necessarily adhere to the consensus sequence."[607] The Federal Circuit rejected defendant's argument because it "assumes too strict a legal standard." "Adequate written description does not require a perfect correspondence between the members of the genus and the asserted common structural feature; for a functionally defined genus like the one at issue here, we have spoken more modestly of a *'correlation* between structure and function.'"[608]

[E] Genus Based on Generic Description

When the knowledge in the art allows, a genus may be adequately described by a generic description without the need for representative examples.[609] Thus, the art is sufficiently developed when the mere

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604. *Juno*, 10 F.4th at 1339.
605. Ajinomoto Co. v. ITC, 932 F.3d 1342, 1358–59 (Fed. Cir. 2019).
606. *Id*. at 1359–60.
607. *Id*. at 1360.
608. *Id*. (quoting Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010)).
609. Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006) ("examples are not necessary to support the adequacy of a written description"); LizardTech, Inc. v. Earth Res. Mapping, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005) ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language."); *In re* Koller, 613 F.2d 819, 823 (C.C.P.A. 1980) ("[N]either a listing of representative compounds nor an example is always necessary in completely describing a generic class."); *In re* Robins, 429 F.2d 452, 456–57 (C.C.P.A. 1970) ("Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 . . . . But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language.").

mention of the name of a genus conveys a description of its members to a skilled artisan, which is all the law requires.[610] The term antibiotic today describes a well-known genus of compounds but in the early twentieth century merely described a hoped-for property in unknown compounds.

If a generic term by itself informs the skilled artisan, the use of examples does not necessarily limit the genus.[611] Making arguments, however, that a particular feature distinguishes it from the prior art is evidence that the invention does not extend to a broader genus containing that feature.[612]

[F] Range Cases

Ranges—like chemical formulas, permutations to DNA sequences, and generic terms such as solvents or salts—can define a genus. Yet courts sometimes treat ranges differently. The Court of Customs and Patent Appeals saw "an important practical distinction between broad generic chemical compound inventions" and inventions in which a range "is but one of several *process* parameters."[613] Sometimes, varying a parameter within a range produces results predictable to the skilled artisan.[614] Where there is no evidence "in terms of the operability of

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610. *Koller*, 613 F.2d at 823 ("liquid medium" sufficient to describe broad class); Streck Labs. v. Beckman Coulter, Inc., 2002 WL 1012965, at *6 (N.D. Neb. May 20, 2002) ("The evidence shows that there was no need to describe 'analogs' or 'surrogates' in Streck's patent documents because the use of an analog or surrogate . . . was commonly known[.]"); *cf.* Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998) (disclosing "two species of cups" does not support the "later-claimed, generic" shaped hip prosthesis).

611. *Koller*, 613 F.2d at 823 ("[D]isclosure of specifics adds to the understanding one . . . would glean from a generic term, but it does not follow that such added disclosure limits the meaning thereof.").

612. *Tronzo*, 156 F.3d at 1159 ("Instead of suggesting that the '589 patent encompasses additional shapes, the specification specifically distinguishes the prior art as inferior and touts the advantages of the conical shape of the '589 cup. Such statements make clear that the '589 patent discloses *only* conical shaped cups and nothing broader.") (citations omitted); *In re* Sus, 306 F.2d 494, 505 (C.C.P.A. 1962) (affirming rejection for lack of written description: "It is sufficient to say that [the claims] cannot be read with the inclusiveness required by their broad language without eliminating therefrom the distinctions over the prior art which are here asserted by appellants as their invention.").

613. *In re* Wertheim, 541 F.2d 257, 264 (C.C.P.A. 1976) (emphasis added).

614. *Id.* ("What those skilled in the art would expect from using 34% solids content in the concentrated extract prior to foaming instead of 35% is a different matter from what those skilled in the art would expect from the next adjacent homolog of a compound whose properties are disclosed in the specification.").

[patentee's] process or of the achieving of any desired result, between the claimed lower limit of solids content and that disclosed in the" priority application, a court found that disclosure of "25 to 60%" solids content and examples of content at 36% and 50% supported claiming "between 35% and 60%."[615] Whether such disclosure of a broader range and examples is adequate support depends on the art. "Where it is clear, for instance, that the broad described range pertains to a different invention than the narrower (and subsumed) claimed range, then the broader range does not describe the narrower range."[616]

Claims including limitations to a specified range must be supported by the specification's description. Open-ended ranges can cause written description and enablement problems when the range refers to a property such as potency or purity that becomes increasingly difficult to satisfy at the upper limits of the range.[617]

Courts have struck down range claims for inadequate support on numerous occasions.[618] On the other hand, where support is found,

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615. *Id*. at 263–65.

616. *Id*. at 265.

617. *In re* Fisher, 427 F.2d 833, 838–40 (C.C.P.A. 1970) (claim setting forth a lower but not upper limit for the activity of a protein not enabled because the specification did not teach potencies "much greater" than the lower limit).

618. *See* Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323, 1328–29 (Fed. Cir. 2021) ("there is no written description support in the '571 application for the range of 'about 30 wt % to about 60 wt %'" because "the values of '30 wt %' and '60 wt %' are not stated in the" application, and the mere fact that the examples fall within this range does "not constitute ranges; they are only specific, particular examples"); Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1324–25 (Fed. Cir. 2000) (affirming that a patentee's specification describing invention as possessing a "generally flat" or "substantially flat" morphine plasma concentration curve failed to support limitation in claims that maximum plasma concentration was to be more than twice the plasma level of the opioid twenty-four hours after it was dispensed because "a person skilled in the art would not necessarily interpret the term flat to be limited to a concentration level ratio less than or equal to two"); *In re* Blaser, 556 F.2d 534, 537–38 (C.C.P.A. 1977) (between 0.6 mols and 1.6 mols not supported by disclosure of six examples in the range of 1.2 to 1.5 mols); Wagoner v. Barger, 463 F.2d 1377, 1380–82 (C.C.P.A. 1972) (extruding temperatures not over 210 degrees Fahrenheit not supported by specification that failed to disclose any examples or teachings of extrusion temperatures); *In re* Smith, 458 F.2d 1389, 1391, 1396 (C.C.P.A. 1972) ("8 to 36 carbon atoms" not supported by "at least 12 carbon atoms"); *In re* Lukach, 442 F.2d 967, 969 (C.C.P.A. 1971) (compound in the range of an Mw/Mn ratio of 2.0 to 3.0 not supported by specification that failed to disclose any range relying on the Mw/Mn ratio and which gave only one example describing a Mw/Mn ratio of 2.6); *In re* Ahlbrecht, 435 F.2d 908, 911–12 (C.C.P.A. 1971) (esters with an m value of 2–12 not supported because

courts uphold range limitations.[619]

[G] Negative Limitations

Either to avoid prior art or simply to delineate an invention, claims may be drafted to cover a genus while excising particular species by employing a negative limitation, often in the form of a proviso.[620] Such "negative claim limitations" must find adequate support in the specification and "are adequately supported when the specification describes a reason to exclude the relevant limitation."[621] The support "need not rise to the level of disclaimer."[622] Negative limitations can be supported by disclosing the disadvantages of a particular element[623] or disclosing the genus and the particular excluded species.[624]

[H] Unclaimed Optional Features

"A specification can adequately communicate to a skilled artisan that the patentee invented not just the combination of all identified features but combinations of only some of those features (subcombinations)—which may achieve stated purposes even without omitted

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the only esters described in the specification had an m value of 3–12); *In re* Baird, 348 F.2d 974, 982 (C.C.P.A. 1965) (temperatures of 40 to 60 degrees Fahrenheit not supported by disclosure of 32 to 176 degrees Fahrenheit and an example of a specific temperature of 44.6 degrees Fahrenheit); Ralston Purina Co. v. Far-Mar-Co, Inc., 586 F. Supp. 1176, 1203–05 (D. Kan. 1984) (moisture content in excess of 20% not supported by specification that provided two examples of extruding soybean meal after adding 25% and 27% moisture because skill in the art yielded an estimate that the maximum moisture content of the soybean meal prior to adding water was in the range of total moisture content at 25% to 40%), *aff'd in part and rev'd in part*, 772 F.2d 1570 (Fed. Cir. 1985).

619. *Wertheim*, 541 F.2d at 265 ("25 to 60%" solids content and examples of content at 36% and 50% supported claiming "between 35% and 60%").

620. *See, e.g.*, *In re* Johnson, 558 F.2d 1008, 1013 (Fed. Cir. 1977) (claiming a specified genus of compounds "with the provisos that E and E′ may not both include a divalent sulfone group and may not both include a divalent carbonyl group linking two aromatic nuclei").

621. Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344 (Fed. Cir. 2012).

622. *Id*.

623. *Id*. at 1351 ("The claim limitation that the *Phillips* formulations contain no sucralfate is adequately supported by statements in the specification expressly listing the disadvantages of using sucralfate.").

624. *Johnson*, 558 F.2d at 1018 ("Appellants' grandparent application clearly describes the genus and the two special classes of polymer materials excluded therefrom."); M.P.E.P. § 2173.05(i) ("If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.").

features."[625] The Federal Circuit, in *Scriptpro, LLC v. Innovation Associates*, reversed a grant of summary judgment for lack of written description based on a specification that described a dispensing machine with sensors while claiming "a machine that need not have 'sensors.'"[626] The specification stated that "'[t]he collating unit of the present invention *broadly includes*' several components: 'an infeed conveyor, a base, a collating unit conveyor, a frame, a plurality of holding areas, a plurality of guide arms, *a plurality of sensors*, and *a control system*.'"[627] The court found that "the qualifier 'broadly' suggests that exceptions are allowed to the assertion of what occurs most (perhaps even almost all) of the time."[628] Furthermore, the specification "suggests that slot sensors are an optional, though desirable, feature of the contemplated collating unit" because it says "'[i]f the sensor . . . does *confirm* the presence of the container,' the collating unit selects the next empty holding area for storage."[629] Finally, the court noted that an originally filed claim "did not include a requirement of sensors" and that, while this may be insufficient on its own to describe a machine without a sensor, when combined with the other disclosure in the specification it helped to resolve any ambiguity.[630]

§ 5:4.4 Inherency

A specification that lacks express support for a claim limitation may still satisfy the written description requirement if the disclosure inherently teaches the claim limitation. Disclosure is inherent if the "necessary and only reasonable construction to be given the disclosure by one skilled in the art is one which will lend clear support to" the claim limitation.[631] Inherency, in the written description context,

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625. Scriptpro, LLC v. Innovation Assocs., 762 F.3d 1355, 1359 (Fed. Cir. 2014).
626. *Id*. at 1362.
627. *Id*. at 1357 (emphasis added by the court).
628. *Id*. at 1360.
629. *Id*. (emphasis added by the court).
630. *Id*. at 1361.
631. Kennecott Corp. v. Kyocera Int'l, Inc., 835 F.2d 1419, 1423 (Fed. Cir. 1987) ("The court has generally applied this standard of the 'necessary and only reasonable construction' as a basis for determining whether an application could, on the basis of an inherent property, support a limitation in an interference count."); *see also* Yeda Research & Dev. Co. v. Abbott GmbH, 837 F.3d 1341, 1345 (Fed. Cir. 2016) ("Under the doctrine of inherent disclosure, when a specification describes an invention that has certain undisclosed yet inherent properties, that specification serves as adequate written description to support a subsequent patent application that explicitly recites the invention's inherent properties."); *In re* Reynolds, 443 F.2d 384, 389 (C.C.P.A. 1971) ("By disclosing in a

requires that a person of ordinary skill would recognize that which is asserted as inherent upon reading the disclosure.[632] Inherency also requires that one skilled in the art must be able to produce the invention "employing any combination of the variables set forth" in the patent.[633] For an inherent disclosure to adequately support a claim, it must provide sufficient support for the full breadth of the claim, not merely fall within the claim's scope.[634] If a specification provides inherent support for a potential claim, "[t]he application may later be amended to recite" what the specification inherently discloses "without introducing prohibited new matter."[635]

Several examples illustrate claims adequately supported by an inherent disclosure.[636] Other examples illustrate failures to satisfy the requirement for adequate inherent disclosure.[637]

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patent application a device that inherently performs a function, operates according to a theory, or has an advantage, a patent applicant necessarily discloses that function, theory or advantage even though he says nothing concerning it.") (quoting Technicon Instruments Corp. v. Cole Instruments, Inc., 255 F. Supp. 630 (N.D. Ill. 1966), *aff'd*, 385 F.2d 391 (7th Cir. 1967)).

632. Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998) ("In order for a disclosure to be inherent, however, the missing descriptive matter must necessarily be present in the parent application's specification such that one of skill in the art would recognize such a disclosure.").

633. *Wagoner*, 463 F.2d at 1381 (inherency requires "not simply that one skilled in the art might come within the scope of the count in following the teachings of the parent application, but that he necessarily would").

634. *Fisher*, 427 F.2d at 836 (parent application inherently disclosed a set of hormones, all of which consisted of 39 amino acids containing a common twenty-four amino acid sequence within, but the application failed to enable a claim for hormones "of at least 24 amino acids" specified by that common sequence, since one skilled in the art could not make or obtain sequences "other than 39 amino acids in the chain" without undue experimentation).

635. *Reynolds*, 443 F.2d at 389 (quoting *Technicon*, 255 F. Supp. at 640–41).

636. *See, e.g.*, *Kennecott*, 835 F.2d at 1420, 1423 ("ceramic structure" that has a "predominantly equiaxed microstructure" supported by disclosure of method that "invariably produces a ceramic product having an equiaxed microstructure"); Therma-Tru Corp. v. Peachtree Doors, Inc., 44 F.3d 988, 992–93 (Fed. Cir. 1995) (glass fibers at least 0.005 inch below the surface supported by disclosure "that the textured pattern of the mold had a depth between 0.003 and 0.009 inch" and by testimony that this mold depth "necessarily pushed the glass fibers at least 0.005 inch below the surface"); *In re* Kirchner, 305 F.2d 897 (C.C.P.A. 1962); Pall Corp. v. Micron Separations, Inc., 792 F. Supp. 1298, 1315 (D. Mass. 1992) (certain property "was well-recognized as an inherent property of nylons" and was therefore "impliedly disclosed").

637. *See, e.g.*, Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1326 (Fed. Cir. 2000) ("Although the examples provide the data from which one can

§ 5:4.5 Application to Particular Inventions

[A] Compound and Composition Claims and Methods of Using Them

A method claim that includes "structural recitation" can be "construed as a limitation on the claim."[638] "Regardless [of] whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."[639] Even if a method claim does not explicitly recite a compound or composition, the specification must describe the compound or composition if required to perform the method.[640]

New compounds and compositions generally must be described structurally or in terms of a method of synthesis,[641] rather than functionally. The Federal Circuit, in *University of Rochester v. G.D. Searle & Co.*,[642] invalidated a claim reciting a method for selectively inhibiting the COX-2 enzyme by administering "a non-steroidal compound that selectively inhibits activity" of the COX-2 enzyme. The patent disclosed no compounds that could be used in the claimed method and there was no evidence that "the ordinarily skilled artisan would be able to identify any compound based on [the patent's] vague functional description."[643] The court held that absent a disclosure of

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piece together the Cmax/C24 limitation, neither the text accompanying the examples, nor the data, nor anything else in the specification in anyway emphasizes the Cmax/C24 ratio."); Snitzer v. Etzel, 531 F.2d 1062 (C.C.P.A. 1976); Langer v. Kaufman, 465 F.2d 915, 918–19 (C.C.P.A. 1972) ("specification [did] not necessarily lead to the conclusion that the" example satisfied the interference count); Noyce v. Kilby, 416 F.2d 1391 (C.C.P.A. 1969) ("conductor adherent" not supported by disclosure because preferred embodiment is not adherent).

638. Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1271 (Fed. Cir. 1986) (holding "that claim 3 is limited . . . to a method for restoring a 2 x 2 x 2 composite cube").

639. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004); *Ariad*, 560 F.3d at 1372 ("The same is true for both process claims and composition claims.") (citing *Rochester*, 358 F.3d at 926).

640. *Ariad*, 560 F.3d at 1373 ("Regardless of whether the asserted [method of treatment] claims recite a compound, Ariad still must describe some way of performing the claimed methods.").

641. *See In re* Edwards, 568 F.2d 1349, 1352 (C.C.P.A. 1978) ("[T]he description in the parent is not intrinsically defective merely because appellants chose to describe their claimed compound by the process of making it.").

642. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004).

643. *Id*. at 927–28.

what compounds would have the desired characteristics of selectively inhibiting COX-2, "the claimed methods cannot be said to have been described."[644]

"[T]here is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure."[645] A compound or composition may be described in terms of its chemical properties, rather than in terms of molecular structures or specific ingredients, if the claimed characteristics identify the claimed product to those of skill in the art.[646]

Compounds are usually claimed as a species or as part of a genus.[647]

[B] DNA

[B][1] General Rule

"An adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention."[648] That does not mean that "all functional descriptions of genetic material fail to meet the written description requirement."[649]

Although disclosing "only a general method for obtaining the human cDNA . . . along with the amino acid sequences of human insulin A and B chains" does not support claiming a recombinant microorganism using human insulin-encoding,[650] disclosing "a partial

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644. *Id*. at 927.

645. Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006).

646. Union Oil Co. of Cal. v. Atl. Richfield Co., 208 F.3d 989 (Fed. Cir. 2000) (holding that gasoline fuels were properly claimed in terms of chemical characteristics such as vapor pressure, distillation points, olefin content, and paraffin content where skilled refiners already knew how to increase or decrease components to arrive at claimed combinations).

647. For a discussion of adequate support for species and genus claims, see *supra* section 5:4.3[B] and [C].

648. Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997); Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993) ("A bare reference to a DNA with a statement that it can be obtained by reverse transcription is not a description; it does not indicate . . . possession of the DNA."); *cf.* Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052, 1073 (Fed. Cir. 2005) (distinguishing *Lilly* because "at the time of the invention, the sequences of RT genes were known [in the art] and members of the RT gene family shared significant homologies from one species of RT to another"); *see also infra* section 7:6.4.

649. Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002).

650. *Eli Lilly*, 119 F.3d at 1567 ("While the [patent] example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe

N-terminus sequence [of TBP-II], a protocol for obtaining the protein from its biological source, and additional properties of the protein, such as molecular weight, biological activity, and degradation characteristics when exposed to trypsin" provides an adequate written description for claiming the entire TBP-II amino acid sequence.[651]

The written description requirement, however, does not mandate that "every invention must be described in the same way."[652] When claiming an invention involving known sequences, the sequence need not be provided in the specification or a deposit.[653]

For example, the Federal Circuit held that claims to chimeric genes comprised of gene segments encoding both an antibody and an endogenous protein expressed on the surface of immune cells did not violate the written description requirement even though the claimed gene segments were described functionally, not structurally.[654] The court pointed out that the "chimeric genes here at issue are prepared from known DNA sequences of known function."[655] The invention was "not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result."[656]

Similarly, in another decision, the Federal Circuit held that an application's general reference to the poxvirus combined with expert testimony demonstrating that "articles describing essential genes for poxvirus were well-known in the art" provided adequate support for

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human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes . . . does not necessarily describe the cDNA itself.").

651. Yeda Research & Dev. Co. v. Abbott Gmbh & Co. KG, 837 F.3d 1341 (Fed. Cir. 2016); Cubist Pharm., Inc. v. Hospira, Inc., 805 F.3d 1112, 1120 (Fed. Cir. 2016) (patent sufficiently described daptomycin as "the product of the fermentation of *Streptomyces roseosporus*" characterized by disclosed "identifying characteristics" despite containing an "error in the structural diagram" for the claimed compound); Sanofi-Aventis v. Pfizer, Inc., 733 F.3d 1364 (Fed. Cir. 2012) (count to polynucleotide sequence supported by disclosed sequence that "was correct as to 1135 of 1143 nucleotides" and disclosed "method for obtaining it"); *cf. In re* Wallach, 378 F.3d 1330, 1334–35 (Fed. Cir. 2004) (disclosure of 5% of the amino acids encoded by the nucleic acids for the full protein held insufficient support to claim all DNA encoding for the full protein).

652. Capon v. Eshhar, 418 F.3d 1349, 1358 (Fed. Cir. 2005).

653. Monsanto Co. v. Scruggs, 459 F.3d 1328, 1336 (Fed. Cir. 2006) ("[N]either a specific DNA sequence nor a biological deposit is required if the biological material is known and readily available to the public.").

654. *Capon*, 418 F.3d at 1357–58.

655. *Id*. at 1358.

656. *Id*.

a claim to a vaccine comprising a poxvirus with an inactivated essential gene.[657]

Accordingly, there is no "requirement that a patent holder justify its decision to omit specific sequence information from a patent."[658]

[B][2] Deposits

The written description requirement for claims to nucleotide sequence can be satisfied by referring to a publicly available deposit of the sequence:

> [R]eference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1.[659]

[B][3] Genus Claims

Disclosing a single cDNA species does not generally support claiming an entire genus containing that species.[660] Thus, when claiming a new DNA genus, courts may require more examples than would be required for a chemical genus:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled

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657. Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366–68 (Fed. Cir. 2006); *Monsanto*, 459 F.3d at 1337 ("Given the knowledge in the art, it was unnecessary for the '605 patent to include specific gene sequence when referring to the CaMV 355 promoter to meet the written description requirement.").

658. *Monsanto*, 459 F.3d at 1337.

659. Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 965 (Fed. Cir. 2002).

660. *See* Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997) (rat insulin-encoding DNA did not support patent claiming all cDNA encoding vertebrate insulin).

> in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function . . . does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.[661]

Alternatively, the Federal Circuit held that claims to a genus of nucleotide sequences that preferentially hybridize to one set of deposited bacterial strains compared to a second set of deposited bacterial strains might be adequately described "by means of the disclosed correlation of the function of hybridization with the bacterial DNA."[662] The court noted that the PTO's written description guidelines cite, by way of example, genus claims to nucleic acids based on their hybridization properties that may be adequately described if the sequences "hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." The court directed the district court to decide "whether one skilled in the art would consider the subject matter [of the genus claims] to be adequately described, recognizing the significance of the deposits and the scope of the claims."[663]

The Federal Circuit explained its reasoning as follows:

> Because the claimed nucleotide sequences preferentially bind to the genomic DNA of the deposited strains of *N. gonorrhoeae* and have a complementary structural relationship with that DNA, those sequences, under the PTO Guidelines, may also be adequately described. Although the patent specification lacks description of the location along the bacterial DNA to which the claimed sequences bind, Enzo has at least raised a genuine issue of material fact as to whether a reasonable fact-finder could conclude that the claimed sequences are described by their ability to hybridize to structures that, while not explicitly sequenced, are accessible to the public. Such hybridization to disclosed organisms may meet the PTO's Guidelines stating that functional claiming is permissible when the claimed material hybridizes to a disclosed substrate. That is a fact question.[664]

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661. *Id.*; Carnegie Mellon Univ. v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1125 (Fed. Cir. 2008) ("generic claims . . . not limited to a single bacterial species, but broadly encompass[ing] coding sequences from *any* bacterial species" not supported by disclosure of "the *poIA* gene coding sequence from one bacterial source" when "at the time of the invention, only three bacterial *poIA* genes . . . out of thousands of bacterial species had been cloned").
662. *Enzo Biochem*, 323 F.3d at 967.
663. *Id.*
664. *Id.* at 968.

[B][4] Possession of Polypeptides

Although having the amino acid sequence of a particular protein does not necessarily put one in possession of the particular naturally occurring DNA that codes for the protein,[665] having such an amino acid sequence may allow one to claim the genus of DNA sequences coding for a particular protein.[666] Yet, because of the degeneracy of the genetic code,[667] possession of a naturally occurring protein does not constitute a description of the genus of DNA sequences encoding analogous, but unspecified, proteins having the same activity.[668]

One decision suggests that a claim for a protein with a specified amino acid sequence can be supported by disclosure in a parent application of a method for isolating the amino acid from a natural source that inherently yields the later-claimed sequence.[669]

Whether or not a claim to a specific amino acid sequence is supported by disclosure of a different sequence combined with disclosure that may suggest certain modifications to that sequence is a fact question dependent upon what the skilled artisan would understand from the disclosure.[670]

The Federal Circuit adopted the PTO guidelines statement that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics."[671]

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665. *See In re* Deuel, 51 F.3d 1552, 1558–59 (Fed. Cir. 1995).
666. *See In re* Wallach, 378 F.3d 1330, 1333 (Fed. Cir. 2004) ("[T]he state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it.").
667. A nucleic acid sequence specifies a unique amino acid sequence; the reverse is not true.
668. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213–14 (Fed. Cir. 1991).
669. *In re* Fisher, 427 F.2d 833, 836 (C.C.P.A. 1970).
670. *In re* Alton, 76 F.3d 1168, 1171, 1174 (Fed. Cir. 1996) (reversing rejection of polypeptide specific claim where Board refused to consider an expert declaration stating that, "as of the filing date of [the] application, one skilled in the art would have interpreted . . . the specification as specific guidance for a class of interferon analogs lacking the cys-tyr-cys residues at the amino terminus").
671. Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) (quoting PTO Guidelines, 66 Fed. Reg. 1099–1101, 1106 (Jan. 5, 2001)).

[C] Antibodies

The Federal Circuit remarked in *Noelle v. Lederman* that "as long as an applicant has disclosed a *'fully characterized* antigen,' either by its structure, formula, chemical name or physical properties or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."[672]

The Federal Circuit has since clarified its approach.[673] In *Amgen Inc. v. Sanofi*, the court stated that the "newly characterized antigen test" was announced in prior cases as dicta and is therefore "not based on any binding precedent": "The test was not central to the holding in either *Enzo* or *Noelle* and neither case explored it in much depth."[674] It further criticized and rejected the test:

> [T]he "newly characterized antigen" test flouts basic legal principles of the written description requirement. Section 112 requires a "written description of the invention." But this test allows patentees to claim antibodies by describing something that is not the invention, i.e., the antigen. The test thus contradicts the statutory "quid pro quo" of the patent system where "one describes an invention, and, if the law's other requirements are met, one obtains a patent."[675]

In view of this ruling, applicants cannot continue to satisfy the written description requirement for antibodies merely by describing the antigen to which they bind.

However, even with disclosure of a fully characterized antigen, an applicant cannot claim antibodies with specific characteristics such as "high affinity, neutralizing activity, and the ability to bind in the same place as the mouse A2 antibody" without disclosing specific techniques to find these antibodies or demonstrating they existed in the prior art.[676] Where "the asserted claims constitute a wish list of properties that . . . a[n] antibody should have" and the "specification at best describes a plan for making" antibodies to a known antigen and then simply "identifying those that satisfy the claim limitations," that is not sufficient to satisfy the written description requirement.[677]

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672. Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004); see also *infra* section 7:7 and Appendix B for a further discussion of antibodies.
673. Amgen Inc. v. Sanofi, 872 F.3d 1367, 1379 (Fed. Cir. 2017).
674. *Id*. at 1376.
675. *Id*. at 1378–79 (quoting Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1345 (Fed. Cir. 2010)).
676. Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1351 (Fed. Cir. 2011).
677. *Id*.

Furthermore, describing structurally similar antibodies that support the full range of a claimed functional property, such as binding affinity, may not be sufficient to claim the entire genus of such antibodies if it contains structurally diverse antibodies.[678]

[D] Other Biological Material

The Federal Circuit affirmed a grant of summary judgment that the specification supported claims covering an "integrated control" with "true" or naturally occurring reticulocytes, a type of red blood cell.[679] The court found several examples of "true reticulocytes" in the specification.[680] Furthermore, "the mere fact that [the inventor] chose to reduce his invention to practice using a reticulocyte analog rather than a true reticulocyte is not relevant to the written description inquiry."[681] Nor is the fact that using "true reticulocytes" would not be commercially practical.[682]

§ 5:5 Enablement*

If a patent represents a bargain with the public—granting rights to exclude in exchange for disclosure of the invention—the trade-off is unsatisfactory without a disclosure sufficient to teach the public how to make and use the invention. The law enforces the bargain by requiring an enabling disclosure as a condition for patentability. The enablement requirement also helps to ensure that the inventors actually conceived the invention by the filing date. If an inventor cannot teach one of ordinary skill to practice the claimed invention, as evidenced by the patent specification, there may be no invention.

§ 5:5.1 Statutory Provision: Section 112

As part of the *quid pro quo* for obtaining a patent, the first paragraph of 35 U.S.C. § 112 requires a patent application to contain "a written description of the invention, and of the manner and process of making and using it . . . as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

678. AbbVie Deutschland Gmbh & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1290, 1299–1302 (Fed. Cir. 2014).
679. Streck, Inc. v. Research & Diagnostic Sys., 665 F.3d 1269, 1287 (Fed. Cir. 2012).
680. *Id*.
681. *Id*.
682. *Id*.

* Written by Krista M. Rycroft.

make and use the same."[683] The enablement requirement is separate and distinct from the written description and best mode requirements also set forth in section 112.[684]

§ 5:5.2 The Policy Behind Enablement

The enablement requirement enforces the patentee's bargain with the public by "ensur[ing] that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims."[685] If an applicant were to be awarded a patent without disclosing how to make and how to use his invention as required by section 112, "applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success."[686] Then, if "one of the guesses later proved true, the 'inventor' would be rewarded the spoils" even though another person actually placed the knowledge necessary to practice the invention within the public domain.[687] The enablement requirement guards against this potential inequity.

§ 5:5.3 Enablement: Question of Law

Whether a patent specification is enabling is a question of law based on numerous underlying factual determinations.[688] Conclusory expert declarations do not create fact issues sufficient to defeat summary judgment.[689] In the appropriate case, a court may find a patent

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683. *See* 35 U.S.C. § 112, ¶ 1. See also *supra* section 5:4 and *infra* section 5:6 for a discussion of the written description and best mode requirements.

684. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 921 (Fed. Cir. 2004).

685. Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 1195–96 (Fed. Cir. 1999).

686. Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325 (Fed. Cir. 2005).

687. *Id.*; *see also In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970) (A patentee "must not be permitted to achieve this dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. § 112."). The enablement requirement guards against this potential inequity.

688. Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1339 (Fed. Cir. 2003).

689. Sitrick v. Dreamworks, LLC, 516 F.3d 993, 1001 (Fed. Cir. 2008) (rejecting patentee's "[c]onclusory" expert opinion insufficient to raise genuine factual dispute); Pharm. Res., Inc. v. Roxane Labs., Inc., 253 F. App'x 26, 30 (Fed. Cir. 2007) (finding two enablement declarations "are conclusory and lack evidentiary support" and therefore fail "to raise a genuine issue of material fact"); Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1367 (Fed. Cir. 1997) (rejecting conclusory testimony offered by patentee on enablement); *In re* Buchner, 929 F.2d 660, 661 (Fed. Cir.

invalid as a matter of law.[690] Furthermore, even though an issued U.S. patent enjoys a presumption of validity pursuant to 35 U.S.C. § 282, the failure of the U.S. Patent Office to issue an enablement rejection during prosecution of a patent does not create an "especially weighty presumption" of compliance with section 112.[691]

§ 5:5.4 Role of the Specification

[A] General Principles

"[A] patent need not teach, and preferably omits, what is well known in the art."[692] The extent to which a patent enables its claims is based on "that which is disclosed in the specification plus the scope

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1991) (rejecting declaration submitted to overcome enablement rejection because it "must be supported by something more than a conclusory statement"); Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 234 n.12 (W.D.N.Y. 2003) (rejecting "conclusory" expert declarations or enablement), *aff'd on other grounds*, 358 F.3d 916 (Fed. Cir. 2004).

690. *Sitrick*, 516 F.3d at 1001 (affirming summary judgment of nonenablement); McRO, Inc. v. Bandai Namco Games Am. Inc., 959 F.3d 1091, 1102 (Fed. Cir. 2020) (same); *Pharm. Res.*, 253 F. App'x at 27 (same); Monsanto Co. v. Syngenta Seeds, Inc., 503 F.3d 1352, 1361 (Fed. Cir. 2007) (same); Auto. Tech. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274, 1285 (Fed. Cir. 2007) (same); Ormo Corp. v. Align. Tech., Inc., 498 F.3d 1307, 1319 (Fed. Cir. 2007) (same as to some claims); Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1380 (Fed. Cir. 2007) (same); Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 1198 (Fed. Cir. 1999) (same); *AK Steel*, 344 F.3d at 1245 (same); *Rochester*, 216 F. Supp. 2d at 325 (same); *see also Genentech*, 108 F.3d at 1367 (finding nonenablement "as a matter of law").

691. *AK Steel*, 344 F.3d at 1245.

692. Hybritech, Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *see also AK Steel*, 344 F.3d at 1244 (specification need not describe how to make and use every variant of claimed invention because skilled artisan's knowledge "can often fill gaps, interpolate between embodiments, and perhaps even extrapolate information beyond the disclosed embodiments, depending on the predictability of the art"); Ajinomoto Co. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1346–47 (Fed. Cir. 2000) ("Requiring inclusion in the patent of known scientific/technological information would add an imprecise and open-ended criterion to the content of patent specifications, could greatly enlarge the content of patent specifications and unnecessarily increase the cost of preparing and prosecuting patent applications, and could tend to obfuscate rather than highlight the contribution to which the patent is directed. A patent is not a scientific treatise, but a document that presumes a readership skilled in the field of the invention.").

of what would be known to one of ordinary skill in the art without undue experimentation."[693]

The specification, however, "not the knowledge of one skilled in the art . . . must supply the novel aspects of an invention in order to constitute adequate enablement."[694] One may "resort to material outside of the specification" for other known aspects of the claimed invention "because it makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention."[695] However, for the "novel aspects" of the invention, the disclosure must be in the specification itself.[696] The law also requires an enabling disclosure for nascent or emerging technology if needed to practice the invention because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction.[697]

A patent specification therefore must disclose "more than a 'plan' or 'invitation'" for research that might lead to the invention; it must "provide sufficient guidance or specificity as to how to execute that plan."[698] "[T]he law requires that the disclosure in the application shall inform [skilled artisans] how to use [the invention], not how to find out how to use [it] for themselves."[699] It is not sufficient for the disclosure to say, "if you wish to practice our invention, go and find out how

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693. *Nat'l Recovery*, 166 F.3d at 1196; Amgen, Inc. v. Hoescht Marion Roussel, Inc., 314 F.3d 1313, 1334 (Fed. Cir. 2003) ("The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'").

694. *Genentech*, 108 F.3d at 1366; *Auto. Tech.*, 501 F.3d at 1284 ("Given that side impact sensing was a *new field* and that there were no electronic sensors in existence that would detect side impact crashes, it was especially important for the specification to discuss how an electronic sensor would operate to detect side impacts and to provide details of its construction.") (emphasis added).

695. Atmel Corp. v. Info. Storage Devices, Inc., 198 F.3d 1374, 1382 (Fed. Cir. 1999).

696. *Genentech*, 108 F.3d at 1366.

697. Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1254 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.'").

698. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1374 (Fed. Cir. 1999); *see also Genentech*, 108 F.3d at 1366 ("Tossing out the mere germ of an idea does not constitute enabling disclosure."); Medtronic, Inc. v. Daig Corp., 221 U.S.P.Q. (BNA) 595, 602 (D. Minn. 1983) ("One skilled in the art must be able to devise the invention without further genuine inspiration or undue experimentation.").

699. *In re* Gardner, 427 F.2d 786, 789 (C.C.P.A. 1970).

to use it."[700] Accordingly, the Federal Circuit has invalidated patents that only disclose "a starting point . . . [for] further research."[701]

On the other hand, "[p]atents are not production documents, and nothing in the patent law requires that a patentee must disclose data on how to mass-produce the invented product."[702] The patent law "does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."[703]

[B] Means-Plus-Function Claims

Even though "the knowledge of one skilled in the particular art may be used to understand what structure(s) the specification discloses" to satisfy the enablement requirement, when a patentee drafts the claims in means-plus-function language pursuant to section 112, paragraph 6, he or she must expressly disclose some corresponding structure in the specification even if that structure would be known to one of skill in the art.[704] Section 112, paragraph 6 requires that the patentee "recite some structure corresponding to the means in the specification, as the statute states, so one can readily ascertain what the claim means and comply with the particularity [definiteness] requirement of ¶ 2."[705] Because only "some structure" need be described to fulfill section 112, paragraph 6 that express disclosure "does not raise the specter of the unending disclosure of what everyone in the field knows that such a requirement in § 112, ¶ 1 would entail."[706]

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700. *Id*.
701. *Nat'l Recovery*, 166 F.3d at 1998; *Genentech*, 108 F.3d at 1366 (same); *Rochester*, 249 F. Supp. 2d at 234 n.12 (fact that skilled artisans reading the specification "would understand the use and function of the screening assay" used to search for a compound needed to practice the claim has been held to be insufficient).
702. Christianson v. Colt Indus. Operating Corp., 822 F.2d 1544, 1562 (Fed. Cir. 1987); CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1339 (Fed. Cir. 2003).
703. *CFMT*, 349 F.3d at 1338.
704. Atmel Corp. v. Info. Storage Devices, Inc., 198 F.3d 1374, 1382 (Fed. Cir. 1999).
705. *Id*.
706. *Id*. ("Paragraph 6 does not contemplate the kind of open-ended reference to extrinsic works that ¶ 1, the enablement provision, does.").

§ 5:5.5 *The Person Skilled in the Art*

[A] Who Is the Person Skilled in the Art?

In determining whether a patent is enabled, the inquiry focuses on what the specification discloses or teaches to a person of ordinary skill in the art.[707] For purposes of determining enablement, the person skilled in the art shares the same qualifications, such as education, experience, and field of technical expertise, as the person of skill in the art for determining obviousness under section 103.[708]

It is black letter law that to be enabling, the disclosure must be sufficient for a skilled artisan to practice the invention using only "ordinary skill." Thus, a skilled artisan reading the specification must be able to practice the claimed invention without the exercise of inventive skill.[709]

[B] What General Knowledge Does the Person Skilled in the Art Possess?

Unlike the person of skill in the art under section 103, for the purposes of enablement, the hypothetical person of skill is not charged

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707. Ajinomoto Co. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1345 (Fed. Cir. 2000) ("Enablement is determined from the viewpoint of persons of skill in the field of the invention.").

708. *In re* Van Geuns, 988 F.2d 1181, 1185 n.1 (Fed. Cir. 1993) ("Van Geuns similarly asserted skill in the art as support for enablement of his claims under 35 U.S.C. § 112. Although the enablement issue is not before us, it would be inconsistent to permit Van Geuns to rely on ordinary skill in the art, while precluding the board from relying on evidence of such skill [in determining obviousness]."). See *supra* section 5:3.6 for further discussion of the person of ordinary skill.

709. *See* Mosler Safe & Lock Co. v. Mosler, Bahman & Co., 127 U.S. 354, 360 (1888) ("ordinary skill" involves "no exercise of the inventive faculty"); Cross v. Iizuka, 753 F.2d 1040, 1051–52 (Fed. Cir. 1985) (enablement requires practice of the invention "without the exercise of inventive skill or undue experimentation"); *Ex parte* Brasseler U.S.A., I, L.P. v. Stryker Sales Corp., 93 F. Supp. 2d 1255, 1258 n.4 (S.D. Ga. 1999) ("The disclosure must be enough to enable a person of ordinary skill to devise the invention 'without further genuine inspiration or undue experimentation.'"), *aff'd*, 267 F.3d 1370 (Fed. Cir. 2001); *Ex parte* Kropp, 143 U.S.P.Q. (BNA) 148, 152 (B.P.A.I. 1959) ("the description in the specification must be such that a person skilled in the art can reproduce the invention from the description without unreasonable experimentation or without the exercise of inventive skill; if either is required to reproduce the invention, then the specification is defective"); *see also* Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) (inventors "possess something . . . which sets them apart from the workers of *ordinary* skill").

with knowing all the prior art.[710] Instead, the person of ordinary skill in the art under section 112 is charged with "the basic knowledge of the particular art to which the invention pertains" and "the knowledge of where to search out information."[711] Thus, foreign patents and publications are relevant only if "anyone skilled in the art would have actually possessed the requisite knowledge or would reasonably be expected to check the source" and "would be able to locate the information with no more than reasonable diligence."[712] Accordingly, not all prior art available under section 102 is necessarily within the knowledge of one of skill in art for purposes of enablement.[713]

[C] Time Frame for Determining Enablement

[C][1] Enablement Measured As of Filing Date

Enablement is determined as of the effective filing date of the patent.[714] "[A]n enablement determination is made *retrospectively, i.e.*, by looking back to the filing date of the patent application and determining whether undue experimentation *would have been* required to make and use the claimed invention at that time."[715]

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710. *In re* Howarth, 654 F.2d 103, 106 (C.C.P.A. 1981) ("Foreign 'patents' and foreign 'printed publications' preclude the grant of a patent whether or not the information is commonly known. Under § 102 [and, thus, § 103] a conclusive presumption of knowledge of such prior art is, in effect, a statutorily required fiction. Such presumption cannot be found in § 112.").
711. *Id*.
712. *Id*. at 107.
713. *In re* Glass, 492 F.2d 1228, 1231–32 (C.C.P.A. 1974) ("[I]t is clear that the contents of a patent application which may be available as 'prior art' under § 102(e) to show that another was the first inventor may not have been known to anyone other than the inventor, his attorney, and the Patent Office examiner, and perhaps the assignee, if there was one, until it issued as a patent. As of its filing date it does not show what is known generally to 'any person skilled in the art,' to quote from § 112."); *Howarth*, 654 F.2d at 106 ("Not everything that may be cited as prior art to preclude the grant of a patent in accordance with 35 U.S.C. § 102 can be equated with common knowledge for purposes of enablement under § 112.").
714. Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1339 (Fed. Cir. 2003).
715. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371 (Fed. Cir. 1999).

[C][2] Using Post-Filing References to Show State of the Art at Filing

References that post-date the filing date of the patent application can still potentially serve as evidence that the disclosure was enabling as of the patent's effective filing date.[716] Post-filing references can also show lack of enablement by, for example, showing that something was unknown even after the filing date.[717]

On the other hand, using a reference that discloses a *later existing* state of the art to determine whether an earlier application complies with the enablement requirement is not permissible.[718] The enablement requirement "does not expect an applicant to disclose knowledge invented or developed after the filing date" of the patent at issue because "[s]uch disclosure would be impossible."[719] Thus, it logically follows that patents or publications of later improvements that post-date the effective filing date of a patent may not be used "to 'reach back' and preclude or invalidate a patent on the underlying invention."[720] "The use of a subsequently-existing improvement to show lack of enablement in an earlier-filed application on the basic invention would preclude issuance of a patent to the inventor of the thing improved, and in the case of issued patents, would invalidate all claims."[721]

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716. *See, e.g.*, Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1335 (Fed. Cir. 2003) ("numerous post-filing publications . . . demonstrated the extent of the enabling disclosure"); Hormone Research Found., Inc. v. Genentech, Inc., 904 F.2d 1558, 1568 (Fed. Cir. 1990) (later publications' suggestion that claimed method for solid phase peptide synthesis may have been enabled sufficient to defeat summary judgment of nonenablement); Amgen Inc. v. Sanofi, 872 F.3d 1367, 1375 (Fed. Cir. 2017) (evidence "that the patent purportedly did not disclose a representative number of species . . . should not have been excluded simply because it post-dated the claims' priority date").
717. *See, e.g.*, Adang v. Fischhoff, 286 F.3d 1346, 1357–58 (Fed. Cir. 2002) (later references suggested non-enablement); Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (later references showing that particular method was not used for years suggests that knowledge was not within the skill in the art at time of filing).
718. *In re* Hogan, 559 F.2d 595, 605 (C.C.P.A. 1977) ("This court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application. That approval does not extend, however, to the use of a later (1967, Edwards) publication disclosing a later (1962) existing state of the art in testing an earlier (1953) application for compliance with § 112, first paragraph.") (emphasis added).
719. Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1254 (Fed. Cir. 2004).
720. *Hogan*, 559 F.2d at 606.
721. *Id*.

[C][3] Nascent Technology Must Be Disclosed

Nascent technology is emerging technology that is not known by the person of ordinary skill at the time of the invention.[722] Whether a disclosure of nascent technology satisfies the enablement requirement is a question that arises in unpredictable fields such as chemical reactions and physiological activity.[723] The Federal Circuit has set forth a "knowledge continuum" against which a disclosure has to be evaluated in order to determine whether it is enabling or not. Routine technology does not require an enabling disclosure.[724] Future technology, which does not exist at the time of filing, also does not require an enabling disclosure.[725] Nascent technology, however, which falls between routine and future technology on the knowledge continuum, if needed to practice the invention, must be enabled with a "specific and useful teaching."[726]

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722. *See Chiron*, 363 F.3d at 1254; *see also* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558, 622 (Fed. Cir. 2000) ("For inventions in rapidly evolving fields, application filings are often made while the inventions are still in their nascent stages, *i.e.*, early in the evolutionary process . . . .").

723. *Hogan*, 559 F.2d at 606; *Genentech*, 108 F.3d at 1367–68.

724. *Chiron*, 363 F.3d at 1254 ("[A] patent disclosure need not enable information within the knowledge of an ordinary skilled artisan. Thus, a patentee preferably omits from the disclosure any routine technology that is well known at the time of the application.").

725. *Id*. ("At the other end of the knowledge continuum, a patent cannot enable technology that arises after the date of application. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible."); Plant Genetic Sys. v. DeKalb Genetics Corp., 315 F.3d 1335, 1340–41 (Fed. Cir. 2003); Hormone Research Found., Inc. v. Genentech Inc., 904 F.2d 1558, 1567–68 (Fed. Cir. 1990) ("Merely because purer and more potent forms of [a] . . . compound might be produced using later-discovered technology does not necessarily mean that the . . . patent specification did not provide sufficient enabling disclosures as of the filing date of the application."); *Hogan*, 559 F.2d at 605–06; *see also* U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1250–53 (Fed. Cir. 1989).

726. *Chiron*, 363 F.3d at 1254 ("Nascent technology . . . must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."); *Genentech*, 108 F.3d at 1367–68 ("Where, as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching."). See *infra* section 7:7.4[C] for further discussion of the nascent technology analysis found in *Chiron*.

[C][4] Loss of Material Needed to Practice Invention

If a patent specification is otherwise enabling at the time of the invention, it may not be deemed inadequate merely because the disclosure relies on materials that may not be available at a later date.[727] This unique scenario may occur if the disclosure relies on necessary starting materials that may become unavailable in the future because the manufacturer of the starting material changes the product or discontinues the product necessary to practicing the claimed invention.[728] "[W]hether a given disclosure which identifies a material to be employed in the practice of the claimed invention is 'enabling' within the meaning of 35 U.S.C. § 112, must be decided by a rule of reason applied to the facts of the case."[729] To preserve enablement, a disclosure should preferably describe the starting material in addition to identifying the manufacturer and trademarked name.[730]

§ 5:5.6 Requirements for Enablement

The enablement requirement consists of two distinct parts: (1) whether the specification enables one of skill in the art to make the claimed invention and (2) whether the specification enables one of skill in the art to use the claimed invention.[731] Both the "how-to-make" and "how-to-use" prongs must be met for a disclosure to be enabling.

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727. *In re* Metcalfe, 410 F.2d 1378, 1382–83 (C.C.P.A. 1969) ("[T]he possibility that at some future date appellants' disclosure will no longer be sufficient to enable one skilled in the art to practice appellants' invention is too speculative to justify a holding that the disclosure is insufficient under § 112."); *In re* Coleman, 472 F.2d 1062, 1064 (C.C.P.A. 1973) ("[W]e find no real likelihood of all, or even most, of either the specific materials disclosed being removed from the market or the trademarks or trade names being applied to significantly different products such as to render the present disclosure nonenabling.").
728. *Metcalfe*, 410 F.2d at 1381–82 (starting material may become unavailable due to "change in the product," "the manufacturer may decide to discontinue the product completely," "lack of raw materials" or public disaster).
729. *Id*. at 1382.
730. *Id*. (disclosure enabled where resins were "also identified by type, viz., 'long seed oil modified alkyd resin' and 'isophthalic oil alkyd'" in addition to trademark and manufacturer); *Coleman*, 472 F.2d at 1064 ("The implicit allegation that those skilled in the art could not ascertain suitable adhesives without exhaustive investigation is, to us, unreasonable and unrealistic in this case.").
731. *See* 35 U.S.C. § 112 (applicant must enable skilled artisan "to make and use the" invention); *see also* Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1322 (Fed. Cir. 2005); Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1469 (Fed. Cir. 1993) (section 112 requires that the patent specification enable a skilled artisan to "make and use" the invention).

[A] How to Make the Claimed Invention

The patent specification must adequately disclose to one with skill in the relevant art how to make the claimed invention. In general, the enablement requirement is met if the specification enables one mode of making the invention.[732] For example, disclosure of a single way to synthesize a claimed compound should satisfy the how to make requirement despite the existence of numerous routes of synthesis. One way of teaching how to make a claimed invention covering a genus is the "inclusion of a number of representative examples in a specification."[733]

[A][1] Compound and Composition of Matter Claims

To be enabling, the specification must teach one of skill in the pertinent art how to make a claimed composition.[734] If the method for making a claimed composition is "well known" or described, courts will find enablement.[735] Thus, the how-to-make requirement is met if a method for synthesizing the claimed compound or composition would have been known to one of skill in the art prior to the effective

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732. *See, e.g.*, Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1361 (Fed. Cir. 1998) (A party may meet its burden to prove lack of enablement "only by showing that all of the alternative modes are insufficient to enable the claims, because 'the enablement requirement is met if the description enables any mode of making and using the invention.'"); *see also* Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1335 (Fed. Cir. 2003) ("'the law makes clear that the specification need teach only one mode of making and using a claimed composition'") (citing *Hogan*, 559 F.2d at 606).

733. *In re* Robins, 429 F.2d 452, 457 (C.C.P.A. 1970); *see also In re* Angstadt, 537 F.2d 498, 503 (C.C.P.A. 1976) ("If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex."); *cf. In re* Goodman, 11 F.3d 1046, 1050 (Fed. Cir. 1993) ("This single example, however, does not enable a biotechnician of ordinary skill to produce any type of mammalian protein in any type of plant cell.").

734. *See, e.g.*, *Morton Int'l*, 5 F.3d at 1469–70 (affirming judgment of nonenablement of compound claim because the skilled artisan "could not make the claimed compounds using the procedures of the specification, and no evidence that such compounds even exist"); *In re* Howarth, 654 F.2d 103, 104 (C.C.P.A. 1981) (specification did not disclose how to make clavulanic acid or direct one of skill in the art to reference materials containing such information).

735. *See* Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986) (the Kolher-Milstein "method for producing" the compounds needed to practice the invention was "well known"); *Johns Hopkins*, 152 F.3d at 1359 (infringer conceded that patent disclosed method of producing one of the claimed antibodies).

filing date of the application.[736] Patents claiming compounds or compositions of matter need not teach how to make necessary starting materials if the method for making them known is in the art.[737]

Compound and composition of matter patents do not need to provide dosing information to satisfy the how to make requirement because the claims do not require dosing. The how to use requirement discussed below, however, requires that the skilled artisan be able to use the compound or composition for some practical purpose (known as utility). This practical purpose may include treatment and therefore require some teaching in the patent or in the art on dosing.[738]

[A][2] Method of Use Claims

Method of use claims for pharmaceutical inventions often involve administration of one or more compounds to treat a person or animal.[739] Such a claim is not enabled when a way to make a compound needed to practice the claimed method is not disclosed and not taught by the prior art.[740] Nor is the claim enabled when the specification and the art fail to teach the dose required for the treatment without undue experimentation.[741]

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736. Martin v. Johnson, 454 F.2d 746, 775 (C.C.P.A. 1972) (evidence of foreign patents and expert affidavit established that one of skill in the art would have known how to make the substituted urea compound without undue experimentation); *cf. In re* Budnick, 537 F.2d 535, 537 (C.C.P.A. 1976) ("record is barren of any showing that the claimed compounds would, in fact, be formed" using the process set forth in a prior art patent reference cited in the specification).

737. *In re* Brebner, 455 F.2d 1402, 1404–05 (C.C.P.A. 1972) (method for making copolymers necessary to a claimed blend of copolymer and acid was known in the art).

738. *See infra* section 5:5.6[B][2].

739. See *infra* section 7:4 for further discussion of method of treatment claims.

740. *See In re* Collier, 427 F.2d 831, 832–33 (C.C.P.A. 1970) (method claims not enabled because neither applicant's specification nor the art disclosed "how to make the epoxy silane starting material" recited in the claim); Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 232–33 (W.D.N.Y. 2003) (patent not enabled because it "essentially calls for the use of trial and error to attempt to find a compound that will selectively inhibit PGHS-2 activity in a human host, which is the method claimed by the patent"), *aff'd on other grounds*, 358 F.3d 916 (Fed. Cir. 2004); *Ex parte* Kropp, 143 U.S.P.Q. (BNA) 148, 152 (B.P.A.I. 1959) (method claim not enabled because "the starting material [in the claim] obviously cannot be reproduced from the written description, nor does the specification give any source where it can be found").

741. *In re* Gardner, 427 F.2d 786, 789 (C.C.P.A. 1970) ("We consider the [dose] range so great [10 to 450 mg] as not to be an enabling or how-to use disclosure as contemplated by the statute."); *In re* Colianni, 561 F.2d 220, 222 (C.C.P.A. 1977) ("The application of 'sufficient' ultrasonic

Courts may refer to the requirement that a patent enable the skilled artisan to determine the dose needed to practice a method of treatment claim as an application of enablement's how-to-use requirement. This makes sense as a matter of grammar because method claims are used, not made. The nature of the requirement, however, can be better understood as a consequence of the how to make (or better termed how to practice) prong because dosing, like synthesis of the drug, is required to practice a method of treatment claim.[742] In contrast, a skilled artisan can make a claimed compound without knowing how to dose the compound. Knowledge of dosing is only needed to use the claimed compound (if it is a drug), but not to make it. As a consequence, the required disclosure of dosing information for compound claims is lower than it is for method of treatment claims. The required dosing disclosure for compound claims is based on the requirement that one must be able to derive a utility from any patentable invention, not the how to make requirement.[743]

[B] How to Use the Claimed Invention

[B][1] Practical Utility[744]

There exists a relationship between utility (the requirement that an invention be "useful") and enablement. Thus, if a claimed invention lacks "utility, the specification cannot enable one to use it."[745]

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energy is essential to appellant's claimed method, yet his specification does not disclose what a 'sufficient' dosage of ultrasonic energy might be or how those skilled in the art might make the appropriate selection of frequency, intensity, and duration. There is not a single specific example or embodiment by way of an illustration of how the claimed method is to be practiced."); Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 374 (D. Del. 1991) (claims invalid because the disclosed dose range of 25 to 1,200 mg and more preferably 200 to 600 mg is broad "and is very high in comparison to the dose range of 50 mg to 100 mg approved by the FDA" and because "the patent disclosure would not offer guidance but misdirect one attempting to determine an effective dose"), *aff'd mem.*, 972 F.2d 1354 (Fed. Cir. 1992).

742. *In re* Gleave, 560 F.3d 1331, 1335 (Fed. Cir. 2009) ("For method claims, the 'make' requirement *becomes*, in effect, a 'use' requirement.").

743. *See infra* section 5:5.6[B][2].

744. See chapter 3 for a more complete discussion of utility. *See also* 35 U.S.C. § 101 ("Whoever invents . . . any new and useful . . . composition . . . may obtain a patent therefor.").

745. *In re* Brana, 51 F.3d 1560, 1564 (Fed. Cir. 1995); *In re* Kirk, 376 F.2d 936, 942 (C.C.P.A. 1967) ("[S]urely Congress intended § 112 to presuppose *full satisfaction* of the requirements of § 101."); 2001 Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (stating that claims rejected under section 101 should also be rejected "under § 112, first

Accordingly, the how to use prong of the enablement requirement "incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention."[746]

The "how to use" prong of section 112's how to "make and use" requirement has two parts. First, it "incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention."[747] Second, in addition to disclosing the existence of a practical utility, a specification must also enable the skilled artisan to use the invention so as to achieve that utility.[748]

The requirement for "practical utility" is sometimes referred to as "substantial utility."[749] The Supreme Court set the bar for the utility requirement: "Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field."[750]

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paragraph, on the basis that the disclosure fails to teach how to use the invention as claimed").

746. *In re* Ziegler, 992 F.2d 1197, 1200 (Fed. Cir. 1993); Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318 (Fed. Cir. 2005); *see also* M.P.E.P. §§ 2107.01, 2100-24 (2006) ("Inventions asserted to have utility in the treatment of human or animal disorders are subject to the same legal requirements for utility as inventions in any other field.").

747. *Rasmusson*, 413 F.3d at 1322–23; *In re* Fouche, 439 F.2d 1237, 1243 (C.C.P.A. 1971) ("It appears that the examiner and the board doubted that compositions having heterocyclic moieties would be useful at all for therapeutic purposes. While this position could have led to a rejection under § 101, it also leads to a rejection under the how-to-use provision of § 112, since if such compositions are in fact useless, appellant's specification cannot have taught how to use them.").

748. *Rasmusson*, 413 F.3d at 1323 ("applicant's failure to disclose how to use an invention may support a rejection under either section 112, paragraph 1 for lack of enablement, or 'section 101 for lack of utility when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention'" (quoting *In re* Cortright, 165 F.3d 1353, 1356 (Fed. Cir. 1999))).

749. Brenner v. Manson, 383 U.S. 519, 534 (1966) ("The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility."); Cross v. Iizuka, 753 F.2d 1040, 1046 n.13 (Fed. Cir. 1985) ("For purposes of the present opinion, we consider the *phrase* 'substantial utility,' as enunciated by Brenner, to be synonymous with the phrase 'practical utility' as used in subsequent opinions of the C.C.P.A.") (emphasis added).

750. *Brenner*, 383 U.S. at 534.

[B][2] Satisfying the How to Use Requirement

The "how-to-use" prong of the enablement requirement is not met by merely disclosing a practical utility for an invention. The specification must also enable one of skill to use the invention so as to realize the benefit of that utility.[751]

For claims strictly directed to a compound, the how-to-use prong of enablement may be proven by sufficient evidence of pharmacological activity.[752] "What is necessary to satisfy the how-to-use requirement of § 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."[753] When a patent claims a compound, it is sufficient that one of ordinary skill in the art would know how to use the novel compound "to determine the specific dosages for the various biological purposes" disclosed by the applicant.[754] Accordingly, the higher standard for determining the enablement of a method of use or method of treatment claim does not apply to determining whether the disclosure of the pharmacological use that underlies the utility for a claimed compound is adequate.[755]

By comparison, to satisfy the how-to-use requirement for method of treatment claims or claims with express limitations directed to therapeutic uses, the patent specification must disclose sufficient

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751. *See* M.P.E.P. §§ 2164.07, 2100-185 (2001) ("If an applicant has disclosed a specific and substantial utility for an invention and provided a credible basis supporting that specific utility, that fact alone does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. § 112, first paragraph. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. § 112, but not 35 U.S.C. § 101.").

752. *See, e.g.*, *Cross*, 753 F.2d at 1051–52 ("there was sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine the IC50 dosage level for the imidazole derivatives").

753. *In re* Bundy, 642 F.2d 430, 434 (C.C.P.A. 1981).

754. *Id*. (reference to broad dosages of prior art compound sufficient); *Cross*, 753 F.2d at 1052 (molar concentration provided necessary information to one of skill in the art to achieve the desired pharmacological effect, "*i.e.*, the 50% inhibition of thromboxane synthetase in human or bovine platelet microsomes").

755. *See, e.g.*, *Cross*, 753 F.2d at 1052 ("This is not a case such as *In re Gardner* . . . where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would be required to discover appropriate dosages for humans, *i.e.*, a therapeutic use. In the instant case, we are confronted with a pharmacological activity or practical utility, not a therapeutic use.").

dosing data to enable one to achieve the claimed treatment.[756] This requirement may be satisfied by disclosing appropriate human dosing information through posological (dosing) theory, animal data from which proportional dosing can be derived, and comparison to standard compounds with known dosing.[757] For example, to enable a therapeutic use claim, "a human dose for a new compound can be determined by obtaining the dose in rats for the related activity of the new compound, establishing an animal dose-activity ratio between the new and old drugs, and then applying the ratio to the human dose of the old drug to obtain the proper dose for the new drug."[758]

[B][3] Inoperability May Negate Enablement

If a patent claim fails to meet the requirement of section 101 because it is inoperative, then it also fails to meet the how-to-use aspect of the enablement requirement.[759] However, because "[i]t is not a function of the claims to specifically exclude . . . possible inoperative substances," claims are not necessarily invalid under section 112 if some claimed compounds are inoperative.[760] For example, a claim

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756. *In re* Gardner, 427 F.2d 786, 788 (C.C.P.A. 1970) ("[Applicants] are not claiming the compounds. In effect, by claiming pharmaceutical compositions 'having antidepressant activity' and methods 'of producing antidepressant activity' which consist of administering the compounds, they are claiming in terms of use.").

757. *Id*. at 790 (pharmaceutical composition claims including the express limitation of "having antidepressant activity" and claims directed to methods of "producing antidepressant activity" were not enabled because the specification "contains neither the theory, the animal data, nor the information about the existence or the properties of the alleged standard antidepressant, imipramine").

758. *Id*.

759. *In re* Swartz, 232 F.3d 862, 863 (Fed. Cir. 2000) ("[I]f the claims in an application fail to meet the utility requirement because the invention is inoperative, they also fail to meet the enablement requirement because a person skilled in the art cannot practice the invention."); Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1358 (Fed. Cir. 1999) ("If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement."); *see also* M.P.E.P. §§ 2164.07, 2100-202 (2006) ("If a claim fails to meet the utility requirement of U.S.C. § 101 because it is shown to be nonuseful or inoperative, then it necessarily fails to meet the how-to-use aspect of the enablement requirement of 35 U.S.C. § 112, first paragraph.").

760. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984); *In re* Dinh-Nguyen, 492 F.2d 856, 858–59 (C.C.P.A. 1974) ("It is not a function of the *claims* to specifically exclude either possible inoperative substances or ineffective reactant proportions."); Merck & Co. v. Danbury Pharmacal, Inc., 694 F. Supp. 1, 36 (D. Del.

covering thousands of emulsion blasting agents formed by combinations of "numerous salts, fuels and emulsifiers" was properly enabled because "it would have been impossible for [the patentee] to list all operable emulsions and exclude the inoperable ones."[761] On the other hand, "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid."[762] If the claims specify multiple embodiments and one of them is impossible to make, the claim is not enabled.[763]

§ 5:5.7 Enabling the Full Scope of the Claim

The how to make and use requirements explained in the proceeding section must be satisfied for the full scope of the claims.[764] "Enabling the full scope of each claim is part of the *quid pro quo* of the patent bargain."[765] The Supreme Court explained:

1988) (claims enabled even though cyclobenzaprine did not effectively treat spasticity in all cases); CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1339 (Fed. Cir. 2003) ("where a patent discloses several alternative combinations of methods (as most system claims will), the party asserting inoperability must show that all disclosed alternatives are inoperative or not enabled"); Crown Operations Int'l, Ltd. v. Solutia Inc., 289 F.3d 1367, 1380 (Fed. Cir. 2002) (existence of inoperative embodiments raised genuine issue of material fact with respect to enablement).

761. *Atlas Powder*, 750 F.2d at 1576.

762. *Id*. at 1576–77; Durel Corp. v. Osram Sylvania Inc., 256 F.3d 1298, 1306–07 (Fed. Cir. 2001) ("If [the evidence] had shown that a significant percentage of oxide coatings within the scope of the claims were not enabled, that might have been sufficient to prove invalidity."); *In re* Corkill, 771 F.2d 1496, 1501 (Fed. Cir. 1985) ("Claims which include a substantial measure of inoperatives . . . are fairly rejected under 35 U.S.C. § 112.").

763. Trs. of Bos. Univ. v. Everlight, 896 F.3d 1357, 1364 (Fed. Cir. 2018) (holding that a claim specifying six embodiments was "not enabled as a matter of law" because although five embodiments were enabled, the sixth embodiment would have "required undue experimentation—indeed, . . . it is *impossible*").

764. Auto. Tech. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274, 1282 (Fed. Cir. 2007) (affirming summary judgment of nonenablement for failure to enable claim to the extent it covers "electronic side impact sensors" in addition to mechanical sensors); Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1380 (Fed. Cir. 2007) (affirming summary judgment of non-enablement for failure to enable claim to the extent it covers "a disposable syringe without a pressure jacket"); Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys. Inc., 166 F.3d 1190, 1196 (Fed. Cir. 1999) ("the scope of the claims must be less than or equal to the scope of enablement"); M.P.E.P. §§ 2164.08, 2100-203 (2006).

765. *Sitrick*, 516 F.3d at 999.

> If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.[766]

"That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art."[767] Thus, as a general rule, when assessing "whether there is a reasonable correlation between the scope of the claims and the scope of enablement," the nature of the relevant art and the degree of predictability within that art will be considered.[768] Accordingly, the scope of the claim as construed by the court will affect the scope of the enablement that must be satisfied by the specification.[769]

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766. Amgen Inc. v. Sanofi, 143 S. Ct. 1243, 1254 (2023).

767. AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

768. Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1340 (Fed. Cir. 2003); PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) ("In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim."); *see also infra* section 5:5.8[A][4].

769. Trs. of Bos. Univ. v. Everlight Elecs. Co., 896 F.3d 1357, 1365 (Fed. Cir. 2018) ("Having obtained a claim construction that included a purely amorphous layer within the scope of the claim, BU then needed to successfully defend against an enablement challenge as to the claim's full scope."); Promega Corp. v. Life Tech. Corp., 773 F.3d 1338, 1348 (Fed. Cir. 2014) ("Promega has chosen broad claim language 'at the peril of losing any claim that cannot be enabled across its full scope of coverage.'"); Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1380 (Fed. Cir. 2007) (applying the motto "beware of what one asks for" to a patentee who successfully pressed for a certain claim construction only to find that the construction invalidated the patent for lack of enablement); *see also* Pharm. Res., Inc. v. Roxane Labs., Inc., 86 U.S.P.Q.2d 1501 (Fed. Cir. 2007) (unpublished) ("Par sought extremely broad claims in a field of art that it acknowledged was highly unpredictable, therefore, Par has set a high burden that its patent disclosure must meet to satisfy the requisite *quid pro quo* of patent enablement."); Ariad Pharm., Inc. v. Mass. Inst. of Tech., 560 F.3d 1366, 1376–77 (Fed. Cir. 2009) (invalidating claims for lack of written description while noting that "Ariad maintained the breadth of these claims through claim construction and into trial. . . .

To enable the full scope "when a range is claimed, there must be reasonable enablement of the scope of the [entire] range."[770] Courts will not find enablement of claims that include open-ended ranges or claim limitations with values much greater than the range disclosed by the specification.[771] Similarly, claims to a broad genus need not disclose "every species encompassed," but must give "sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed."[772]

Ariad chose to assert claims that are broad far beyond the scope of the disclosure provided in the specification."), *vacated on other grounds*, 595 F.3d 1329 (Fed. Cir. 2009).

770. *See, e.g.*, *AK Steel*, 344 F.3d at 1244 (limitation that "aluminum coating metal contains up to about 10% by weight silicon" not enabled because "the specification warns that silicon content over 0.5% in the aluminum coating causes coating problems" and evidence showed the patentee's inability to use 9% silicon Type 1 aluminum); *CFMT*, 349 F.3d at 1338 ("[I]f a patent claimed a system that achieved cleanliness up to a specified numerical particle-free range, then enablement would require disclosure of a method that enables one of ordinary skill to achieve that range without undue experimentation.").

771. *Amgen Inc.*, 143 S. Ct. at 1256 ("calling on scientists to create a wide range of candidate antibodies and then screen each to see which happen to bind to PCSK9 in the right place and block it from binding to LDL receptors" does not enable the full scope of the claimed antibodies that bind to PCSK9 as required by the claims); *In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970) ("appellant has not enabled the preparation of ACTHs having potencies much greater than 2.3, and the claim recitations of potency of 'at least 1' render the claims insufficiently supported under the first paragraph of 35 U.S.C. 112" and, therefore, the inventor should not be "allowed to dominate *all* such compositions having potencies far in excess of those obtainable from his teachings plus ordinary skill").

772. *In re* Vaeck, 947 F.2d 488, 495–96 (Fed. Cir. 1991) (claims to expression in cyanobacteria cells not enabled because cyanobacteria comprises "150 different genera" and specification discloses working examples using only one species of cyanobacteria); *see also* Monsanto Co. v. Syngenta Seeds, Inc., 503 F.3d 1352, 1361 (Fed. Cir. 2007) (affirming summary judgment of nonenablement of claims covering "chimeric plant gene . . . which functions in plant cells," including monocots and dicots because patent "filed before transformation of monocot cells was possible"); Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380, 1384–85 (Fed. Cir. 2013) ("claims covering a broad class of drug compounds with certain structures and properties" numbering in the "tens of thousands" lacked enablement because the specification only disclosed one species with these characteristics requiring the skilled artisan to synthesize and screen every possible compound to determine the full scope of the claims); *cf.* Edwards Lifesciences AG v. CoreValve, Inc., 699 F.3d 1305 (Fed. Cir. 2012) (upholding finding that heart valve patent was not invalid for lack

In one case, the Federal Circuit reversed a district court's grant of summary judgment that patents were not invalid for lack of enablement, and found them to be invalid for lack of enablement because the disclosure did not support the claim's broad scope.[773] The claims were construed to cover "not only the 3-plex co-amplification recited in the claims, but it also encompasses *any other larger, more complex multiplex reaction*, so long as it includes the three recited loci."[774] The patentee argued that unrecited multiplex reaction that includes more than the specifically recited 3-plex "are merely 'unrecited elements'" and therefore need not be enabled, however the court disagreed, finding "they are part of the claim scope" and must be supported by an enabling disclosure.[775]

§ 5:5.8 No Enablement If Undue Experimentation Required

The preceding sections set forth the how to make and use requirements and explain that they must apply to the full scope of the claims. Yet the question remains, how does one determine whether the how to make and use requirements are satisfied for any part of a claim. The answer from the case law is that a patent specification may enable a claim even if a reasonable amount of routine experimentation is required to practice the claimed invention. However, any required experimentation must not be unduly extensive.[776] The term "undue experimentation" does not appear in the patent statute but has been used extensively in the cases.

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of enablement where testing in patent was performed on pigs: "it has long been recognized that when experimentation on human subjects is inappropriate, as in the testing and development of drugs and medical devices, the enablement requirement may be met by animal tests or *in vitro* data"). Although the Supreme Court has never sanctioned application of the *Wands* factors, it did affirm a Federal Circuit decision in which that court applied the *Wands* factors. *See Amgen Inc.*, 143 S. Ct. 1243.

773. Promega Corp. v. Life Tech. Corp., 773 F.3d 1338, 1341, 1347–50 (Fed. Cir. 2014).

774. *Id*. at 1346.

775. *Id*. at 1347, 1350 ("Promega argues that its 'open loci set' limitations 'permit' its claims to encompass a potentially limitless number of primers and multiplex reactions that are not enabled by the specification."); *see also* Trs. of Bos. Univ. v. Everlight Elecs. Co., 896 F.3d 1357, 1364 (Fed. Cir. 2018) (disclosure of how to make five of six claimed permutation insufficient).

776. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

[A] Undue Experimentation: The *Wands* Factors

Whether experimentation is "undue" is a matter of degree. "What constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art."[777] "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations."[778]

The court in *In re Wands* "set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation."[779] These factors include:

(1) the quantity of experimentation needed,

(2) the amount of direction or guidance provided by the specification,

(3) the presence or absence of working examples set forth in the specification,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the relative skill of a person of ordinary skill in the art,

(7) the predictability or unpredictability of the art, and

(8) the breadth of the claim.[780]

"The *Wands* factors . . . are a useful methodology for determining enablement."[781] However, "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory."[782]

[A][1] Quantity of Experimentation Needed

A court may consider different types of evidence reflecting the quantity of experimentation needed to practice the claimed invention. For example, courts have considered the following:

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777. *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).
778. *Id*.
779. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372 (Fed. Cir. 1999) (citing *Wands*, 858 F.2d at 736–37).
780. *Wands*, 858 F.2d at 737.
781. *Enzo Biochem*, 188 F.3d at 1372.
782. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213 (Fed. Cir. 1991); *see also Enzo Biochem*, 188 F.3d at 1371 ("We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling.").

- the amount of time required to practice the claimed invention[783]
- the ability of a testifying expert to make multiple claimed species using materials disclosed in the patent specification[784]
- proof of failed attempts by either the patentee[785] or third

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783. *See, e.g.*, Wyeth v. Abbott Labs., 720 F.3d 1380 (Fed. Cir. 2013) (finding claims to rapamycin compounds with particular structural and functional characteristics not enabled where one would need to synthesize and screen tens of thousands of compounds to practice the scope of the claim); Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (affirming the PTO's finding that the "mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation."); New Eng. Med. Ctr. Hosps., Inc. v. Peprotech, Inc., 1994 WL 613021, at *2 (D.N.J. Oct. 17, 1994) (experimentation was routine even though methods may "be tedious and take months to plan and perform by experts"); *cf.* White Consol. Indus., Inc. v. Vega Servo-Control, Inc., 713 F.2d 788, 790–92 (Fed. Cir. 1983) (a requirement of eighteen months to two years' work to practice the patented invention is "undue experimentation"); *In re* Ghiron, 442 F.2d 985, 992 (C.C.P.A. 1971) (a developmental period of "many months or years . . . does not bespeak a routine operation but of extensive experimentation and development work"); Gerber Optical, Inc. v. Nat'l Optronics, Inc., 1994 U.S. Dist. LEXIS 863, at *9 (W.D. Va. Jan. 25, 1994) (granting summary judgment of invalidity for lack of enablement because it would take "at least eighteen months of skilled programmer's time" to develop the software needed to practice the claim); Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330 (D. Del. 1991) (finding patent invalid for lack of enablement because "[i]t was not until several years of dose studies" that one could determine "the effective dose for achieving the benefit of cardio-selectivity").

784. *See, e.g.*, Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1360–61 (Fed. Cir. 1998) (ability to produce thirteen antibodies suggests that the disclosure of those immunogens was enabled).

785. *See, e.g.*, AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (patentee's "own failures to make and use the later claimed invention at the time of the application" evidence of undue experimentation); *Enzo Biochem*, 188 F.3d at 1371 (considering "inventor's own failed attempts to control the expression of other genes in prokaryotes and eukaryotes using antisense technology"); Pharm. Res., Inc. v. Roxane Labs., Inc., 253 F. App'x 26, 31 (Fed. Cir. 2007) (finding that inventor's own "unsuccessful attempts . . . to practice" the invention support summary judgment of nonenablement); Ormco Corp. v. Align Tech., Inc., 498 F.3d 1307, 1319 (Fed. Cir. 2007) (inventor's failed attempt "to enable his invention in a commercial . . . embodiment of the patented invention" was "strong evidence that the patent specification lacks enablement," supporting summary judgment of nonenablement); Bio-Tech. Gen. Corp. v.

parties to make the claimed invention[786]

- for claims requiring screening, the quantity and type of screening required to practice the invention.[787]

If a party seeks to prove that the claims of a patent are not enabled by relying on a failed attempt to make the disclosed invention, the party must show that the patent's disclosure was followed.[788] Likewise, in attempting to establish that post-filing successes support a finding of enablement, those experiments also must be "accomplished by following the teachings of the specification."[789]

Novo Nordisk Pharm., Inc., 2004 WL 1739722, at *24 (D. Del. Aug. 3, 2004) (finding Novo's own failed attempts at producing ripe hGH pursuant to the teaching of the 1983 PCT application "persuasive evidence of non-enablement"); *cf.* Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984) (experiments deemed "failures" were not indicative of nonenablement).

786. Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1367 (Fed. Cir. 1997) ("This failure of skilled scientists, who were supplied with the teachings that Genentech asserts were sufficient and who were clearly motivated to produce human proteins, indicates that producing hGH via cleavable fusion expression was not then within the skill of the art.").

787. Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 234 n.12 (W.D.N.Y. 2003); *In re* Interference A v. B v. C, 159 U.S.P.Q. (BNA) 538, 542 (Comm'r of Patents 1967) (rejecting argument that microorganism needed to practice method claim was "readily available to persons skilled in the art" because if people who were "regularly running routine soil screening tests . . . would run across the present organism . . . it could hardly be stated that the subject matter of these applications was unobvious"); *Ex parte* Kropp, 143 U.S.P.Q. (BNA) 148, 152 (B.P.A.I. 1959) ("[R]eproduction of the invention from the specification alone would require the initiation of a screening program similar to the screening programs followed in discovering antibodies in the first instance. Such a program would involve the collection of soil samples from different sources, making cultures from the samples, isolating organisms, reculturing the isolates, and testing the resultant cultures to determine if the particular antibiotic was produced.").

788. *Johns Hopkins Univ.*, 152 F.3d at 1360 ("A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed. Because Sutherland deviated from the teachings of the patent in his failed attempts to make the claimed antibodies, his testimony is insufficient to disprove enablement as a matter of law.").

789. *Enzo Biochem*, 188 F.3d at 1376; *see also* Edwards Lifesciences AG v. Corevalve, Inc., 699 F.3d 1305 (Fed. Cir. 2012) (affirming judgment of enablement based on "evidence that the stent/valve prosthetic device was successfully implanted in pigs, in accordance with the" specification).

[A][2] Direction or Guidance Provided/Working Examples and Teaching Away

Patent applicants are not required to disclose every species covered by a claim even in an "unpredictable" art.[790] However, there must be adequate disclosure either through direction or illustrative examples to teach a person of ordinary skill in the art how to make and use the invention as broadly as claimed.[791] Thus, a patent that includes broad claims to unpredictable technology should include greater guidance and direction through working examples.[792] On the other hand, a patent may not need multiple examples when the claimed species are similar.[793] Under some circumstances, the use of prophetic examples may be sufficient to enable claims. Prophetic examples based on modifications to experiments that were actually performed may help enable a disclosure if the prophetic examples "reflect what the inventor believed to be optimum."[794]

On the other hand, a specification that teaches against the way to practice the invention can render any amount of experimentation undue.[795]

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790. *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991); *see also In re* Angstadt, 537 F.2d 498, 502 (C.C.P.A. 1976) (no requirement to disclose every species covered by a claim).

791. *Vaeck*, 947 F.2d at 496 n.23.

792. *Enzo Biochem*, 188 F.3d at 1374 ("Outside of the three genes regulated in *E. coli*, virtually no guidance, direction, or working examples were provided for practicing the invention in eukaryotes, or even any prokaryote other than *E. coli.*"); *In re* Goodman, 11 F.3d 1046, 1050 (Fed. Cir. 1993) ("This single example, however, does not enable a biotechnician of ordinary skill to produce any type of mammalian protein in any type of plant cell."); *Angstadt*, 537 F.2d at 502 (forty runs using various transition metals was sufficient to enable claim); *Pharm. Res.*, 253 F. App'x at 30–31 (that "specification discloses only three working examples, utilizing only one new surfactant" supports summary judgment of nonenablement in view of "the extremely broad scope of the claims").

793. Streck, Inc. v. Research & Diagnostic Sys., 665 F.3d 1269, 1289–90 (Fed. Cir. 2012) ("Unlike the situation in *Automotive Technologies*, where the electronic sensors differed in structure and operation from mechanical sensors, here, there was unrebutted evidence that true reticulocytes and Ryan's reticulocyte analogs 'work in exactly the same way in a hematology control, and are virtually indistinguishable, even to one skilled in the art.'").

794. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984); *see also* M.P.E.P. §§ 2164.02, 2100-189 (2006).

795. AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("[T]he specification clearly and strongly warns that such an embodiment would not wet well. . . . Such a statement discourages experimentation."); Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1379 (Fed. Cir. 2007) (granting summary judgment of nonenablement where "specification

Claims directed to treatment of humans are often supported by experimentation on animals or *in vitro* tests. "[I]t has long been recognized that when experimentation on human subjects is inappropriate, as in the testing and development of drugs and medical devices, the enablement requirement may be met by animal tests or *in vitro* data."[796]

[A][3] Nature of the Invention/State of Prior Art/ Level of Skill in the Art

As discussed previously a patent disclosure need not disclose information that is known to one of skill in the art. A patent disclosure, however, "must supply the novel aspects of an invention in order to constitute adequate enablement" even in a well-developed technical field where the knowledge of one of skill in the art already includes basic techniques or methods to assist in practicing the claimed invention.[797]

[A][4] Predictability in the Art

To determine whether there is a reasonable correlation between the scope of a claim and the scope of enablement provided by the

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teaches away from a disposable syringe without a pressure jacket by stating that such syringes are 'impractical.'").

796. Edwards Lifesciences AG v. Corevalve, Inc., 699 F.3d 1305 (Fed. Cir. 2012) (affirming judgment of enablement based on "evidence that the stent/valve prosthetic device was successfully implanted in pigs, in accordance with the" specification) (citing MPEP § 2164.02 ("An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention.")); *In re* Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995) ("one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans"); Scott v. Finney, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration. Title 35 does not demand that such human testing occur within the confines of Patent and Trademark proceedings.").

797. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (rejecting arguments "focused almost exclusively on the level of skill in the art"); *see also* Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1254 (Fed. Cir. 2004) (specification must also provide "disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instructions").

disclosure, courts consider the degree of predictability in the relevant art.[798] In "predictable arts" such as mechanical or electrical inventions, a single embodiment may provide broad enablement because other embodiments may be made without undue difficulty and expected performance characteristics may be predicted by known scientific laws.[799] Chemical reactions and physiological activity, by contrast, have frequently been described as "unpredictable arts" in which the scope of enablement varies inversely with the degree of unpredictability of the factors involved.[800]

The following arts were found to be unpredictable:

- adrenocorticotrophic hormone preparation[801]
- antisense technology[802]
- heterologous gene expression in cyanobacteria[803]
- gene expression in plant tissue[804]
- organic chemistry and catalytic action[805]
- "many chemical processes, and catalytic processes."[806]

A court may also consider the specification, prosecution history, or expert testimony as a basis for finding unpredictablity.[807]

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798. *See* Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1340 (Fed. Cir. 2003).
799. Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1533 (Fed. Cir. 1987) ("If an invention pertains to an art where the results are predictable, *e.g.*, mechanical as opposed to chemical arts, a broad claim can be enabled by disclosure of a single embodiment."); *see also* Bilstad v. Wakalopulos, 386 F.3d 1116, 1126 (Fed. Cir. 2004) (characterizing mechanical arts as a "fairly predictable field"); *Goodman*, 11 F.3d at 1050–52 ("This single example, however, does not enable a biotechnician of ordinary skill to produce *any type* of mammalian protein in *any type* of plant cell.") (emphasis added); *In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970) (characterizing mechanical and electrical arts as predictable arts).
800. *Fisher*, 427 F.2d 833.
801. *Id.*; *In re* Hogan, 559 F.2d 595, 606 (C.C.P.A. 1977).
802. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371 (Fed. Cir. 1999).
803. *In re* Vaeck, 947 F.2d 488, 495 (Fed. Cir. 1991).
804. Adang v. Fischhoff, 286 F.3d 1346, 1358 (Fed. Cir. 2002).
805. *In re* Robins, 429 F.2d 452, 456 (C.C.P.A. 1970).
806. *In re* Angstadt, 537 F.2d 498, 502 (C.C.P.A. 1976).
807. Pharm. Res., Inc. v. Roxane Labs., Inc., 253 F. App'x 26, 28–29 (Fed. Cir. 2007) (finding art "highly unpredictable" based on specification statement that "predictability based on the prior art does not apply in this case," an argument of no reasonable expectation of success during prosecution, and admission by patentee's expert).

The fact that a court found any of the foregoing arts unpredictable does not mean that under different circumstances, or at a later point in time after advancements in the field, a court would again find that art unpredictable.

[A][5] Breadth of the Claim

The amount of supporting disclosure depends on the patent claim's breadth and the degree of predictability in the pertinent art. The broader the claim and the less predictable the art, the greater the disclosure must be.[808]

Typically, evaluating claim breadth involves "concrete identification of at least some embodiment or embodiments asserted not to be enabled . . . so that breadth is shown concretely and not just as an abstract possibility, and how much experimentation a skilled artisan would have to undertake to make and use those products or processes."[809] This is done by identifying "products or processes that were or may be within the scope of the claims and were allegedly not enabled."[810]

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808. *See, e.g.*, Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213–14 (Fed. Cir. 1991) ("This disclosure might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them."); *In re* Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (the skilled artisan would not have been able to carry out the steps required to practice the full scope of claims that encompass "*any and all* live, non-pathogenic vaccines, and processes for making such vaccines, which elicit immunoprotective activity in *any* animal toward *any* RNA virus"); *Goodman*, 11 F.3d at 1052 (the specification did not enable the broad scope of the claims for producing mammalian peptides in plant cells because the specification contained only an example of producing gamma-interferon in a dicot species, and there was evidence that undue experimentation would have been required for encoding mammalian peptide into a monocot plant at the time of filing).

809. McRO, Inc. v. Bandai Namco Games Am. Inc., 959 F.3d 1091, 1100 (Fed. Cir. 2020).

810. *Id*. at 1101; *see, e.g.*, Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1367–68 (Fed. Cir. 1997) (noting that a wide range of enzyme-protein combinations were not enabled); MagSil Corp. v. Hitachi Glob. Storage Techs., Inc., 687 F.3d 1377, 1381–83 (Fed. Cir. 2012) (claim covering a process resulting in any resistance in excess of 10% or more not enabled by failing to teach increases in resistance even slightly beyond 10%); Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999–1001 (Fed. Cir. 2008) (claim covering video games and movies not enabled merely by enabling video games); *In re* Vaeck, 947 F.2d at 495 (claims covering use of any species of cyanobacteria not enabled by teaching only a small

A party seeking to challenge the enablement of a claim has the "burden" of identifying what "is or may be within the scope of the claim" that is not enabled.[811] Using the teachings of the patent coupled with a demonstration, the skilled artisan would not be able to predict what other embodiments would satisfy the full range of the functional limitations. The Federal Circuit, for example, held claims invalid for lack of enablement because they were "far broader in functional diversity than the disclosed examples" and the undisputed evidence showed "that this invention is in an unpredictable field of science with respect to satisfying the full scope of the functional limitations."[812]

[B] Routine Experimentation Is Allowed

Some amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[813] For example, "[e]nablement is not precluded by the necessity for some experimentation such as routine [antibody] screening."[814] Likewise, under certain circumstances, a reasonable amount of trial and error does not constitute "undue experimentation" if one of ordinary skill in the art "would pursue more promising options" instead of the "less promising ones."[815] Moreover, experimentation is not rendered unreasonable merely because there is a technical or factual

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subset); Trs. of Bos. Univ. v. Everlight Elecs. Co., 896 F.3d 1357, 1360, 1362 (Fed. Cir. 2018) (claim covering six permutations not enabled by merely teaching how to do five of them).

811. *McRO*, 959 F.3d at 1100.

812. Amgen Inc. v. Sanofi Aventisub LLC, 987 F.3d 1080 (Fed. Cir. 2021).

813. *See, e.g.*, United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988) (one of skill in the art "would know how to conduct a dose response study to determine the appropriate current to be used with other materials"); Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1360–61 (Fed. Cir. 1998) (success with technique used for producing monoclonal antibodies "commonly required repetition").

814. *In re* Wands, 858 F.2d 731, 736–37 (Fed. Cir. 1988) (screening of negative hybridomas was routine); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986) (screening methods to identify affinity were routine).

815. *See, e.g.*, Ciba-Geigy Corp. v. Alza Corp., 37 U.S.P.Q.2d (BNA) 1337, 1341 (Fed. Cir. 1995) (unpublished) (developing a transdermal nicotine patch by substituting nicotine for one of four available nitroglycerin/scoplamine patches is not undue experimentation); Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("[O]ne of skill in the art would know how to select a salt and fuel and then apply 'Bancroft's Rule' to determine the proper emulsifier.").

error in the specification's examples, provided that the error is easily detectable by one of ordinary skill in the art.[816]

[C] Trial and Error of Large Numbers of Candidates Is Undue Experimentation

In *Wyeth*, *Enzo*, *Idenix*, and *Amgen*, the Federal Circuit invalidated functionally defined genus claims for lack of enablement as a matter of law because the specification merely taught trial-and-error testing of a large number of candidate compounds.[817] It matters not that the number of species covered by the claim may, at the end of the day, turn out to be few in number, if a "large number" of candidates must first be tested to find these.[818]

§ 5:5.9 *Use of Deposits to Satisfy Enablement*

"The deposit of biological organisms for public availability satisfies the enablement requirement for materials that are not amenable to written description or that constitute unique biological materials which cannot be duplicated."[819] "A deposit has been held necessary for enablement where the starting materials (*i.e.*, the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public."[820] Likewise,

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816. PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996).

817. Enzo Life Scis. v. Roche Molecular Sys., Inc., 928 F.3d 1340, 1346 (Fed. Cir. 2019) ("We noted [in *Wyeth*] the breadth of the claims, the limited guidance provided in the specification, the large number of *possible candidates* falling within the claimed genus (tens of thousands), and the fact that it would be necessary to first synthesize and then screen each of those candidates to determine whether it had the required functionality."); Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380, 1385 (Fed. Cir. 2013) ("First, there is no dispute that, even if *potential* rapamycin compounds must have a molecular weight below 1,200 Daltons, there are still at least tens of thousands of *candidates*."); Idenix Pharm. LLC v. Gilead Scis. Inc., 941 F.3d 1149 (Fed. Cir. 2019); Amgen Inc. v. Sanofi Aventisub LLC, 987 F.3d 1080 (Fed. Cir. 2021) ("The facts of this case are thus more analogous to those in *Enzo*, *Wyeth*, and *Idenix*, where we concluded a lack of enablement.").

818. *Enzo Life Scis.*, 928 F.3d at 1346.

819. Ajinomoto Co. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1344–46 (Fed. Cir. 2000) (patent enabled where applicant deposited four bacterial strains specifically described by patent for producing threonine); see also chapter 6 for a more complete discussion of biological deposits.

820. *Wands*, 858 F.2d at 735 (citing *In re* Jackson, 217 U.S.P.Q. (BNA) 804, 807–08 (B.P.A.I. 1982); Feldman v. Aunstrup, 517 F.2d 1351 (C.C.P.A. 1975); *In re* Argoudelis, 434 F.2d 1390, 1392 (C.C.P.A. 1970); *In re* Kropp, 143 U.S.P.Q. (BNA) 148 (B.P.A.I. 1959)).

"[a] deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials."[821] However, if the invention "can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required."[822]

"The deposit rules (37 CFR 1.801–1.809) set forth examining procedures and conditions of deposit which must be satisfied in the event a deposit is required."[823] However, "the rules do not address the substantive issue of whether a deposit is required under any particular set of facts."[824]

When a biologic material is specifically identified in a patent application as filed, an original deposit "may be made at any time before filing the application for patent or during the pendency of the application subject to the conditions of 37 CFR 1.809."[825] "Where a deposit is needed to satisfy the requirements of 35 U.S.C. § 112 and it is made during the pendency of the application, it must be made no later than the time period set by the examiner at the time the Notice of Allowance and Issue Fee is mailed."[826]

If a deposit is made after the effective filing date of the patent application the applicant must "promptly submit a statement from a person in a position to corroborate that the biological material which is deposited is a biological material specifically identified in the application (the filing date of which is relied upon) as filed."[827] However, while the deposit of a biological material subsequent to the effective filing date of a U.S. application satisfies section 112, an applicant may not be able to rely on the filing date of such a U.S. application for a related patent sought in a foreign country.[828] Therefore, it is recommended that applicants intending to file patent applications in foreign countries deposit a biological material before the filing date of the U.S. priority application.[829]

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821. *Wands*, 858 F.2d at 735 (citing *In re* Forman, 230 U.S.P.Q. (BNA) 546, 547 (B.P.A.I. 1986); *In re* Lundak, 773 F.2d 1216 (Fed. Cir. 1985)).
822. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1211 (Fed. Cir. 1991).
823. M.P.E.P. §§ 2401, 2400-2 (2006).
824. M.P.E.P. §§ 2402, 2400-2 (2006).
825. M.P.E.P. §§ 2406, 2400-10 (2006); 37 C.F.R. § 1.804(a); *see also* 37 C.F.R. § 1.809 (setting forth examination procedures for patent applications requiring a deposit).
826. M.P.E.P. §§ 2406, 2400-11 (2006).
827. M.P.E.P. §§ 2406.02, 2400-11 (2006); 37 C.F.R. § 1.804(b).
828. M.P.E.P. §§ 2406.03, 2400-12 (2006).
829. *Id*.

If a deposit is made, it must be made at an International Depository Authority (IDA) established under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedures or at a depository "recognized as suitable" by the U.S. Patent and Trademark Office.[830] "As new depositories are recognized as suitable by the Commissioner [of Patents], their identity will be announced in the *Official Gazette*" of the Patent and Trademark Office.[831]

§ 5:6 Best Mode*

§ 5:6.1 *Overview*

[A] Statutory Provision: Section 112

A patent must set forth the "best mode contemplated by the inventor of carrying out his invention."[832] This means the best mode known to the inventor at the time of filing.[833] If a patent contains multiple claims, the best mode requirement must be satisfied for each claim.

[B] AIA's Elimination of Best Mode As Grounds for Invalidity or Unenforceability

As part of the United States' effort to conform its patent system with the rest of the world, the AIA eliminated failure to comply with the best mode requirement as a ground for invalidating or rendering unenforceable an issued U.S. patent. The remainder of this section is included as guidance for prosecution, which still requires compliance with the best mode requirement and as a guide for historical purposes. The AIA amended 35 U.S.C. § 282 to state:

> (b) Defenses.—The following shall be defenses in any action involving the validity or infringement of a patent and shall be pleaded:
>
> * * *
>
> (3) Invalidity of the patent or any claim in suit for failure to comply with—

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830. M.P.E.P. §§ 2405, 2400-08 (2006) (listing approved International Depository Authorities recognized under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure); *see also* 37 C.F.R. § 1.803(a)(2), (b) (setting forth requirements for "any other depository recognized to be suitable").

831. M.P.E.P. §§ 2405, 2400-7 (2006); 37 C.F.R. § 1.803(d).

* Written by Sapna Walter Palla.

832. 35 U.S.C. § 112 (2004).

833. Chemcast Corp. v. Arco Indus. Corp., 913 F.2d 923, 926 (Fed. Cir. 1990).

> (A) any requirement of section 112, except that the failure to disclose the best mode shall not be a basis on which any claim of a patent may be canceled or held invalid or otherwise unenforceable . . . .

The amended language of section 282 applies "to proceeding commenced on or after" the September 16, 2011, date of its enactment.[834]

Elimination of best mode as grounds for invalidity or unenforceability, however, does not eliminate best mode as a requirement for patentability. Compliance with best mode is still required by 35 U.S.C. § 112,[835] although the Patent Office is rarely in a position to evaluate best mode during prosecution.

The AIA also eliminated the requirement that an earlier-filed application relied upon for its filing date pursuant to sections 119 and 120 disclose the inventor's best mode. It is unclear whether this change will have any practical effect, because, as the Patent Office explained to its examiners in a memorandum, "MPEP 201.08 provides that there is no need to determine whether the earlier-filed application contains a disclosure of the invention claimed in the later-filed application in compliance with 35 U.S.C. § 112, first paragraph, unless the filing date of the earlier-filed application is actually necessary (*e.g.*, to overcome a reference)."[836]

§ 5:6.2 Purpose of the Best Mode Requirement

The purpose of the best mode requirement is to prevent inventors from obtaining patent protection while at the same time concealing preferred embodiments of their inventions.[837]

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834. 35 U.S.C. § 282(c).

835. Patent Office Memorandum to Patent Examining Corps, Sept. 11, 2011, www.uspto.gov/aia_implementation/best-mode-memo.pdf (noting that the amended section 282 "does not alter current patent examining practices set forth in MPEP 2165 for evaluation of an application for compliance with the best mode requirement of 35 U.S.C. § 112").

836. *Id*.

837. *See* Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 963 (Fed. Cir. 2001) ("The best mode requirement creates a statutory bargained-for-exchange by which a patentee obtains the right to exclude others from practicing the claimed invention for a certain time period, and the public receives knowledge of the preferred embodiments for practicing the claimed invention."); Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 1209–10 (Fed. Cir. 1991) ("[T]he best mode requirement . . . is intended to ensure that a patent applicant plays 'fair and square' with the patent system. It is a requirement that the quid pro quo of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him

§ 5:7 Indefiniteness and the Requirement to Claim the Invention*

§ 5:7.1 Statutory Provision: Section 112

Section 112, paragraph two, of the patent statute requires that the patent "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[838] This phrase requires that a claim satisfy two distinct requirements: "first, it must set forth what 'the applicant regards as his invention,' and second, it must do so with sufficient particularity and distinctness, *i.e.*, the claim must be sufficiently 'definite.'"[839]

§ 5:7.2 The Requirements

[A] Must Claim What Applicant Regards As the Invention

The requirement to claim "the subject matter which the applicant regards as his invention" has rarely been applied to invalidate issued claims.[840] Nevertheless, it remains a requirement for obtaining patents and a basis for invalidity. The requirement is, like indefiniteness, evaluated as a matter of law.[841]

[A][1] During Prosecution

"During the prosecution of a patent application, a claim's compliance with both portions of section 112, paragraph 2, may be analyzed by consideration of evidence beyond the patent specification, including an inventor's statements to the Patent and Trademark Office."[842]

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of carrying out his invention."); *In re* Gay, 309 F.2d 769, 772 (C.C.P.A. 1962) (best mode prevents "inventors from applying for patents while at the same time concealing from the public preferred embodiments of their inventions which they have in fact conceived").

* Written by Daniel L. Reisner.

838. 35 U.S.C. § 112.

839. Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1377 (Fed. Cir. 2000).

840. *But see* Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1349 (Fed. Cir. 2002).

841. *Solomon*, 216 F.3d at 1377.

842. *Id*. at 1377; *see also In re* Conley, 490 F.2d 972, 976 (C.C.P.A. 1974) (first requirement of section 112, paragraph 2 "has been relied upon in cases where some material submitted by applicant, *other than his specification*, shows that a claim does not correspond in scope with what *he regards* as his invention").

[A][2] Issued Patents

"[I]nventor testimony, obtained in the context of litigation, should not be used to invalidate issued claims under section 112, paragraph 2."[843] Nevertheless, where "a simple comparison of the claims with the specification [demonstrates] the inventor did not" claim what he regarded as his invention, the claim will not withstand scrutiny.[844]

[B] Indefiniteness

The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise."[845] A patent is "like any property right" and "its boundaries should be clear."[846] Without unambiguous claims "there would be '[a] zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims.'"[847] In 2014, the Supreme Court adopted the "reasonable certainty" standard for measuring indefiniteness: "[W]e read § 112, ¶ 2 to require that a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty."[848] The "presumption of validity does not alter the degree

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843. *Solomon*, 216 F.3d at 1378–80 ("A more limited range of evidence should be considered in evaluating validity as opposed to patentability under either portion of section 112, paragraph 2, because the language of issued claims is generally fixed (subject to the limited possibilities of reissue and reexamination), the claims are no longer construed as broadly as is reasonably possible, and what the patentee subjectively intended his claims to mean is largely irrelevant to the claim's objective meaning and scope.").

844. Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1349 (Fed. Cir. 2002) (claim invalid where specification demonstrated "inventor did not regard" the claimed apparatus for which one component pivoted only in a "perpendicular"—instead of parallel—direction as his invention).

845. United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

846. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 730 (2002); *see also* Markman v. Westview Instruments, Inc., 517 U.S. 370, 373 (1996) ("It has long been understood that a patent must describe the exact scope of an invention and its manufacture . . . .").

847. Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2129 (2014) (without a meaningful indefiniteness standard, "patent applicants face powerful incentives to inject ambiguity into their claims" therefore "[e]liminating that temptation is in order, and 'the patent drafter is in the best position to resolve the ambiguity in . . . patent claims.'").

848. Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2129 (2014). Biosig Instruments, Inc. v. Nautilus, Inc. (III), 783 F.3d 1374, n.2 & n.3

of clarity that § 112, ¶ 2 demands from patent applicants; to the contrary, it incorporates that definiteness requirement by reference."[849] The presumption of validity may, however, have an effect upon underlying factual disputes.[850]

Federal Circuit case law prior to *Nautilus* (including many of the cases described below) may need to be re-evaluated in light of the Supreme Court's 2014 decision, accordingly many of the cases described below may have reduced precedential value. There has been some indication that the Federal Circuit is still receptive to considering pre-*Nautilus* indefiniteness case law.[851]

[B][1] Evolution of the Standard for Indefiniteness

The standard for determining indefiniteness has come around full circle. The "essence" of the definiteness requirement, as originally understood by the Federal Circuit, "is that the language of the claims must make it clear what subject matter they encompass."[852] "Whether a claim is invalid for indefiniteness requires a determination whether those skilled in the art would understand what is claimed when the claim is read in light of the specification."[853]

(Fed. Cir. 2015) (collecting Federal Circuit and Supreme Court decisions applying a "reasonable certainty" standard in a variety of contexts beyond indefiniteness).

849. *Nautilus II*, 134 U.S. at 2130 n.10.

850. *Nautilus II*, 134 U.S. at 2130 n.10 ("The parties nonetheless dispute whether factual findings subsidiary to the ultimate issue of definiteness trigger the clear-and-convincing-evidence standard and, relatedly, whether deference is due to the PTO's resolution of disputed issues of fact. We leave these questions for another day."); Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2253, 180 L. Ed. 2d 131 (Breyer, J., concurring) ("in this area of law as in others the evidentiary standard of proof applies to questions of fact and not to questions of law").

851. On remand from the Supreme Court, the Federal Circuit noted that Judge Bryson, sitting by designation in Texas, stated that "[c]ontrary to the defendant's suggestion, [the *Nautilus*] standard does not render all of the prior Federal Circuit and district court cases inapplicable" and "all that is required is that the patent apprise [ordinary-skilled artisans] of the scope of the invention." *Nautilus III*, 783 F.3d 1374, 1381 (Fed. Cir. 2015).

852. *In re* Hammack, 427 F.2d 1378, 1382 (C.C.P.A. 1970); Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to [each other's] rights'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369 (1938)).

853. Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470 (Fed. Cir. 1993) (invalidating compound claim because "the claimed compounds cannot be identified by testing and [because] one skilled in the art could not determine whether a given compound was within the scope of the

In the early 2000s, the Federal Circuit began adopting a more stringent test for invalidating a claim as indefinite. The court explained that "[i]f the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds."[854] Under this now-defunct Federal Circuit standard, claims were found indefinite only if they were "insolubly ambiguous, and no narrowing construction [could] properly be adopted."[855] On the other hand, "[i]f the court determines that a claim is not 'amendable to construction,' then the claim is invalid as indefinite."[856] If a claim cannot be meaningfully construed, a court will "not redraft claims to contradict their plain meaning to avoid a nonsensical result."[857]

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claims"); *see also* United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 233 (1942) ("To sustain claims so indefinite as not to give the notice required by the statute would be in direct contravention of the public interest which Congress therein recognized and sought to protect."); S3 Inc. v. nVIDIA Corp., 259 F.3d 1364, 1371–72 (Fed. Cir. 2001) (definiteness inquiry "focuses on whether the claims, as interpreted in view of the written description, adequately perform their function of notifying the public of the [scope of the] patentee's right to exclude"); J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1570 (Fed. Cir. 1997) (although patentee's construction "may have some common sense appeal, it provides no certainty to [patentee's] competitors, who are entitled to know the point in time at which their products will infringe"); N. Am. Vaccine, Inc. v. Am. Cyanamid Co., 7 F.3d 1571, 1579 (Fed. Cir. 1993) ("Whether a claim is invalid for indefiniteness depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification.").

854. Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

855. *Id.*, *overruled by Nautilus II*, 134 S. Ct. at 2124 ("We conclude that the Federal Circuit's formulation, which tolerates some ambiguous claims but not others, does not satisfy the statute's definiteness requirement. In place of the 'insolubly ambiguous' standard, we hold that a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.").

856. Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1338 (Fed. Cir. 2003); Halliburton Energy Serv., Inc. v. M-I LLC, 514 F.3d 1244, 1251 (Fed. Cir. 2008) ("Even if a claim term's definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope.").

857. Haemonetics Corp. v. Baxter Healthcare Corp., 607 F.3d 776, 782 (Fed. Cir. 2010).

The Supreme Court, in *Nautilus*, returned the standard for indefiniteness back toward the pre-2000s precedent. "We conclude that the Federal Circuit's formulation, which tolerates some ambiguous claims but not others, does not satisfy the statute's definiteness requirement. In place of the 'insolubly ambiguous' standard, we hold that a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention."[858] "The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable. The standard we adopt accords with opinions of this Court stating that 'the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter.'"[859]

The Court explained that the reason for its adoption of a new standard was to protect the public from the effects of uncertain claim scope. Without unambiguous claims "there would be '[a] zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims.'"[860] And without a meaningful indefiniteness standard, "patent applicants face powerful incentives to inject ambiguity into their claims."[861] "Eliminating that temptation is in order, and 'the patent drafter is in the best position to resolve the ambiguity in . . . patent claims.'"[862]

In adopting its new standard, the Court noted with apparent approval several principles upon which the parties agreed:

- "[D]efiniteness is to be evaluated from the perspective of someone skilled in the relevant art."[863]
- "[I]n assessing definiteness, claims are to be read in light of the patent's specification and prosecution history."[864]
- "[D]efiniteness is measured from the viewpoint of a person skilled in [the] art at the time the patent was filed."[865]

On remand from the Supreme Court, the Federal Circuit had an immediate opportunity to apply the new standard. "[W]e may now steer by the bright star of 'reasonable certainty,' rather than the

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858. Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2124 (2014).
859. *Id*. (quoting Minerals Separation, Ltd. v. Hyde, 242 U.S. 261, 270 (1916)); *see also* United Carbon Co. v. Binney & Smith Co., 337 U.S. 228, 236 (1942) ("[C]laims must be reasonably clearcut.").
860. *Nautilus*, 134 S. Ct. at 2129.
861. *Id*.
862. *Id*.
863. *Id*. at 2128.
864. *Id*.
865. *Id*.

unreliable compass of 'insoluble ambiguity.'"[866] The claim term at issue required "a first live electrode and a first common electrode mounted on said first half" of "an elongate member" of an exercise apparatus to be gripped by person who is exercising where these electrodes are "in spaced relationship with each other."[867] The court turned to the specification which provided both structural and functional guidance to help a person of ordinary skill understand what constitutes a "spaced relationship with each other."

The specification provided the following structural guidance:[868]

- "[T]he distance between the live electrode and the common electrode cannot be greater than the width of a user's hands because claim 1 requires the live and common electrodes to independently detect electrical signals at two distinct points of a hand."
- "[I]t is not feasible that the distance between the live and common electrodes be infinitesimally small, effectively merging the live and common electrodes into a single electrode with one detection point."

The specification also provided functional guidance:[869]

- "[A] skilled artisan could apply a test and determine the 'spaced relationship' as pertaining to the function of substantially removing EMG signals."

The court concluded that "a skilled artisan would understand the inherent parameters of the invention as provided in the intrinsic evidence."[870]

[B][2] Standard of Proof

The presumption of validity has no effect on the "reasonable certainty" standard: The "presumption of validity does not alter the

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866. Biosig Instruments, Inc. v. Nautilus, Inc., 783 F.3d 1374, 1791 (Fed. Cir. 2015).
867. *Id*. at 1376.
868. *Id*. at 1382–83.
869. *Id*. at 1383.
870. *Id*. at 1384. *See also* Nevro Corp. v. Bos. Sci. Corp., 955 F.3d 35, 39 (Fed. Cir. 2020) (vacating judgment that "paresthesia-free" is indefinite because the specification gives "detailed guidance and examples of systems and devices that generate and deliver paresthesia-free signals with high frequency, low amplitude, and other parameters"); *but see* IBSA Institut Biochimique, S.A. v. Teva Pharm. USA, Inc., 966 F.3d 1374, 1381 (Fed. Cir. 2020) ("half-liquid" indefinite because no definition provided by the intrinsic or extrinsic evidence and the patentee's expert had difficulty identifying the boundaries of the term during his deposition).

degree of clarity that § 112, ¶ 2 demands from patent applicants; to the contrary, it incorporates that definiteness requirement by reference."[871] The presumption of validity may however have an effect upon underlying factual disputes: "The parties nonetheless dispute whether factual findings subsidiary to the ultimate issue of definiteness trigger the clear-and-convincing-evidence standard and, relatedly, whether deference is due to the PTO's resolution of disputed issues of fact. We leave these questions for another day."[872]

[B][3] Role of the Jury

Although indefiniteness is a legal determination, the Federal Circuit held on one occasion prior to *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*,[873] that it "is amenable to resolution by the jury where the issues are factual in nature."[874] Although *Teva* did not address the role of the jury in an indefiniteness determination, its guidance does not appear to leave much room for a jury issue: "if a district court resolves a dispute between experts and makes a factual finding that, in general, a certain term of art had a particular meaning to a person of ordinary skill in the art at the time of the invention, the district court must then conduct a legal analysis: whether a skilled artisan would ascribe that same meaning to that term *in the context of the specific patent claim under review*."[875]

[B][4] Standard of Review

The Supreme Court held "that the appellate court must apply a 'clear error,' not a de novo, standard of review" when reviewing the evidentiary underpinnings of a claim construction ruling.[876] The Court explained:

> Construction of written instruments often presents a "question solely of law," at least when the words in those instruments are "used in their ordinary meaning." But sometimes, say when a

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871. Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2132, n.10 (2014).
872. *Id.*; Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2253 (2011) (Breyer, J., concurring) ("[I]n this area of law as in others the evidentiary standard of proof applies to questions of fact and not to questions of law.").
873. Teva Pharm. USA, Inc. v. Sandoz, Inc., 135 S. Ct. 831 (2015).
874. BJ Servs. Co. v. Halliburton Energy Servs., Inc., 338 F.3d 1368, 1372 (Fed. Cir. 2003).
875. *Id.*; Personalized Media Commc'ns v. Int'l Trade Comm'n, 161 F.3d 696, 705 (Fed. Cir. 1998) (an indefiniteness determination "is drawn from the court's performance of its duty as the construer of claims").
876. Teva Pharm. USA, Inc. v. Sandoz, Inc., 135 S. Ct. 831, 835 (2015).

> written instrument uses "technical words or phrases not commonly understood," those words may give rise to a factual dispute. If so, extrinsic evidence may help to "establish a usage of trade or locality."[877]

When the only evidence considered for claim construction is intrinsic, the determination is a matter of law and the review is therefore de novo.[878] "[I]f a district court resolves a dispute between experts and makes a factual finding that, in general, a certain term of art had a particular meaning to a person of ordinary skill in the art at the time of the invention, the district court must then conduct a legal analysis: whether a skilled artisan would ascribe that same meaning to that term in the context of the specific patent claim under review."[879] The factual determination is subject to a clear error standard of review and the legal analysis based on that determination subject to a de novo review.

[B][5] Dependent Claims

In the absence of a limitation in a dependent claim that cures indefiniteness, the indefiniteness of an independent claim will result in finding the dependent claims indefinite.[880]

§ 5:7.3 Relationship of Indefiniteness to Other Determinations

[A] Indefiniteness and Claim Construction

Prior to *Nautilus*, the Federal Circuit held that indefiniteness is bound up with claim construction.[881] Nevertheless, indefiniteness is a distinct legal determination apart from claim construction.[882]

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877. *Id*. at 833 (citations omitted).
878. *Id*. at 841 ("As all parties agree, when the district court reviews only evidence intrinsic to the patent (the patent claims and specifications, along with the patent's prosecution history), the judge's determination will amount solely to a determination of law, and the Court of Appeals will review that construction *de novo*.").
879. *Id*.
880. Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1347 (Fed. Cir. 2005) (affirming district court's finding that "grant of summary judgment of indefiniteness as to claim 1 invalidated" the remaining dependent claims).
881. *Exxon*, 265 F.3d at 1375. Whether this still holds true today remains to be seen.
882. Intervet Am., Inc. v. Kee-Vet Labs., Inc., 887 F.2d 1050, 1053 (Fed. Cir. 1989) ("Ambiguity, undue breadth, vagueness, and triviality are matters which go to claim validity for failure to comply with 35 U.S.C. § 112, ¶ 2, not to interpretation or construction."); *see also In re* Wallach, 378 F.3d

Accordingly, parties sometimes choose to pose claim construction and indefiniteness arguments in the alternative.[883] Likewise, courts may reject proffered claim constructions because they are not sufficiently definite.[884]

[B] Indefiniteness and Infringement

An indefiniteness determination can be informed by the infringement analysis.[885] It can also be informed by the inability of experts to explain the scope of the claim.[886]

An inventor's "inability to understand [a claim] phrase on its own, however, does not automatically mean that [the claim] is indefinite."[887] Furthermore, the fact that it may be difficult to determine whether the accused product or process falls within a claim because, for example, it only contains a trace amount of a claimed compound, does not

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1330, 1334 (Fed. Cir. 2004) ("claim to the genus of DNA molecules . . . defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants").

883. Lacks Indus., Inc. v. McKechnie Vehicle Components USA, Inc., 55 F. Supp. 2d 702, 709 n.1, 711 (E.D. Mich. 1999) ("Defendants propose this construction as an alternative to their primary argument that this phrase is indefinite. . . . Defendants argue that if it has any meaning at all, it must describe the entire area of the outer face of the wheel . . . .").

884. J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1570 (Fed. Cir. 1997) (rejecting construction as not sufficiently definite "because it sets no times for testing, but simply tests until failure, and then asks if the time to failure is within reasonable real world exposure times").

885. Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1336 (Fed. Cir. 2003) (considering fact that the accused product falls within claimed ranges only if one of four possible testing methods is used).

886. Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1354 (Fed. Cir. 2005) ("while indefiniteness does not depend on the difficulty experienced by a particular person in comparing the claims with the prior art or the claims with allegedly infringing products . . . , even the expert could not determine whether the look and feel of particular interface screens are 'aesthetically pleasing' using the parameters he specified . . . . The inability of the expert to use the parameters he himself identified . . . militates against the reasonableness of those parameters as delineating the metes and bounds of the claim."); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1218 (Fed. Cir. 1991) (considering "fact that no expert testified as to a definite meaning for the term in the context of the prior art" and inventor could not explain term); Semmler v. Am. Honda Motor Co., 990 F. Supp. 967, 975 (S.D. Ohio 1997) (considering opinion of patentee's expert "that fuel savings of one percent, or even less, fall within the definition of 'considerable'" in finding that term indefinite).

887. LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc., 275 F.3d 1347, 1359 (Fed. Cir. 2001).

render the claim indefinite.[888] "The test for indefiniteness does not depend on a potential infringer's ability to ascertain the nature of its own accused product to determine infringement, but instead on whether the claim delineates to a skilled artisan the bounds of the invention."[889] The fact that a potential infringer may need to practice the claimed invention and test the results to determine infringement does not render the claim indefinite.[890]

Although issues raised during infringement determinations can inform indefiniteness analysis, infringement and indefiniteness are distinct determination.[891]

[C] Indefiniteness Separate from Enablement

"[A]n inoperable claim construction would render the claim invalid for lack of enablement rather than for indefiniteness."[892] As one court explained: "A patent claim to a fishing pole would not be invalid on indefiniteness grounds if it contained a limitation requiring that the pole be 'at least three feet long,' even though a 50 foot long fishing pole

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888. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1340–41 (claim to "crystalline paroxetine hydrochloride hemihydrate" is "plain on its face" to a chemist; fact that it "is broad enough to embrace undetectable trace amounts" relates to claim breadth, not indefiniteness).

889. *Id.*; *see also* Marley Mouldings Ltd. v. Mikron Indus., Inc., 417 F.3d 1356, 1360 (Fed. Cir. 2005) (fact "that shaking the wood flour may change its compactness, and thus produce different weight values for a given volume . . . relates to whether there is infringement" not indefiniteness).

890. Invitrogen Corp. v. Biocrest Mfr., L.P., 424 F.3d 1374, 1384 (Fed. Cir. 2005) ("*Stratagene* is really talking about the difficulty of avoiding infringement, not indefiniteness of the claim.").

891. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1341 (Fed. Cir. 2003) (finding erroneous "conclusion that invalidity for indefiniteness should be found only in the alternative" to infringement).

892. Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1341 (Fed. Cir. 2003); Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1382 (Fed. Cir. 2001) ("The government's real objection to the claims as written is that they may include some inoperable embodiments. . . . However, that is an issue of enablement, and not indefiniteness."); N. Am. Vaccine, Inc. v. Am. Cyanamid Co., 7 F.3d 1571, 1579 (Fed. Cir. 1993) ("the parties' stipulation of possible inoperativeness of some species does not constitute an admission that those skilled in the art would not be reasonably apprised of the scope of the claims"); Miles Labs., Inc. v. Shandon, Inc., 997 F.2d 870, 875 (Fed. Cir. 1993) ("The invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim."); *cf.* Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470 (Fed. Cir. 1993) (invalidating compound claim because "the claimed compounds cannot be identified by testing and [because] one skilled in the art could not determine whether a given compound was within the scope of the claims").

would not be very practical."[893] Removing a limitation will broaden a claim and may raise questions about the sufficiency of the disclosure but will not ordinarily render the claim indefinite.[894]

[D] Indefiniteness and Prior Art

An indefiniteness determination can be affected by the proximity of the prior art. "When the meaning of claims is in doubt, especially when . . . there is close prior art, they are properly declared invalid."[895] That does not mean that a patent applicant is required "to determine what is going on in the technological gap between the claimed invention and the prior art, or to set the claim limits at the precise technological edge of the invention. A claim is not fatally indefinite for failing to delineate the point at which . . . change . . . occurs."[896]

Science's advance often produces more precise tools for measurement and terminology to describe those measurements. This can create difficulties when trying to compare prior art that uses older terminology and less precise measurements with claimed inventions described by new terminology based on more precise measurements.[897] The Court of Customs and Patent Appeals, however, rejected the argument that using more precise terminology rendering comparison with the prior art difficult justified rejecting claims as indefinite.[898]

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893. *Exxon*, 265 F.3d at 1382.

894. *In re* Fisher, 427 F.2d 833, 838 (C.C.P.A. 1970) (requiring only that a composition have "at least 24 amino acids in a certain sequence . . . obviously broadens the claim and raises questions of sufficiency of disclosure, it does not render the claim indefinite. The absence of the limitation has a precise meaning. Regardless of the specification, the claimed subject matter is in no way limited by the presence, absence or sequence of amino acids beyond the 24th position.").

895. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1218 (Fed. Cir. 1991); Halliburton Energy Serv., Inc. v. M-I LLC, 514 F.3d 1244, 1251 (Fed. Cir. 2008) ("We disagree that the evaluation of a claim's definiteness cannot include whether the patent expressly or at least clearly differentiates itself from specific prior art. Such differentiation is an important consideration in the definiteness inquiry because in attempting to define a claim term, a person of ordinary skill is likely to conclude that the definition does not encompass that which is expressly distinguished as prior art.").

896. Andrew Corp. v. Gabriel Elecs., Inc., 847 F.2d 819, 823 (Fed. Cir. 1988).

897. *Fisher*, 427 F.2d at 838 ("We recognize a problem in determining differences over the prior art where the claim uses language which is now accepted and precise but which was not used in the art at the time the prior-art references were published.").

898. *Id.* (reversing indefiniteness rejection, explaining "that the proper solution to this problem is to allow the use of new expressions when they are definite, and to allow the Patent Office, as it has always done, to call for comparative evidence when there is reason to believe that the prior art discloses matter which renders the claimed subject matter old or obvious").

Even if a patent distinguishes the invention clearly from the prior art it may be indefinite if it does "not place any limit on the scope of what was invented beyond the prior art."[899] The Federal Circuit found the term "fragile gel" indefinite because "[b]y failing to identify the degree of the fragility of its invention, Halliburton's proposed definition would allow the claims to cover not only that which it invented that was superior to the prior art, but also all future improvements to the gel's fragility."[900]

§ 5:7.4 *Indefiniteness in Different Situations*

[A] Terms of Degree

"Definiteness problems often arise when words of degree are used in a claim."[901] Lack of precision, however, "does not automatically render a claim invalid."[902] "When a word of degree is used the district court must determine whether the patent's specification provides some standard for measuring that degree."[903] "Reference to undefined standards" or subjective criteria, however, is insufficient.[904] Where "the written description provides objective boundaries for determining whether a" claim limitation is satisfied, that limitation is not indefinite.[905]

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899. *Halliburton*, 514 F.3d at 1253.
900. *Id*.
901. Seattle Box Co. v. Indus. Crating & Packing, Inc., 731 F.2d 818, 826 (Fed. Cir. 1984).
902. *Id*.; Interval Licensing LLC v. AOL, Inc., 766 F.3d 1364, 1370 (Fed. Cir. 2014) ("We do not understand the Supreme Court to have implied in *Nautilus*, and we do not hold today, that terms of degree are inherently indefinite."); *Exxon*, 265 F.3d at 1381 ("mathematical precision is not required—only a reasonable degree of particularity and definiteness"); Modine Mfg. Co. v. U.S. Int'l Trade Comm'n, 75 F.3d 1545, 1557 (Fed. Cir. 1996) ("technical terms are not per se indefinite when expressed in qualitative terms without numerical limits").
903. *Seattle Box Co.*, 731 F.2d at 826.
904. Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1352–53 (Fed. Cir. 2005) ("[T]he definition of 'aesthetically pleasing' cannot depend on the undefined views of unnamed persons, even if they are experts, specialists, or academics."); *see also Interval Licensing*, 766 F.3d at 1371 ("The patents' 'unobtrusive manner' phrase is highly subjective and, on its face, provides little guidance to one of skill in the art" and therefore claims containing that phrase are indefinite); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1218 (Fed. Cir. 1991) ("'[A]bout' 160,000 gives no hint as to which mean value between the [prior art] value of 128,620 and the mean specific activity level of 160,000 constitutes infringement.").
905. Niazi Licensing Corp. v. St. Jude Med. S.C., Inc., ___ F.4th ___ (Fed. Cir. 2022).

Accordingly, in some contexts terms of degree have been found to render claims indefinite.[906] Even use of the same terms of degree found indefinite in those cases, however, have not been found indefinite in other cases.[907]

[B] Patent Does Not Identify Test to Measure Claimed Property

If the patent does not provide guidance as to which of several prior art methods should be used to measure a claimed property, and thereby ascertain the claim's scope, that claim may be indefinite. The answer depends in part on how much the testing method affects the measurement of the claimed property. The ambiguity in testing methods must either be resolved using the normal tools of claim construction or, to the extent ambiguity remains, must "produce essentially identical results" in the context of the claimed property.[908]

[B][1] Examples of Claims Found Indefinite

[B][1][a] Leading Example: *Honeywell International v. International Trade Commission*

The Federal Circuit grappled with the issue of uncertain measurement methods at some length in *Honeywell International, Inc. v. International Trade Commission*.[909] The claims required that a

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906. Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 453 (Fed. Cir. 1985) ("partially soluble" indefinite); *Amgen*, 927 F.2d at 1218 ("at least about 160,000" indefinite because it "gives no hint as to which mean value between" the prior art value of 128,620 and 160,000 constitutes infringement); Semmler v. Am. Honda Motor Co., 990 F. Supp. 967, 975 (S.D. Ohio 1997) ("considerable fuel saving" indefinite because it could have been expressed precisely "in terms of a percentage").

907. BJ Servs. Co. v. Halliburton Energy Servs., Inc., 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (the term "about 0.06" not indefinite because it could be construed "to encompass the range of experimental error that occurs in any measurement"); Verve, LLC v. Crane Cams Inc., 311 F.3d 1116, 1120 (Fed. Cir. 2002) ("'substantially constant wall thickness' does not of itself render the claims of the '315 patent indefinite"); LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc., 275 F.3d 1347, 1359–60 (Fed. Cir. 2001) ("substantially completely wetted" construed as "[l]argely, but not necessarily wholly, surrounded by resin"); *Exxon*, 265 F.3d at 1380–81 ("substantial absence of slug flow" not indefinite because specification teaches that such absence "can be determined with reference to whether reactor efficiency is materially affected"); Ecolab, Inc. v. Envirochem., Inc., 264 F.3d 1358, 1369 (Fed. Cir. 2001) ("substantially uniform" construed as "largely, but not wholly" uniform).

908. PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558 (Fed. Cir. 1996).

909. Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332 (Fed. Cir. 2003).

polyethylene yarn used to make tires exhibit "mechanical properties within a claimed range before proceeding from one step to the next."[910] The dispute focused "on the method of measuring one claimed feature—the melting point elevation (MPE)."[911]

The patent gave an "example of how to measure the MPE, including a sample size, the rate of temperature increase for performing the test, and the equipment to be used" but did "not disclose any method that must be used to" obtain the sample for measurement.[912] Unfortunately for the patentee, the prior art taught four different ways to obtain a sample.[913] Crucial to the court's finding of invalidity was the fact that, "[d]epending on which sample preparation is used, the calculated MPE for a given sample can vary greatly."[914] The court refused to arbitrarily pick one of the four methods as the appropriate construction to save the claim. The court also rejected construing the claim to cover a manufacturing process that satisfied the temperature requirement under any one of the available sampling methods. The court distinguished an earlier case because there the prior methods of testing "produce[d] essentially identical results" but here they did not.[915]

[B][1][b] Other Examples

Courts have found claims indefinite in several other cases involving ambiguous testing criteria for determining whether a claim limitation has been satisfied.[916]

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910. *Id*. at 1335.
911. *Id*.
912. *Id*. at 1336.
913. *Id*.
914. *Id*.
915. *Id*. at 1341. See *infra* section 5:7.4[B][2][a] for a description of the earlier case.
916. HZNP Meds. LLC v. Actavis Labs. UT, Inc., 940 F.3d 680, 696–99 (claims indefinite because specification disclosed "two tests" for determining "better drying time" "but those tests do not provide consistent results"); Dow Chem. Co. v. Nova Chem. Corp., 803 F.3d 620, 633–34 (Fed. Cir. 2015) (claims found indefinite where "[t]here is no question that each of these four methods may produce different results, i.e., a different slope."); Teva Pharm. USA, Inc. v. Sandoz, Inc., 789 F.3d 1335, 1341 (Fed. Cir. 2015) (claims found indefinite where the parties "agree that each of these measures . . . would typically yield a different result for a given polymer sample."); Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1340–41 (Fed. Cir. 2003) ("glycosylation which differs from that of human urinary erythropoietin" indefinite because no evidence of method for measuring glycosylation of human urinary erythropoietin that yields results sufficiently uniform to compare with other forms); Union Pac. Res. Co. v. Chesapeake Energy Corp., 236 F.3d 684, 692 (Fed. Cir. 2001)

[B][2] Examples of Claims Found Definite

[B][2][a] Leading Example: *PPG Industries, Inc. v. Guardian Industries Corp.*

The issue in *PPG Industries, Inc. v. Guardian Industries Corp.*[917] arose because "the inventors failed to state the method they used to measure the [claimed] ultraviolet transmittance of the invention."[918] The court, however, found the claims sufficiently definite because the evidence "established that, setting aside the equipment error that plagued PPG's testing procedures, all of the conventional methods of testing ultraviolet transmittance produce essentially identical results."[919]

[B][2][b] Other Examples

Courts have found claims definite in several other cases where there were potentially ambiguous testing criteria for determining whether a claim limitation was satisfied.[920]

(claimed comparing step indefinite because the "patent does not define the means to 'compare' the two sets of characterizing information" and "comparing" is not clearly defined by the art); W.L. Gore & Assocs., Inc. v. Int'l Med. Prosthetics Research Assocs., Inc., 1990 WL 180490, at *20 (D. Ariz. July 9, 1990) ("matrix tensile strength . . . above 9,200 psi" is indefinite because skilled artisans "were as likely to follow the test method of ASTM D-638 or D-1708 as to follow ASTM D-882," which would result in infringement); *In re* Hammack, 427 F.2d 1378, 1382 (C.C.P.A. 1970) ("[T]he various steps as recited in the process claims, and the elements of sole apparatus claim 59, are not set out with sufficient particularity or adequately related to one another to define a process or apparatus for determining position or the like attributed to the subject matter in the preamble."); *see also* J.T. Eaton Co. v. Atl. Paste Glue Co., 106 F.3d 1563, 1570 (Fed. Cir. 1997) (rejecting construction as not sufficiently definite "because it sets no times for [length of] testing").

917. PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558 (Fed. Cir. 1996).

918. *Id*. at 1562.

919. *Id*. at 1563.

920. Takeda Pharm. Co. v. Zydus Pharm. USA, 743 F.3d 1359, 1366–67 (Fed. Cir. 2014) (refusing to find claims indefinite despite no guidance as to which method should be used to measure claimed property because "there was evidence before the trial court that although the results may be different, there is a 'high degree of correlation for the results' between the two techniques, which should 'give equivalent numbers with respect to any variants associated with either technique'"); Takeda Pharm. Co. v. Zydus Pharm. USA, Inc., 741 F.3d 1359, 1367 (Fed. Cir. 2014) (claim requiring measurement of particle diameter subject to several possible ways to measure not indefinite because "there is no evidence that the differences between these techniques are in fact significant"); Wellman, Inc. v. Eastman Chem., 642 F.3d 1355, 1368 (Fed. Cir. 2011) (finding

[C] Single Claim to Both Method and Apparatus Indefinite

A patent applicant may patent an invention as a "process," also known as a method, or as an apparatus, such as a "machine, manufacture or composition of matter."[921] Just as section 101 limits one patent to one invention,[922] it also limits one claim to one type of patentable subject matter—either method or apparatus, but not both. A claim that attempts to cover both a method and an apparatus is indefinite.[923] Several cases finding method-apparatus claims

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Honeywell "inapposite" because, "[w]hile the claims do not recite specific moisture conditions, the well-known practice in this field as illustrated in the 1997 ISO made this a routine concern to a person of ordinary skill in the art"); Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc., 554 F.3d 1010, 1022 (Fed. Cir. 2009) ("Example 2 of the '643 patent describes a particular method [for measuring bacterial density]. *Honeywell* [341 F.3d 1332 (Fed. Cir. 2003)] does not control where, as here, several methods for calculating reduction in bacterial density are available but the specification discloses one particular method."); Marley Mouldings Ltd. v. Mikron Indus., Inc., 417 F.3d 1356, 1360 (Fed. Cir. 2005) (claim requiring measurement of "volume of wood flour" not indefinite because skilled artisans "would understand how to measure parts by volume"); Grain Processing Corp. v. Am. Maize-Prods. Co., 185 F.3d 1341, 1346 (Fed. Cir. 1999) (recounting prior decision construing claim term as requiring use of "the School test to measure D.E."; prosecution history indicates that test was used by the inventors and rejecting construction permitting use of "any scientifically acceptable method to show noninfringement"); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385 (Fed. Cir. 1986) (antibody affinity claim not indefinite despite imprecision of the calculations and lack of a "standard set of experimental conditions" because court found claim "as precise as the subject matter permits").

921. 35 U.S.C. § 101.

922. *See infra* section 5:8.1.

923. IPXL Holdings, L.L.C. v. Amazon.com, 430 F.3d 1377, 1384 (Fed. Cir. 2005) (claim that "recites both a system and the method for using that system . . . is invalid under section 112, paragraph 2"); *In re* Collier, 397 F.2d 1003, 1005–06 (C.C.P.A. 1968) (rejecting claim "to a structure" as indefinite because some of the limitations attempted to claim the "structure which will result upon the performance of future acts"); *Ex parte* Lyell, 17 U.S.P.Q.2d (BNA) 1548, 1551 (B.P.A.I. 1990) (rejecting claim as indefinite and as claiming unpatentable subject matter because the same claim attempted to cover "both a product or machine and a process"); M.P.E.P. § 2173.05(p)(II) ("A single claim which claims both an apparatus and the method steps of using the apparatus is indefinite."); *cf.* Collaboration Props., Inc. v. Tandberg ASA, 2006 WL 1752140, at *7 n.3 (N.D. Cal. June 23, 2006) ("The court questions whether the ambiguity posited by the Federal Circuit actually exists" because the claim in IPXL "unambiguously required that a step be performed."; "The Federal Circuit

indefinite illustrate the point.[924]

When permissible under the rules of claim construction, courts reject constructions that would otherwise result in indefinite method-apparatus claims.[925] This can affect how courts construe functional language.[926] When claiming an apparatus, a "patent applicant is free to recite features of an apparatus either structurally or functionally."[927] In such cases, courts may interpret that functional language in an apparatus claim as requiring that the apparatus "need only be capable

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might instead have relied on 35 U.S.C. section 101, which requires that each claim cover one of a disjunctive list of classes of invention.").

924. *In re* Katz Interactive Call Processing Patent Litig., 639 F.3d 1303, 1318 (2011) (a system claim requiring an "interface means for providing automated voice messages . . . to certain of said individual callers, wherein said certain of said individual callers digitally enter data" held invalid for attempting to simultaneously cover a method and an apparatus); *IPXL Holdings*, 430 F.3d at 1384 (claim to "system of claim 2 wherein . . . the user uses the input means . . ."); *Collier*, 397 F.2d at 1004–06 (claim to coaxial cable components comprising a connector and a ground wire "being displaced . . . when [the connector] is crimped" onto a portion of a coaxial cable); *Lyell*, 17 U.S.P.Q.2d at 1549 (claim to a "transmission tool" comprising various structural elements and performing various steps such as "positioning . . ." and "removing . . .").

925. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1384 (Fed. Cir. 2003) (rejecting a proposed claim construction of an antibiotic composition of matter claim as indefinite because infringement would depend on which bacteria is being treated: GSK argued that "a formulation falls outside the scope of the claims if a given antibiotic, bacteria, and disease combination provides no synergy. . . . By GSK's proposed construction, a formulation . . . might infringe or not depending on its usage in changing circumstances. In other words, a given embodiment would simultaneously infringe and not infringe the claims, depending on the particular bacteria chosen for analysis. Thus, one of skill would not know from one bacterium to the next whether a particular composition standing alone is within the claim scope or not. That is the epitome of indefiniteness."); Union Oil v. Atl. Richfield Co., 208 F.3d 989, 999 (Fed. Cir. 2000) ("The scope of these composition claims cannot, as the appellant refiners argue, embrace only certain uses of that composition. . . . Otherwise these composition claims would mutate into method claims. The district court correctly applied this principle, refusing to narrow the scope of the claimed compositions to specific uses.").

926. *See, e.g.*, Research Corp. Techs. Inc. v. Gensia Labs. Inc., 10 F. App'x 856, 861 (Fed. Cir. 2001) (unpublished) (construing "which complex is protected from light" in a composition claim "to be non-limiting" because "[n]o brown bottle appears as part of the claim, nor is there any ingredient in the composition that protects the composition from light").

927. *In re* Schreiber, 128 F.3d 1473, 1478 (Fed. Cir. 1997) ("There is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims.") (citing *In re* Swinehart, 439 F.2d 210, 212 (C.C.P.A. 1971)).

of" performing the function, and need not be actually performing the function.[928] If a court construes language in an apparatus claim as a functional limitation, it will not be interpreted as a method-apparatus claim.[929] Accordingly, "[w]hile features of an apparatus may be recited either structurally or functionally, claims directed to an apparatus must be distinguishable from the prior art in terms of structure rather than function."[930]

[D] Claims Requiring Knowledge or Intent

"The scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention."[931] Claims, however, may require "a person to have foreknowledge of certain facts when practicing the invention."[932]

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928. Intel Corp. v. Int'l Trade Comm'n, 946 F.2d 821, 832 (Fed. Cir. 1991); LifeNet Health v. Lifecell Corp., 837 F.3d 1316, 1327 (Fed. Cir. 2016) (claim to a "plasticized soft tissue graft" requiring "one or more plasticizers are not removed from said internal matrix . . . prior to transplantation" not an impermissible hybrid method-apparatus claim, because "the non-removal limitation defines a property of the recited plasticizer in that the plasticizer is biocompatible and does not need to be removed from the internal matrix before transplantation").

929. R.A.C.C. Indus., Inc. v. Sun-Tech, Inc., 49 U.S.P.Q.2d (BNA) 1793, 1796 (Fed. Cir. 1998) (unpublished) (The Federal Circuit, however, "has never determined that functional language in a claim converts an apparatus claim into a method of use or hybrid claim."); *Collaboration Props.*, 2006 WL 1752140, at *6 (claim requiring a system that "is configured to reproduce images . . . on at least two monitors" is not a hybrid method apparatus claim because it "recites the functionality of the claimed system rather than the act of using the system").

930. M.P.E.P. § 2114; *see also Schreiber*, 128 F.3d at 1477–78 (rejecting claim for popcorn dispenser over prior art spout for dispensing oil having the same "shape" even though the oil spout "does not address the use of the disclosed structure to dispense popcorn"); *In re* Ludtke, 441 F.2d 660, 661, 663–64 (C.C.P.A. 1971) (rejecting claim to parachute requiring that "upon deployment . . . whereby said parachute will sequentially open" even though prior art disclosed "a parachute which is intended to completely open upon deployment").

931. Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1350 (Fed. Cir. 2005) ("A purely subjective construction of 'aesthetically pleasing' would not notify the public of the patentee's right to exclude since the meaning of the claim language would depend on the unpredictable vagaries of any one person's opinion of the aesthetics of interface screens."); *see also In re* Musgrave, 431 F.2d 882, 893 (C.C.P.A. 1970) ("A step requiring the exercise of subjective judgment without restriction might be objectionable as rendering a claim indefinite.").

932. *Datamize*, 417 F.3d at 1355–56; *see also* Koito Mfg. Co. v. Turn-Key-Tech, L.L.C., 381 F.3d 1142, 1150 n.2 (Fed. Cir. 2004) (claims "may require an actor to have knowledge of certain facts"); Combined Sys., Inc. v.

[E] Means-Plus-Function Claims

Paragraph 6 of section 112 permits applicants to draft claims in means-plus-function format. Claim elements are defined as any means for performing a designated function. For example, claims to pharmaceutical formulations could be drafted (although they rarely are) as a pharmaceutical formulation comprising active ingredient *XYZ* combined with a means for delivering the drug to the body in a bioavailable form. To obtain the benefit of the means-plus-function format, the patent must supply the relevant structures to which the means portion of the clause refers.[933] Failure to do so is a failure to comply with the definiteness requirement.[934] Disclosing a generic structure may be insufficient, depending on the claimed function.[935] The patent must also supply linking language that informs the skilled artisan that those structures are meant to be associated with the relevant means clause.[936]

Means-plus-function language is sometimes used in claims to medical devices.[937] For example, in one case a court found indefinite

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Def. Tech. Corp. of Am., 550 F.3d 1207, 1211–14 (Fed. Cir. 2004) ("forming folds" construed to require "deliberate and systematic creation of folds").

933. *In re* Donaldson Co., 16 F.3d 1189, 1195 (Fed. Cir. 1994) (en banc) ("if one employs means-plus-function language in a claim, one must set forth in the specification an adequate disclosure showing what is meant by that language").

934. *Id*. ("If an applicant fails to set forth an adequate disclosure" of the means, "the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of section 112.").

935. Ergo Licensing, LLC v. CareFusion 303, Inc., 673 F.3d 1361, 1363–64 (Fed. Cir. 2012) ("The recitation of 'control device' provides no more structure than the term 'control means' itself, rather it merely replaces the word 'means' with the generic term 'device.'").

936. Default Proof Credit Card Sys., Inc. v. Home Depot U.S.A., Inc., 412 F.3d 1291, 1298 (Fed. Cir. 2005) ("A structure disclosed in the specification qualifies as 'corresponding' structure only if the specification or prosecution history clearly links or associates that structure to the function recited in the claim.").

937. Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293 (Fed. Cir. 2005) ("orthopedic surgical implants"); Utah Med. Prods., Inc. v. Graphic Controls Corp., 350 F.3d 1376 (Fed. Cir. 2003) ("medical device for measuring the pressure within a body cavity"); Med. Instrumentation & Diagnostics Corp. v. Elekta AB, 344 F.3d 1205 (Fed. Cir. 2003) ("system for planning surgical treatment using a presentation of images from multiple scanning sources"); Cardiac Pacemakers, Inc. v. St. Jude Med., Inc., 296 F.3d 1106 (Fed. Cir. 2002) (defibrillator apparatus).

a claim to an implantable defibrillator that required a "monitoring means for monitoring the ECG signal . . . for activating said charging means in the presence of abnormal cardiac rhythm."[938] The court found that the "function identified by the claim language" required "the same means to monitor the ECG signal and to activate the charging means" if needed.[939] "Because only the physician both monitors the ECG signal and activates the charging means in the presence of abnormal cardiac rhythm, and Cardiac Pacemakers concedes that the physician cannot be corresponding structure, the specification discloses no structure that corresponds to the claimed function."[940] In another case, the Federal Circuit found a "control means" in a fluid infusion system indefinite even if the corresponding structure was a general purpose computer, because "special programming" would be required, triggering the "default rule requiring disclosure of an algorithm."[941]

[F] Drafting Errors in Claim Language

If a claim contains a drafting error that cannot be corrected, or remedied through a proper construction, it will be found indefinite.[942] In addition, "[m]erely claiming broadly does not render a claim insolubly ambiguous, nor does it prevent the public from understanding the scope of the patent."[943]

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938. Cardiac Pacemakers, Inc. v. St. Jude Med., Inc., 296 F.3d 1106, 1107–08 (Fed. Cir. 2002).
939. *Id*. at 1114.
940. *Id*.
941. Ergo Licensing, LLC v. CareFusion 303, Inc., 673 F.3d 1361, 1365 (Fed. Cir. 2012).
942. Novo Indus., L.P. v. Micro Molds Corp., 350 F.3d 1348, 1358 (Fed. Cir. 2003) ("Since we cannot know what correction is necessarily appropriate or how the claim should be interpreted, we must hold claim 13 of the '578 patent invalid for indefiniteness."); *see also* Energizer Holdings, Inc. v. Int'l Trade Comm'n, 435 F.3d 1366, 1370 (Fed. Cir. 2006) ("Although neither the Commission nor the courts can rewrite claims to correct material errors, the issue here is not correction of error, but understanding of what the claim covers.").
943. Ultimax Cement Mfg. Corp. v. RC Cement Holding Co., 587 F.3d 1339, 1345 (Fed. Cir. 2009) ("[A] claim to a formula containing over 5000 possible combinations is not necessarily ambiguous if it sufficiently notifies the public of the scope of the claims. If a member of the public had made, for example, a compound of pure C_4A_3Cl or one of C_4A_3Cl with some K molecules substituted for some of the C molecules (using the '684 patent's notation), he would know that the compound fit within the set of compounds described by the claims.").

[F][1] Claims Found Indefinite

The following examples of indefinite claim language illustrate the point.[944]

[F][2] Claims Not Found Indefinite

Other examples illustrate the use of claim construction or allowable corrections to provide the clarity necessary to avoid indefiniteness.[945]

Where an error is introduced in preparing a patent for printing and is "apparent from the prosecution history," the meaning of the claim could be ascertained.[946]

[F][3] Lack of Antecedent Basis

The lack of an antecedent basis[947] does not automatically render a claim indefinite.[948] If the meaning of a claim having terms lacking an antecedent basis "would reasonably be understood by persons of ordinary skill," the claim is not indefinite.[949]

§ 5:8 Double Patenting*

Generally unique to the United States, double patenting is an invalidity defense and a basis for rejecting patent claims. Because of this fact, it poses particular risks to companies who direct their patent prosecution from outside the United States and who may be unaware

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944. *See, e.g.*, *Novo Indus.*, 350 F.3d at 1357 ("a rotatable with"); Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1349 (Fed. Cir. 2002) ("claim ends in the middle of a limitation: 'coupled to said gearbox means by rigid'").

945. *See, e.g.*, Hoffer v. Microsoft Corp., 405 F.3d 1326, 1331 (Fed. Cir. 2005) (claiming dependence to claim that did not exist did not render dependent claim indefinite because "the correct antecedent claim is apparent from the prosecution history").

946. *Id*.

947. *Energizer*, 435 F.3d at 1370 ("The requirement of antecedent basis is a rule of patent drafting, administered during patent examination.").

948. *Id*. at 1370 ("When the meaning of the claim would reasonably be understood by persons of ordinary skill when read in light of the specification, the claim is not subject to invalidity upon departure from the protocol of 'antecedent basis.'"); Slimfold Mfg. Co. v. Kinkead Indus., Inc., 810 F.2d 1113, 1117 (Fed. Cir. 1987) ("the missing antecedent clause, the absence of which was not observed by the examiner of the original patent or by Kinkead in its reissue protest documents, did not fail to 'inform the public during the life of the ['276] patent of the limits of the monopoly asserted'"); M.P.E.P. § 2173.05(e) ("the failure to provide explicit antecedent basis for terms does not always render a claim indefinite").

949. *Energizer*, 435 F.3d at 1370.

* Written by Daniel L. Reisner.

of the risks involved in developing patent portfolios containing U.S. patents. An effort to protect an innovation through multiple patent filings, if not managed properly, creates a risk of shortened patent life or, in the worst case, loss of patent rights.

To understand this risk, one must understand the doctrine of double patenting. Double patenting aims to prevent a single patentee from expanding the scope of its patent protection beyond the normal term of a patent. Without the double patenting doctrine, a patentee could file multiple patent applications arising out of the same invention or obvious variations on the same invention and obtain patents with different expiration dates, thereby extending the effective term of the patent protection. For example, if a patentee invented and obtained a patent covering use of aspirin as a treatment for pain, that patentee could be prevented by double patenting from obtaining a second patent with a later expiration date that covered the use of aspirin to treat pain associated with arthritis unless the patentee could show that such use was not obvious over the first patent. The patentee would need to make this showing to avoid double patenting even though the first patent may not qualify as prior art.

§ 5:8.1 Two Forms of Double Patenting: Statutory and Non-Statutory

The doctrine of double patenting prohibits an inventor from obtaining a patent for either (i) an invention the inventor has already patented or (ii) an obvious modification of an invention the inventor has already patented.[950] The first form of double patenting is referred to as "statutory" or "same invention" double patenting, and it is based on the express language of the Patent Act, which states that an inventor "may obtain *a* patent" for his or her invention.[951] Courts have interpreted use of the singular term "a patent" to preclude the issuance of more than one patent for a single invention.[952] This type of double patenting rarely occurs.

The second form of double patenting is referred to as "nonstatutory" or "obviousness-type" double patenting and, unlike statutory double patenting, it is not based on the language of the Patent Act. Instead, nonstatutory or obviousness-type double patenting "is a

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950. *See In re* Longi, 759 F.2d 887, 892 (Fed. Cir. 1985) (double patenting "precludes one person from obtaining more than one valid patent for either (a) the 'same invention,' or (b) an 'obvious' modification of the same invention").

951. 35 U.S.C. § 101 (emphasis added). *See Longi*, 759 F.2d at 892; *see also In re* Vogel, 422 F.2d 438 (C.C.P.A. 1970) ("same invention" refers to an invention drawn to identical subject matter).

952. *See Longi*, 759 F.2d at 892.

judicially created doctrine grounded in public policy . . . rather than based purely on the precise terms of the statute."[953] Obviousness-type double patenting prevents a person from obtaining "claims in a second patent not patentably distinct from claims of the first patent."[954]

§ 5:8.2 The Policy Behind Double Patenting

The purpose of the Patent Act is to promote research and innovation by granting a successful inventor the right to exclude others from practicing his or her discovery for a fixed period of time. In exchange for this right, the inventor must publicly disclose his or her discovery in the form of a patent. The right to exclude makes a patent a valuable form of intellectual property and provides an incentive to inventors not just to innovate, but also to disclose their innovations. Double patenting prevents an inventor from extending the right to exclude beyond its normal term, either by obtaining a new patent for the same invention or by obtaining a patent on something that is not patentably distinct from a prior invention.

> All proper double patenting rejections, of either type, rest on the fact that a patent has been issued and later issuance of a second patent will continue protection, beyond the date of expiration of the first patent, of the very same invention claimed therein . . . or of a mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art.[955]

Judge Rich explained the policy behind double patenting:

> The public should . . . be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants

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953. *Id.*; *In re* Braat, 937 F.2d 589, 592 (Fed. Cir. 1991) (obviousness-type double patenting is a judicially created doctrine to "prevent improper time wise extension of the patent right by prohibiting the issuance of claims in a second patent which are not 'patentability distinct' from the claims of a first patent").

954. *Longi*, 759 F.2d at 892; Ga.-Pac. Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1326 (Fed. Cir. 1999) ("Under obviousness-type double patenting, a patent is invalid when it is merely an obvious variation of an invention disclosed and claimed in an earlier patent by the same inventor.").

955. *In re* Kaplan, 789 F.2d 1574, 1579–80 (Fed. Cir. 1986); AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1373 (Fed. Cir. 2014) (double patenting "is designed to prevent an inventor from securing a second, later expiring patent for the same invention").

> which would have been obvious to those of ordinary skill in the art at the time the invention was made. . . .[956]

[A] Policy Prior to URAA

Obviousness-type double patenting law evolved prior to the Uruguay Round Agreements Act (URAA), which changed the patent term from seventeen years from issuance to twenty years from the earliest claimed priority date.[957] Prior to the URAA, obviousness-type double patenting was needed to prevent a patentee from obtaining multiple patents for obvious variations of the same invention with different expiration dates based on different issuance dates. The doctrine "is less significant in post-URAA patent disputes."[958]

> "[T]he unjustified patent term extension justification for obviousness-type double patenting" may have "limited force in . . . many double patenting rejections today, in no small part because of the change in the Patent Act from a patent term of seventeen years from issuance to a term of twenty years from filing."[959]

[B] Continued Applicability of Obviousness-Type Double Patenting Post-URAA

Justifications remain for retaining obviousness-type double patenting for URAA patents. For example, "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO" resulting in patent term adjustments.[960] In addition, where

> the applicant chooses to file separate applications for overlapping subject matter and to claim different priority dates for the applications, the separate patents will have different expiration dates since the patent term [for URAA patents] is measured from the claimed priority date. . . . When such situations arise, the

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956. *In re* Zickendraht, 319 F.2d 225, 232 (C.C.P.A. 1963) (Rich, J., concurring) (quoted by *Longi*, 759 F.2d at 892–93) (quoted in M.P.E.P. § 804); *see also* Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 967 (Fed. Cir. 2001) ("Through a statutorily prescribed term, Congress limits the duration of a patentee's right to exclude others from practicing a claimed invention"; therefore a party may not obtain "an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent").

957. Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994).

958. *AbbVie*, 764 F.3d at 1374.

959. *Id*. at 1373–74 (quoting *In re* Fallaux, 564 F.3d 1313, 1318 (Fed. Cir. 2009)); *accord Boehringer*, 592 F.3d at 1346.

960. *AbbVie*, 764 F.3d at 1373.

> doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variants thereof) does not receive an undue patent term extension.[961]

Accordingly, the Federal Circuit held that "obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates."[962]

§ 5:8.3 Double Patenting Requires Common Inventorship or Ownership

Double patenting applies when the two patents or applications in question have the same inventors or the same owners. Double patenting between a patent and a pending application exists where the patent and application are "filed by the same inventive entity, or by an inventive entity having a common inventor with the patent, and/or by the owner of the patent."[963]

§ 5:8.4 Situations in Which Double Patenting May Arise

[A] Prosecution, Reexamination, and Post-Issuance

Double patenting can arise in several procedural contexts. First, double patenting can arise during the examination of a pending patent application. In this context, the claims of the application can be compared with those of an already-issued patent, another pending

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961. *Id*.

962. *Id*. at 1374.

963. M.P.E.P. §§ 804, 800-19 (2001); *see also* M.P.E.P. §§ 804, 800–11 (2001) ("Before consideration can be given to the issue of double patenting, there must be some common relationship of inventorship and/or ownership of two or more patents or applications."); *In re* Hubbell, 709 F.3d 1140 (Fed. Cir. 2013) (holding that the doctrine of double patenting is potentially applicable when two applications share a common inventor, regardless of whether they were ever concurrently owned by the same inventive entity, to avoid multiple infringement suits by different licensees, and denying request to file terminal disclaimer to obviate double patenting because application was not commonly owned with previously issued patent); *Longi*, 759 F.2d at 887 (obviousness-type double patenting rejection is proper when patent applications having no common inventors are assigned to the same entity); *In re* Van Ornum, 686 F.2d 937 (C.C.P.A. 1982) (obviousness-type double patenting rejection proper where application and reference patent had some inventors in common even though they were assigned to different entities).

application, or a published application.[964] Second, double patenting can arise during a reexamination proceeding. In this context, the claims of the reexamined patent can be compared with those of an already-issued patent or of a pending or published application.[965] Finally, double patenting can arise after a patent has issued, where it is raised as a defense in a patent infringement litigation brought in a federal district court.[966] In this context, the claims of the challenged patent would be compared with those of an earlier-issued patent.

[B] Later Issuing, Earlier Expiring Reference Patent

The law as to what qualifies as a reference patent for obviousness-type double patenting has developed over more than a century. "[T]he doctrine of double patenting was primarily designed to . . . limit[ ] a patentee to one patent term per invention or improvement."[967] "[T]hat principle is violated when a patent expires and the public is nevertheless barred from practicing obvious modifications of the invention claimed in that patent because the inventor holds another later-expiring patent with claims for obvious modifications of the invention."[968]

"Traditionally, courts looked at the issuance dates of the respective patents, because, under the law pre-URAA, the expiration date of the patent was inextricably intertwined with the issuance date,

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964. M.P.E.P. §§ 804, 800–19 (2001) ("A double patenting issue may arise between two or more pending applications, between one or more pending applications and a patent, or between one or more pending applications and a published application.").

965. *Id*. ("A double patenting issue may likewise arise in a reexamination proceeding between the patent claims being reexamined and the claims of one or more applications and/or patents."); *see also In re* Lonardo, 119 F.3d 960, 966 (Fed. Cir. 1997) ("it is reasonable to conclude that Congress intended to include double patenting over a prior patent as a basis for reexamination because maintenance of a patent that creates double patenting is as much of an imposition on the public as maintenance of a patent that is unpatentable over the prior art").

966. *See Eli Lilly*, 251 F.3d at 955 (patent held invalid due to obviousness-type double patenting); Gen. Foods v. Studiengesellschaft Kohle mbH, 972 F.2d 1272 (Fed. Cir. 1992) (patent survived double patenting challenge).

967. Gilead Scis., Inc. v. Natco Pharma Ltd., 753 F.3d 1208, 1212 (Fed. Cir. 2014); *In re* Zickendraht, 319 F.2d 225, 232 (C.C.P.A. 1963) (Rich, J., concurring) ("The public should . . . be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also any modifications or variants thereof which would have been obvious to those of ordinary skill in the art at the time the invention was made. . . .").

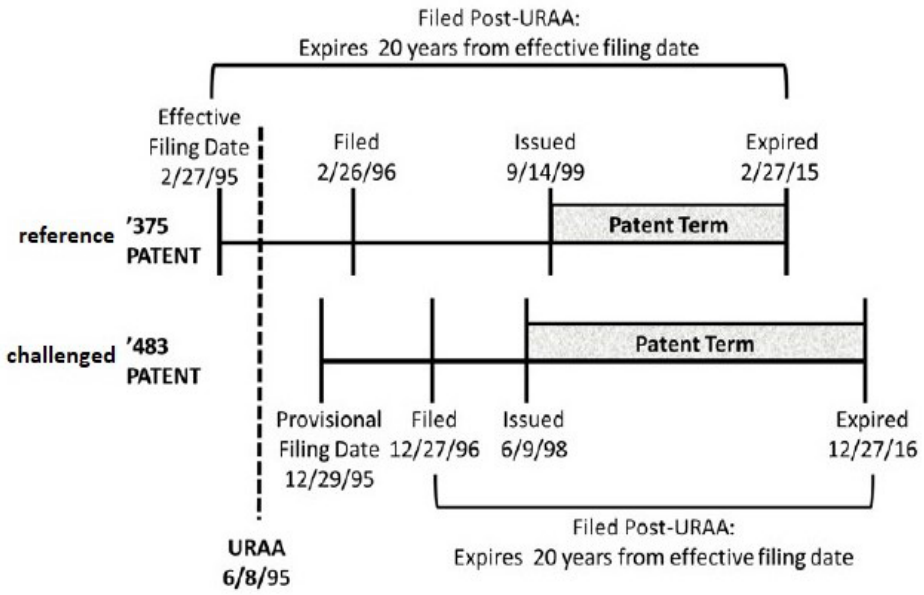
968. *Gilead Scis.*, 753 F.3d at 1214.

and used the earlier-issued patent to limit the patent term(s) of the later issued patent(s)."[969] This made sense in the pre-URAA world where patents invariably expired seventeen years from issuance. Barring unusual circumstances, only earlier-issuing patents could be extended by later-issuing patents, because only later-issuing patents would have later expiration dates.

The "URAA altered the analytical inquiry for double patenting; issuance dates of post-URAA patents did not serve as reliable stand-ins for the expiration date of the patent as is true for pre-URAA patents."[970] Subsequent to the URAA, situations arose where later issuing patents, earlier expiring patents were found to be reference patents for double patenting. Accordingly, issuance dates could no longer be used without further consideration of the circumstances to determine if a patent could serve as reference patent for obviousness-type double patenting.

[B][1] Post-URAA Challenged Patents

One such circumstance arose in *Gilead*, depicted below:



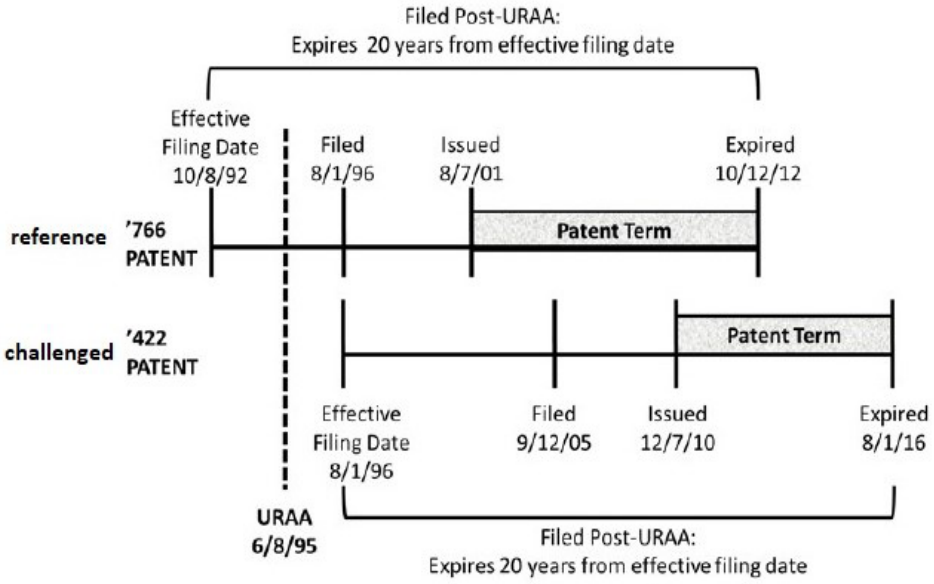
The court could not rely on issuance dates here because the patents were post-URAA and issuance dates did not provide reliable proxy for the expiration date—"the date that really mattered."[971] It also would

969. Novartis Pharm. Corp. v. Breckenridge Pharm., Inc., 909 F.3d 1355, 1362 (Fed. Cir. 2018).
970. *Id*.
971. *Id*. at 1363–64 (quoting *Gilead Scis.*, 753 F.3d at 1215).

not protect against "gamesmanship."[972] In *Gilead*, the post-URAA reference patent ('375) and the challenged patent ('483) were "not part of the same family of patents and were not before the same patent examiner" because the patentee "crafted" a separate chain of applications with a later priority date.[973]

AbbVie[974] provides another "example of the post-URAA scenario . . . where an inventor, seeking to prolong his exclusivity rights over his invention, applies for a second patent on an obvious variant of his invention protected by a first patent but chooses a different, later priority date than the one relied on for the first patent so that the second patent expires later than the first patent."[975]

The reference patent (top) and challenged patent (bottom) in *AbbVie*, found to be invalid for obviousness-type double patenting, are depicted below:



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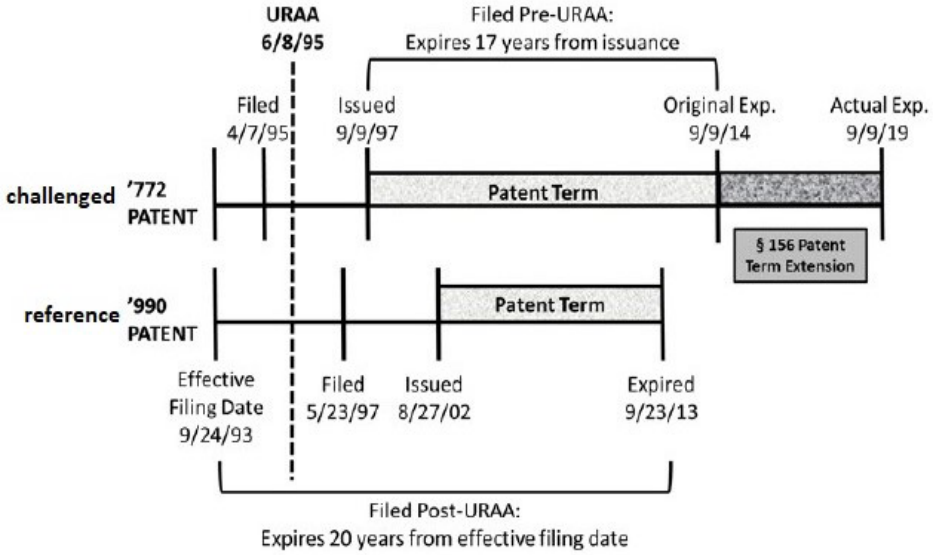
972. *Gilead Scis.*, 753 F.3d at 1215 ("[I]f the double patenting inquiry was limited by issuance date, inventors could routinely orchestrate patent term extensions by (1) filing serial applications on obvious modifications of an invention, (2) claiming priority to different applications in each, and then (3) arranging for the application claiming the latest filing date to issue first. If that were to occur, inventors could potentially obtain additional patent term exclusivity for obvious variants of their inventions while also exploring the value of an earlier priority date during prosecution.").
973. *Id.* at 1210.
974. AbbVie, Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366 (Fed. Cir. 2014).
975. *Novartis Pharm.*, 909 F.3d at 1365.

[B][2] Pre-URAA Challenged Patents

The Federal Circuit declined to read *Gilead* and *AbbVie* as rendering all earlier-expiring patents as potential obviousness-type double patenting reference patents. In *Breckenridge*, the court considered the "narrow legal question: can a post-URAA patent that issues after and expires before a pre-URAA patent qualify as a double patenting reference against the pre-URAA patent?" Its answer "under the circumstances of this case" was that "it cannot."[976] The reference patent ('772) and challenged patent ('990) are depicted below:



The court concluded that here there was no "gamesmanship" because the challenged patent only expired after the reference patent "due to happenstance of an intervening change in patent term law."[977] Unlike *Gilead* and *AbbVie*, in *Novartis*, both patents shared the same effective filing date. The difference in expiration dates was merely due to the intervening passage of the URAA which caused the challenged patent to expire twenty years from filing but permitted the reference patent seventeen years from issuance because it, unlike the challenged patent, issued from an application filed before the URAA critical date.

[B][3] PTE Extended Patents

As explained in section 5:8.5[E][4], obviousness-type double patenting is evaluated based on the normal term of the patent without considering the effect any additional PTE has on the full term of a

976. *Id.* at 1361–62.
977. *Id.* at 1364.

challenged patent. The Federal Circuit explained that "there is no potential gamesmanship issue through structuring of priority claims as identified in *Gilead*" where, but for PTE, the challenged patent "would have expired before the" reference patent.[978]

[B][4] PTA Adjusted Patents

"PTA and PTE should be treated differently from each other when determining whether or not claims are unpatentable under ODP" because they "are dealt with in different statutes and deal with differing circumstances."[979] A patent can serve as an obviousness-type double patenting reference against another related patent when the patents expire at different times solely due to PTA.[980]

§ 5:8.5 Non-Statutory Double Patenting

[A] Anticipation and Obviousness

Although the term non-statutory double patenting is often used interchangeably with obviousness-type double patenting, this form of double patenting includes the possibility that the earlier claim anticipates the later claim. "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim."[981] A double patenting reference anticipates "if it discloses every limitation . . . explicitly or inherently."[982] The approach used for determining obviousness in a double patenting analysis is similar to a section 103 obviousness analysis: "[T]his court has endorsed an obviousness determination similar to, but not necessarily the same as, that undertaken under 35 USC § 103 in determining the propriety of a rejection for double patenting."[983] In conducting an obviousness-type double patenting

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978. Novartis AG v. Ezra Ventures LLC, 909 F.3d 1367, 1374–75 (Fed. Cir. 2018).
979. *In re* Cellect, LLC, 81 F.4th 1216, 1226 (Fed. Cir. 2023).
980. *Id*.
981. *Eli Lilly*, 251 F.3d at 968; *see also In re* Berg, 140 F.3d 1428, 1437 (Fed. Cir. 1998) (affirming a holding of double patenting where an application claim to a genus is anticipated by patent claims to a species within that genus); *In re* Goodman, 11 F.3d 1046 (Fed. Cir. 1993) (affirming rejection of generic claims for double patenting as "anticipated" over earlier issued species claims).
982. *Eli Lilly*, 251 F.3d at 970 ("serotonin uptake inhibition is an inherent property of fluoxetine hydrochloride" administration; therefore, later claim to serotonin uptake inhibition not patentably distinct from earlier claim to administration of fluoxetine hydrochloride).
983. *In re* Braat, 937 F.2d 589, 592 (Fed. Cir. 1991); *see also In re* Longi, 759 F.2d 887, 896 (Fed. Cir. 1985) ("[A] double patenting of the obviousness

analysis, one may consider the prior art in determining whether the claims in the second patent are obvious in view of the subject matter of the claims in the first patent.[984] The courts use a two-part process to determine the existence of double patenting.[985]

There is no requirement in non-statutory double patenting that there be "conflicting" or "overlapping" claims.[986] These "are considerations more significant in a § 101 'same invention' double patenting analysis."[987]

[B] Genus and Species

The "case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim."[988] There are numerous examples of courts finding genus claims anticipated by double patenting references claiming a species within that genus.[989] On the other hand, "[i]t is well-settled

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type rejection is 'analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. § 103,' except that the patent principally underlying the double patenting rejection is not considered prior art."); Affymetrix, Inc. v. PE Corp., 2002 WL 31875401, at *1 n.3 (S.D.N.Y. Dec. 24, 2002) ("The same type of analysis is used for an obviousness-type double patenting inquiry as for a Section 103 obviousness inquiry, except that the scope of a double patenting inquiry is limited to only the claims of the first patent, rather than the entirety of its disclosure. *See* 3 [DONALD S.] CHISUM, [CHISUM ON PATENTS] § 9.03[3][c] [(2002)]."); M.P.E.P. § 804 ("[a] double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103 except that the patent principally underlying the double patenting rejection is not considered prior art").

984. Carman Indus., Inc. v. Wahl, 724 F.2d 932 (Fed. Cir. 1983); *In re* Purdy, 393 F.2d 1010, 1012 (C.C.P.A. 1967) ("It is well established that in a double patenting situation, prior art may be considered in order to determine whether the application claims a mere obvious variation of the patented invention but, . . . the ground of rejection for double patenting should be kept separate from Section 103 as a ground of rejection."); *Longi*, 759 F.2d at 896 (considering prior art in double patenting determination).

985. *See infra* section 5:8.5[C].

986. *Longi*, 759 F.2d at 894.

987. *Id*.

988. *Eli Lilly*, 251 F.3d at 971. The phrase "not patentably distinct from" means that the later patent is invalid for double patenting.

989. Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1374 (Fed. Cir. 2005) ("Sunburn is a species of skin damage"; therefore "the earlier species renders the later genus claims invalid under non-statutory double patenting"); *Eli Lilly*, 251 F.3d at 970–72 (method of treating anxiety in a human by administration of fluoxetine or salt invalidates later claim to a method of blocking serotonin uptake in animals by administration of fluoxetine hydrochloride); *Berg*, 140 F.3d at 1437 (affirming double patenting rejection where earlier patent claimed a species falling within the

that a narrow species can be non-obvious [under the obviousness-type double patenting doctrine] and patent eligible despite a patent on its genus."[990] Nevertheless, double patenting does not depend on determining whether there is a species/genus relationship between the claims of the patent or application and reference patent.[991]

[C] The Test for Double Patenting

[C][1] Two-Part Test

Determining whether double patenting exists is a two-step process:

- First, the claims in the earlier expiring patent and the later expiring patent must be construed,[992] and the court must determine what differences, if any, exist between the claims in each patent.[993]
- Second, the court determines whether the differences in subject matter between the two claims render the claims "patentably distinct." The term "patentably distinct" has been frequently used in the case law but for many years had not been clearly defined.[994] The Federal Circuit "clarified" that the "patentably distinct" determination "looks to the law of

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broader genus covered by the rejected application claims); *Goodman*, 11 F.3d at 1048–49, 1053 (finding double patenting where the earlier issued patent claimed a method of producing recombinant proteins in "dicotyledonas plant cells," a narrower species or sub-genus of the same method of producing recombinant proteins in "plant cells" as claimed in the later application).

990. *AbbVie*, 764 F.3d at 1379. Application of Sarett, 327 F.2d 1005, 1016 (C.C.P.A. 1964) (reversing obviousness-type double patenting rejections because specific claims may be patentably distinct over generic claims).

991. *In re* Metoprolol Succinate Patent Litig., 494 F.3d 1011, 1017 (Fed. Cir. 2007) ("disputes" over a possible genus/species relationship "in a double patenting context are irrelevant").

992. Gilead Scis., Inc. v. Natco Pharma Ltd., 753 F.3d 1208, 1217 (Fed. Cir. 2014) ("We therefore hold that an earlier-expiring patent can qualify as an obviousness-type double patenting reference for a later-expiring patent under the circumstances here."); *AbbVie*, 764 F.3d at 1374; *cf.* Amgen Inc. v. F. Hoffmann-La Roche Ltd., 580 F.3d 1340, 1354 n.5 (Fed. Cir. 2009) ("We note that, because the '933 patent issued on August 20, 1996, which was before the issuance of the '698 patent on April 8, 1997, the '698 patent presumably cannot be used as an obviousness-type double patenting reference against the '933 patent on remand.").

993. *Eli Lilly*, 251 F.3d at 968.

994. Judge Rich, reversing a Patent Office finding of double patenting, remarked in evident frustration: "[W]e cannot agree with the Patent Office that they are not 'patentably distinct'—whatever that means." *In re* Aldrich, 398 F.2d 855, 862 (C.C.P.A. 1968).

obviousness generally."[995] Nevertheless, "when analyzing obviousness-type double patenting in cases involving claimed chemical compounds, the issue is not whether a skilled artisan would have selected the earlier compound as a lead compound. That is so because the analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, lead compound or not."[996] "A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obviousness-type double patenting."[997]

[C][2] Limited Use of the Specification

Whether or not the subject matter claimed in a later patent is patentably distinct is measured by what was claimed in the prior patent, not by the disclosure of prior patent's specification[998] or even by the disclosure of its prior claims.[999] However, the specification of the prior patent can be used to interpret the claims.[1000] The Federal Circuit

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995. *AbbVie*, 764 F.3d at 1378; *Amgen*, 580 F.3d at 1361; Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 689 F.3d 1368, 1377 (Fed. Cir. 2012).

996. Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1297 (Fed. Cir. 2012).

997. *Eli Lilly*, 251 F.3d at 968.

998. *See* Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 943 (Fed. Cir. 1992) ("It is the claims, not the specification, that define an invention. And it is the claims that are compared when assessing double patenting."). *See also* Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 98 F. Supp. 2d 362, 392 (S.D.N.Y. 2000) ("a rejection on grounds of double patenting relies upon an analysis similar to the obviousness analysis . . . the key difference is that a double patenting rejection looks solely to the claims of the prior art reference, and not to the entire disclosure of the prior art reference, as the basis for comparison"); *In re* Kaplan, 789 F.2d 1574 (Fed. Cir. 1986) (reversing board for improperly considering specification's disclosure of the best mode in support of a double patenting rejection).

999. Gen. Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1280 (Fed. Cir. 1992) ("[I]t is important to bear in mind that comparison can be made only with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference."); *see also In re* Sarett, 327 F.2d 1005, 1013 (C.C.P.A. 1964) ("We are not here concerned with what one skilled in the art would be aware from reading the claims but with what inventions the claims define.").

1000. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1385 (Fed. Cir. 2003) ("The challenge of a double patenting analysis . . . is to understand the scope of the compared claims. . . . [T]his court examines the specifications of both patents to ascertain any overlap in the claim scope for the double patenting comparison."); *In re* Basell Poliolefine Italia S.p.A., 547 F.3d 1371, 1379 (Fed. Cir. 2008) ("the Board did not

has repeatedly considered the specification while construing claims for purposes of evaluating double patenting even where there did not appear to be a specific claim term that required construction.[1001] It refused to consider the prior patent's compound claim "in a vacuum, as a simple compound, without considering the compound's disclosed utility."[1002]

[C][3] Use of Prior Art

In a double patenting analysis, prior art may be considered in determining whether the later claimed subject matter is obvious in view of the prior patent claim.[1003] "This part of the obviousness-type double patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103, except that the [reference] patent is not considered prior art."[1004] An obviousness-type double patenting analysis must

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err in referring to the specification of the '987 patent when it determined whether the claims were patentably distinct from the claims of the '687 patent.").

1001. Pfizer, Inc. v. Teva Pharm. USA, Inc., 518 F.3d 1353, 1363 n.8 (Fed. Cir. 2008) (holding that the court may "rely on the teachings of the specification or claims in the [reference] patent" in finding double patenting); Sun Pharm. Indus., Ltd. v. Eli Lilly & Co., 611 F.3d 1381, 1389 (Fed. Cir. 2010) ("where necessary in the obviousness-type double patenting analysis, consulting the specification of the issued patent . . . is consistent with the policy behind double patenting"); *Geneva Pharm.*, 349 F.3d at 1385 (considering reference patent specification's disclosure that the "single" utility of the claimed compound was "administration to patients to combat bacteria that produce—lactamase" when invalidating later claim to method of treating subject in need of—lactamase by administration of the same compound); Research Corp. Tech., Inc. v. Gensia Labs. Inc., 10 F. App'x 856, 864 (Fed. Cir. 2001) (unpublished) ("Here, where Bristol asserts that the saline in the composition claims has a unique significance—maintenance of therapeutic properties after storage—that is lacking in the method claims, and the significance of saline is not evident from the claims themselves, we may look to the specification to construe how saline is used in each claim. The patents share the same written description, which indicates that saline was used to stabilize the solutions for the brief period of time between preparation and administration in the inventions of the various patents.").

1002. *Geneva Pharm.*, 349 F.3d at 1385 ("Standing alone, that [compound] claim does not adequately disclose the patentable bounds of the invention. Therefore, this court examines the specifications of both patents to ascertain any overlap in the claim scope for the double patenting comparison.").

1003. Carman Indus., Inc. v. Wahl, 724 F.2d 932 (Fed. Cir. 1983); *In re* Purdy, 393 F.2d 1010, 1012 (C.C.P.A. 1967); *In re* Longi, 759 F.2d 887, 896 (Fed. Cir. 1985).

1004. *Amgen*, 580 F.3d at 1361 (applying reasonable expectation of success analysis to double-patenting reference).

take into account the scope and content of the pertinent prior art, level of skill in the art and what would have been obvious to a person of ordinary skill.[1005] There is also some authority for permitting consideration of unexpected results in an obviousness-type double patenting analysis.[1006]

[C][4] Use of Post-Filing-Date Art

The Federal Circuit ruled that "later developments in the art may inform the 'patentably distinct' determination for double patenting . . . but only to the extent that the subsequent developments predate the secondary application that triggers a double patenting rejection."[1007] "[P]roduct and process claims are patentably distinct if multiple

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1005. *Amgen*, 580 F.3d at 1358–63 (finding no double patenting where claim required host cell to express EPO polypeptide and reference claim covered only the purified and isolated DNA sequence encoding EPO, because "an ordinarily skilled artisan would not have reasonably expected success in producing recombinant, in vivo biologically active EP in CHO cells"); Studiengesellschaft Kohle mbH v. N. Petrochemical Co., 784 F.2d 351, 355 (Fed. Cir. 1986) (rejecting obviousness-type double patenting defense because infringer "offered no evidence of the scope and content of the pertinent art, other than the '115 patent, the level of skill in the art, or what would have been obvious to a person skilled in the art").

1006. *In re* Emert, 124 F.3d 1458, 1462 (Fed. Cir. 1997) (affirming finding of prima facie obviousness-type double patenting and stating that "[a]bsent some indication of unexpected properties, the combination [A and B] rendered B[1] obvious"); *Longi*, 759 F.2d at 896–97 (considering on its merits applicant's attempt to rebut "a prima facie case of obviousness-type double patenting" by relying on evidence of "unexpected results"); *but see Geneva Pharm.*, 349 F.3d at 1378 n.1 ("Obviousness requires inquiry into a motivation to modify the prior art; nonstatutory double patenting does not. . . . Obviousness requires inquiry into objective criteria suggesting non-obviousness; nonstatutory double patenting does not."); Regents of Univ. of Cal. v. Monsanto Co., 2005 WL 1513093, at *2 (N.D. Cal. June 27, 2005) (non-precedential) ("In assessing obviousness, only the claims are to be compared, and the court neither examines motivation to combine prior art references nor objective standards of non-obviousness as with obviousness inquiries under 35 U.S.C. § 103."); *but see* Eli Lilly & Co v. Teva Parenteral Meds., Inc., 689 F.3d 1368, 1381 (Fed. Cir. 2012) ("The district court's categorical repudiation of Lilly's evidence [of secondary considerations] was therefore erroneous. When offered, such evidence should be considered; a fact-finder 'must withhold judgment on an obviousness challenge until it has considered all relevant evidence, including that relating to the objective considerations.' In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1079 (Fed.Cir.2012).").

1007. Takeda Pharm. Co. v. Doll, 561 F.3d 1372, 1373 (Fed. Cir. 2009).

processes for creating a product exist at the time of the invention,"[1008] and, therefore, evidence of an alternative process for making the product is relevant to evaluating double patenting—so long as the evidence exists prior to the filing of the later application.[1009]

Section 120 states that applications properly claiming priority to earlier applications "cannot be invalided based on art arising after" their priority date.[1010] Therefore, *Takeda* cannot be applied to expand the scope of double-patenting references that can be asserted to include art subsequent to the priority date of the original application.[1011]

[C][5] Claim-by-Claim Analysis

The analysis of claim validity under double patenting, like any other invalidity analysis, is made independently on each claim of the challenged patent.[1012]

[D] Who Is the Same Person for Purposes of Double Patenting?

Double patenting applies to commonly owned patent applications, even if the inventions originated with different inventive entities.[1013] A party must be established as the assignee of the patent or application, pursuant to 37 C.F.R. § 3.71(b), to be recognized as an owner for purposes of taking action in the Patent Office, including filing a

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1008. *In re* Cady, 77 F.2d 106, 109 (C.C.P.A. 1935) ("double patenting is not sustainable when the product can be fabricated by processes other than that secured by the issued process patent").

1009. *Takeda*, 561 F.3d 1372, 1374–76 ("secondary application covering the process for making the cephem compounds claimed in the" earlier reference patents may not be subject to double patenting if there is sufficient evidence of an alternative process for making the cephem compounds prior to the filing of the secondary application).

1010. Amgen Inc. v. F. Hoffmann-La Roche Ltd., 580 F.3d 1340, 1357 (Fed. Cir. 2009).

1011. *Id*. ("Because of § 120, we read *Takeda* to stand for the limited proposition that an applicant can only rely on subsequent developments in the art up to the filing date of the 'secondary application' in order to show that alternative processes to make the product render the product and the process for making that product patentably distinct.").

1012. Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 942 (Fed. Cir. 1992) ("We conclude that the double patenting challenge must be evaluated, like any other ground of invalidity, against individual claims.").

1013. Eli Lilly & Co. v. Barr Labs., 251 F.3d 955, 967 (Fed. Cir. 2001) ("The judicially-created doctrine of obviousness-type double patenting cements that legislative limitation by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a *commonly owned* earlier patent.") (emphasis added); *Longi*, 759 F.2d at 893.

terminal disclaimer.[1014] If there are multiple owners, all owners must file a request for a terminal disclaimer.[1015]

[E] Curing Double Patenting by Filing Terminal Disclaimers

[E][1] Effect of Filing a Terminal Disclaimer

Section 253 permits the filing of a terminal disclaimer, allowing the patentee to disclaim "any terminal part of the term . . . of the patent."[1016] By adding section 253 in 1952, "Congress slightly altered the effect of the bar on double patenting."[1017] Patentees can in some circumstances overcome nonstatutory double patenting by filing a terminal disclaimer pursuant to 35 U.S.C. § 253 and 37 C.F.R. § 1.321. The applicant or patentee disclaims any term of the later application or patent that would extend beyond the expiration date of the earlier issued patent.[1018] A terminal disclaimer should be ineffective if the patent that formed the basis for double patenting has already expired, in which case the later patent claims would be invalid.[1019] After filing a proper terminal disclaimer, both patents will expire at the same time thereby, satisfying the policy that the public should be free to use the invention or any obvious modifications of the invention after patent expiration.[1020] "[A] terminal disclaimer should be a permissible means to overcome the prohibition on double patenting when it aligns the expiration dates of an inventor's several patents that claim mere obvious variations of the same invention to create a single term of limited exclusivity."[1021] The Federal Circuit upheld the efficacy of a petition to the PTO to clarify a terminal disclaimer that became

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1014. M.P.E.P. §§ 324, 300–17 (2001).
1015. *See* M.P.E.P. §§ 301, 300–02 (2001) ("All parties having any portion of the ownership in the patent property must act together as a composite entity in patent matters before the office"); M.P.E.P. §§ 324, 300–18 (2001) ("Where no inventor retains an ownership interest, the combination of all partial assignees is needed to conduct the prosecution of an application.").
1016. 35 U.S.C. § 253.
1017. *Gilead*, 753 F.3d at 1213.
1018. *See Ortho Pharm.*, 959 F.2d at 936.
1019. *See Eli Lilly*, 251 F.3d at 968 n.5; Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc., 592 F.3d 1340, 1349–50 (Fed. Cir. 2010).
1020. *In re* Robeson, 331 F.2d 610, 614 (C.C.P.A. 1964); *see also Longi*, 759 F.2d at 894.
1021. *Gilead*, 753 F.3d at 1213; *In re* Braithwaite, 379 F.2d 594, 601 (C.C.P.A. 1967) (a terminal disclaimer "causes [such] . . . patents to expire together, a situation . . . which is tantamount for all practical purposes to having all the claims in one patent").

ambiguous after Congress passed the Uruguay Round Agreements Act that changed the expiration date of many U.S. patents because the patentee "linked its [original] terminal disclaimer to the expiration date of the" earlier patent whose expiration date was extended by the treaty.[1022]

Infringers have made numerous arguments seeking to undermine patents based on the fact that a terminal disclaimer has been filed. These arguments have usually been rejected:

- The filing of a terminal disclosure, the Federal Circuit has ruled, is not an admission of double patenting and raises no "estoppel on the merits of the rejection."[1023]
- The Federal Circuit rejected the argument "that a terminal disclaimer can bind two related patents together so that inequitable conduct in procuring a later prosecuted patent will automatically infect an earlier issued patent."[1024]
- According to one district court, "there is no authority that would preclude the recovery of damages for any period in the past when there was no actual common ownership once a terminal disclaimer has been filed."[1025]

[E][2] Need for Common Ownership of Patent and Its Reference Patent

If a terminal disclaimer is required to overcome non-statutory double patenting, the disclaimer must, at a minimum, provide that it shall be enforceable only during the period during which the "patent is commonly owned with the application or patent which formed the

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1022. Bayer AG v. Carlsbad Tech., Inc., 298 F.3d 1377, 1382 (Fed. Cir. 2002) (disclaimer reciting "the earlier of the expiration dates of . . ." and that the patent "shall be enforceable only for and during such period that legal title" to the disclaimed patent and earlier patents "shall be the same" demonstrated interdependence of the patents sufficient to permit revision of disclaimer date).

1023. Quad Envtl. Tech. v. Union Sanitary Dist., 946 F.2d 870, 874–75 (Fed. Cir. 1991) ("the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection. It is improper to convert this simple expedient of 'obviation' into an admission or acquiescence or estoppel on the merits").

1024. Pharmacia Corp. v. Par Pharm., Inc., 417 F.3d 1369, 1374 (Fed. Cir. 2005).

1025. Jensen v. Optical Radiation, 1990 U.S. Dist. LEXIS 20959, at *96 (C.D. Cal. Mar. 16, 1990); *see also* 35 U.S.C. § 253 (after filing a disclaimer "it shall thereafter be considered as part of the original patent").

basis for the rejection."[1026] District courts are divided as to whether failure to maintain common ownership of a patent subject to a terminal disclaimer and the disclaimed patent can be cured.[1027]

[E][3] The Timing of a Terminal Disclaimer Filing

"Terminal disclaimers can be used to cure nonstatutory double patenting problems that arise both before the PTO and/or after issuance of the patent."[1028] "Section 253 does not state a time period for the filing of a terminal disclaimer and the case law has not provided a clear answer to this question."[1029] The Federal Circuit has stated its view that the Patent Act permits filing a terminal disclaimer that disclaims any term extending beyond another patent "after issuance of the challenged patent or during litigation, even after a finding that the challenged patent is invalid for obviousness-type double patenting."[1030] Despite the Federal Circuit's statements that a terminal

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1026. 37 C.F.R. § 1.321(c)(3); Merck & Co., Inc. v. Int'l Trade Comm'n, 774 F.2d 483, 486 (Fed. Cir. 1985) ("The provision in the terminal disclaimer that the '284 patent would 'expire immediately' if it ceased to be commonly owned with the other four patents conformed to the requirements of the Patent and Trademark Office that were in effect when the disclaimer was filed. . . . An amendment to 37 C.F.R. § 1.321 (1971) . . . changed this requirement to provide that disclaimers need state only that the patent be unenforceable during the period it is not commonly owned with the other patents recited in the disclaimer."); *see also Eli Lilly*, 251 F.3d at 968 n.5 (terminal disclaimer cannot cure non-statutory double patenting when reference patent has been dedicated to the public); *In re* Lonardo, 119 F.3d 960, 965 (Fed. Cir. 1997) (terminal disclaimer cannot cure non-statutory double patenting when reference patent has expired); *In re* Van Ornum, 686 F.2d 937, 944, 948 (C.C.P.A. 1982).

1027. *Compare* Midwest Athletics & Sports All. LLC v. Ricoh USA, Inc., No. 2:2019-cv-00514 (E.D. Pa. July 25, 2019) ("Because MASA did not own the Terminal Disclaimer Patents until after it filed its complaint, MASA has no standing to enforce the Pentachrome Patents in this action."), *with* Fall Line Patents, LLC v. Zoe's Kitchen, Inc., No. 6:18-cv-00407-RWS (E.D. Tex. July 26, 2019) ("[E]ven if the '748 Patent was unenforceable at the time of filing due to lack of common ownership with the '816 Patent, Plaintiff still held enforceable title to the '748 Patent and had standing to bring suit.").

1028. Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc., 2008 WL 2553237, at *7 (D. Del. June 26, 2008), *rev'd on other grounds*, 592 F.3d 1340 (Fed. Cir. 2010).

1029. *Id*.

1030. *See* Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc., 592 F.3d 1340, 1347 (Fed. Cir. 2010); Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1375 (Fed. Cir. 2005) ("the Patent Act and PTO rules support the filing of a terminal disclaimer even after issuance of the second patent"); *In re* Metoprolol Succinate Patent Litig., 2006 WL 120343, at *12 (E.D. Mo. Jan. 17, 2006) ("Based on the language of the terminal disclaimer

disclaimer may be filed after a finding of invalidity for obviousness-type double patenting, it has had no occasion to rule on the issue.[1031] Several district courts have found that a terminal disclaimer may be filed at various stages in a litigation.[1032]

The terminal disclaimer, however, must be filed before expiration of the other patent.[1033] The Federal Circuit rejected the argument that a terminal disclaimer could be filed after the original expiration date of the reference patent, so long as it was filed before the expiration of any term extension under section 156, because "the rights of a patentee during a term extension are limited in ways that do not normally apply to granted patents."[1034]

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statute and the opinion in Perricone, I find that Astra's terminal disclaimers [filed years after the patents issued] of the '161 patent and the '154 patent effectively avoids a finding of double patenting." Rejecting argument that such terminal disclaimer should be found ineffective as against public policy because listing the patent and its expiration date "in the Orange Book deters others from competing with the patent holder on those patents."), *aff'd in part and vacated in part (both on other grounds)*, 494 F.3d 1011 (Fed. Cir. 2007) (considering appeal on unenforceability even though affirming on double patenting invalidity because "the parties dispute whether a patentee may reinstate the validity of a patent by filing a terminal disclaimer during litigation"; "This court has not decided the issue.").

1031. *Boehringer*, 592 F.3d 1340; *Perricone*, 432 F.3d at 1375; *see also Metoprolol*, 494 F.3d at 1020 n.4 ("[t]his court has not decided the issue" of "whether a patentee may reinstate the validity of a patent by filing a terminal disclaimer during litigation").

1032. *Jensen*, 1990 U.S. Dist. LEXIS 20959, at *96; Syngenta Seeds v. Monsanto, 2004 U.S. Dist. LEXIS 26910, at *9–10 (D. Del. Nov. 19, 2004); *Bayer AG*, 798 F. Supp. at 197–98 (upholding validity where patentee filed terminal disclaimer after receiving the complaint); Bott v. Four Star Corp., 675 F. Supp. 1069, 1074 (E.D. Mich. 1987) (terminal disclaimer properly filed in response to double patenting summary judgment motion), *aff'd*, 856 F.2d 202 (Fed. Cir. 1988); Technicon Instruments Corp. v. Coleman Instruments, Inc., 255 F. Supp. 630, 637, 642 (N.D. Ill. 1966) (upholding validity of patent where terminal disclaimer filed after trial began); *but see* CMI Corp. v. Lakeland Constr. Co., 184 U.S.P.Q. (BNA) 721, 735 (N.D. Ill. 1975) ("The filing of a terminal disclaimer, three days before trial, does not obviate the vices of double patenting.").

1033. *Boehringer*, 592 F.3d at 1348 (holding "that a terminal disclaimer filed after the expiration of the earlier patent over which claims have been found obvious cannot cure obviousness-type double patenting"); *see also In re* Lonardo, 119 F.3d 960, 965 (Fed. Cir. 1997) ("a terminal disclaimer may overcome" obviousness-type double patenting "assuming that the first patent has not expired").

1034. *Boehringer*, 592 F.3d at 1349.

The Federal Circuit has not had occasion yet to apply to patent office practice the reasoning expressed in its more recent decisions addressing the timing of filing a terminal disclaimer. Prior decisions by the Court of Customs and Patent Appeals shed some light on the issue. The Patent Office Board of Appeals should consider a terminal disclaimer entered by the examiner after a final office action[1035] but might not consider the disclaimer filed after a decision by the board.[1036] A patent owner can overcome a double patenting rejection made in a reexamination by filing a terminal disclaimer.[1037]

[E][4] Effect of a Terminal Disclaimer on a Patent Term Extension

Unlike patent term adjustments (see next subsection), the statutory scheme for patent term extensions does not state that terminal disclaimers cut off the term of extensions.[1038] "While § 156 does not expressly reference terminal disclaimers, it does enumerate other requirements that must be met to obtain a patent term extension. It

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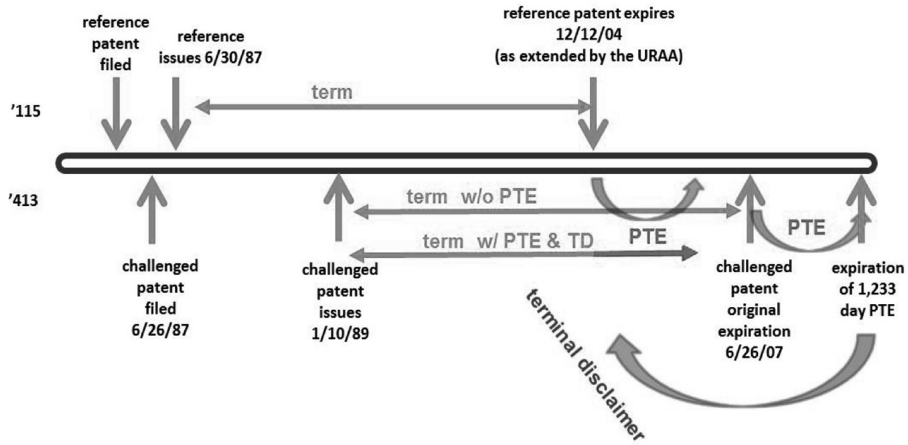
1035. *In re* Jentoft, 392 F.2d 633, 638 (C.C.P.A. 1968) ("[f]aced with an obviousness-type double patenting rejection which was made final, appellant filed a terminal disclaimer" and then the Board considered the terminal disclaimer in making its decision).

1036. *In re* Purdy, 393 F.2d 1010, 1011 (C.C.P.A. 1967) ("Subsequent to the board's decision the appellant filed a terminal disclaimer to avoid the rejection of his application on double patenting. Upon reconsideration, the board refused to consider the disclaimer, pointing out that no good cause was shown why the terminal disclaimer was not filed earlier."); *In re* Thorington, 418 F.2d 528, 533–34 (C.C.P.A. 1969); *In re* Heyl, 379 F.2d 1018, 1012 (C.C.P.A. 1967); *cf. Perricone*, 432 F.3d at 1375 (The existence of "timing requirements" for filing terminal disclaimers during prosecution of patent applications "does not dictate a prohibition on post-issuance terminal disclaimers"); *In re* Doyle, 293 F.3d 1355, 1358 n.4 (Fed. Cir. 2002) (noting that applicant "agreed to file a terminal disclaimer to cure the double patenting rejection in the event he prevails [in the appeal] on the other ground for rejection").

1037. M.P.E.P. § 2258; *Lonardo*, 119 F.3d at 965.

1038. The statute requires issuance of a patent term extension when its requirements are satisfied without any reference to terminal disclaimers: "The term of a patent . . . **shall** be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b)" under certain conditions, including that (1) the term of the patent has not expired, (2) the term of the patent has never been extended under that section before, (3) the product is subject to a regulatory review period before marketing, and (4) it claims a drug product that has not been marketed before (and no other patent on the product has been granted PTE). 35 U.S.C. § 156(a) (emphasis added); *see also* 37 C.F.R. §§ 1.710, 1.750, 1.775 (implementing regulations).

states that, if those requirements are met, the patent term 'shall be extended.' *See* 35 U.S.C. § 156(a). Use of the word 'shall' in a statute generally denotes the imperative."[1039] Accordingly, the Federal Circuit held that a patent subject to a terminal disclaimer filed during prosecution to overcome a double patenting rejection could subsequently be extended pursuant to 35 U.S.C. § 156 to compensate for FDA delay.[1040] Below is a timeline, based on the facts of *Merck*, depicting the timing of the reference patent, the challenged patent, the patent term extension (PTE) and terminal disclaimer (TD):



The Federal Circuit has explained, however, that if a patent would otherwise be invalid for obviousness-type double patenting based on the normal expiration date "without a § 156 extension," it can still be invalidated despite the existence of additional PTE.[1041] "However, if a patent, under its pre-PTE expiration date, is valid under all other provisions of law, then it is entitled to the full term of its PTE."[1042]

The Federal Circuit refused to extend this precedent to permit filing a terminal disclaimer on a patent whose term was extended under section 156 over a reference patent that had already expired because "the rights of a patentee during a term extension are limited in ways that do not normally apply to granted patents."[1043] Below is a

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1039. Merck & Co. v. Hi-Tech Pharmacal Co., 482 F.3d 1317, 1321–22, 1324 (Fed. Cir. 2007).

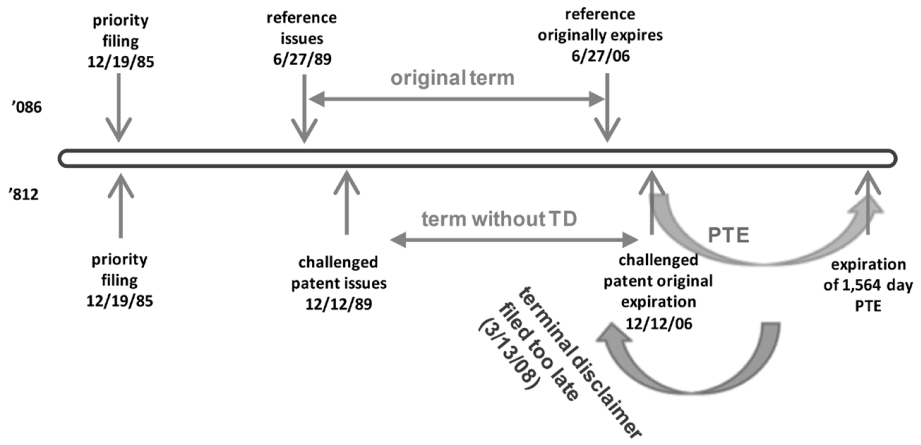
1040. *Id.*; *see also* Novartis AG v. Ezra Ventures LLC, 909 F.3d 1367, 1374 (Fed. Cir. 2018); King Pharm., Inc. v. Teva Pharm., 409 F. Supp. 2d 609 (D.N.J. 2006).

1041. *Novartis AG*, 909 F.3d at 1374.

1042. *Id.*

1043. *Boehringer*, 592 F.3d at 1349–50 (distinguishing *Merck v. Hi-Tech* because "the terminal disclaimer in *Merck* occurred will before the expiration of the patent over which obviousness-type double patenting was asserted").

timeline, based on the facts of *Boehringer*, depicting the timing of the reference patent, the challenged patent, the patent term extension (PTE) and terminal disclaimer (TD):



[E][5] Effect of a Terminal Disclaimer on a Patent Term Adjustment

A terminal disclaimer cuts off any patent term adjustment subsequent to the effective date of the disclaimer.[1044]

[E][6] Effect of a Disclaimer of Claims

In addition to filing a terminal disclaimer, a patentee may also file a disclaimer of one or more claims effective upon filing.[1045] The Federal Circuit addressed the effect of filing a disclaimer of all claims in a footnote:

> **[1]** A patent owner **cannot avoid double patenting by disclaiming the earlier patent**. **[2]** Further, because Lilly disclaimed the '213 patent, it cannot now terminally disclaim the '549 patent to expire at the time the '213 patent would have expired had it not been disclaimed. That is, the fact that the '213 patent has been disclaimed is of no help to Lilly, as double patenting precludes claim 7 of the '549 patent from **extending beyond the**

1044. *See* 35 U.S.C. § 154(b)(2)(B) ("No patent the term of which has been disclaimed beyond a specified date may be adjusted under this section beyond the expiration date specified in the disclaimer."); 37 C.F.R. § 1.703(g) (same); MPEP §§ 2720, 2751 (same).

1045. 35 U.S.C. § 253(a) ("A patentee, whether of the whole or any sectional interest therein, may, on payment of the fee required by law, make disclaimer of any complete claim, stating therein the extent of his interest in such patent.").

> **termination date of the '213 patent**, whether that termination date is at the end of its normal term or, as in this case, is the **date it is terminated via disclaimer**.[1046]

The first proposition [1] was not dicta because it was required for the court to find obviousness-type double patenting.[1047] The second proposition [2], however, was dicta.[1048]

[F] The Two-Way Double Patenting Test

[F][1] Requirements to Qualify for the Two-Way Test

The test described above, referred to as the "one-way" test, is applied in most cases of double patenting. In certain circumstances, however, obviousness-type double patenting can be overcome by means of a "two-way" test, under which nonobviousness in either direction—that is, of the earlier-filed application over the later, or of the later-filed application over the earlier—negates the double patenting. A patentee or applicant may not, however, obtain the benefits of this more lenient test without satisfying two threshold requirements. The two-way test applies "when the applicant could not have filed the claims in a single application *and* there is administrative delay."[1049] "[W]here, through no fault of the applicant, the claims in a later filed application issue first, an obvious-type double patenting rejection is improper, in the absence of a two-way obviousness determination, because the applicant does not have complete control over the rate

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1046. Eli Lilly and Co. v. Barr Labs., Inc., 251 F.3d 955, 967 n.5 (Fed. Cir. 2001).

1047. The court noted that "during the course of this litigation, Lilly disclaimed those ['213 and '356] patents" and found the patent invalid for obviousness-type double patenting over the '213. *Id*. at 959, 972 ("Therefore, we reverse the district court's denial of the portion of Barr's motion for summary judgment contending that claim 7 of the '549 patent is invalid for obviousness-type double patenting over claim 1 of the '213 patent.").

1048. Without identifying which portion of footnote 5 the Board was referring to, it found footnote 5 was dicta and, in any event, inconsistent with prior dicta. Minoru Tsuruta v. Paul Nardella, 60 U.S.P.Q.2d 1827, 1830 (B.P.A.I. 2001).

1049. M.P.E.P. § 804, ¶ II.B.1(b) (citing *In re* Berg, 140 F.3d 1428, 1428 (Fed. Cir. 1998) ("The two-way exception can only apply when the applicant could not avoid separate filings, and even then, only if the PTO controlled the rates of prosecution to cause the later field species claims to issue before the claims for a genus in an earlier application . . . . The two-way test may be appropriate . . . in the unusual circumstance that the PTO is solely responsible for the delay in causing the second-filed application to issue prior to the first.")).

of progress of a patent application through the Office."[1050] "Unless the record clearly shows" that the requirements for applying the two-way test are satisfied, an examiner during prosecution may use the one-way test "and shift the burden to the applicant to show why" the two-way test should be applied.[1051] Several courts have applied the two-way test in one form or another.[1052] Other courts have refused.[1053]

[F][2] Satisfying the Two-Way Test

Section 804 of the MPEP states that the two-way test requires application of the *Graham* obviousness analysis twice, "once with the application claims as the claims in issue, and once with the patent claims as the claims in issue." Under the two-way test, there is no double patenting unless obviousness is found under both analyses.

[G] Overlapping Claims

It is commonplace for a generic claim in one patent to "read on" the narrower claim of another patent. In such a situation, the narrower claim is "dominated" by the broader claim because the narrower claim cannot be practiced without infringing the generic claim.[1054] The fact that a "first patent reads on a device built or process practiced according to the second patent disclosure . . . is not, per se, double patenting."[1055]

1050. M.P.E.P. § 804, ¶ II.B.1(b) (citing *In re* Braat, 937 F.2d 589, 592 (Fed. Cir. 1991)).

1051. M.P.E.P. § 804, ¶ II.B.1(b).

1052. *Braat*, 937 F.2d at 589 (holding that patent on a combination invention did not raise a double patenting issue for an earlier filed but still pending application claiming a subcombination of that invention); *In re* Borah, 354 F.2d 1009 (C.C.P.A. 1966); *In re* Stanley, 214 F.2d 151 (C.C.P.A. 1954); *In re* Calvert, 97 F.2d 638 (C.C.P.A 1938).

1053. *See In re* Goodman, 11 F.3d 1046 (Fed. Cir. 1993) (applying one-way test holding generic claims properly rejected on obviousness-type double patenting grounds over previously issued species claims); *see also In re* Basell Poliolefine Italia S.p.A., 547 F.3d 1371, 1376 (Fed. Cir. 2008) (refusing to apply two-way test because patentees "did not present any claim resembling the claims at issue" until nine years after filing the priority application); Eli Lilly & Co. v. Barr Labs., 251 F.3d 955 (Fed. Cir. 2001); *Berg*, 140 F.3d at 1428; *In re* Emert, 124 F.3d 1458 (Fed. Cir. 1997); *In re* Janssen Biotech, Inc., 880 F.3d 1315 (Fed. Cir. 2018).

1054. *In re* Kaplan, 789 F.2d 1574, 1577–78 (Fed. Cir. 1986).

1055. *Id*. at 1577–78; *see also Sarrett*, 327 F.2d at 1014–15; M.P.E.P. § 804 ("Domination by itself, *i.e.*, in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection.").

§ 5:8.6 Safe Harbor Provision Involving Double Patenting

Section 121 of the Patent Act provides that if a patent application claims "two or more independent and distinct inventions," the PTO can require "the application to be restricted to one of the two inventions."[1056] The third sentence of section 121, referred to as the "safe harbor provision,"[1057] states:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent or the other application.

Although difficult to parse, as explained further in the sections to follow, the safe harbor provision gives the applicant who has been forced to abandon subject matter in one application due to a restriction requirement the chance to claim it in a subsequent application without risking double patenting. Congress enacted the safe harbor provision because, "[p]rior to the 1952 Patent Act, courts and patentees were aware of the unfairness that resulted when the Patent Office required restriction or division between claims in a patent application, thus requiring that a second patent application be carved out of the first, and then rejected the second application on the basis of the first."[1058]

1056. 35 U.S.C. § 121.

1057. *Boehringer*, 592 F.3d at 1350 ("The emphasized third sentence of § 121 is the so-called safe-harbor provision.").

1058. *Boehringer*, 592 F.3d at 1350 (quoting Studiengesellschaft Kohle mbH v. N. Petrochemical Co., 784 F.2d 351, 358 (Fed. Cir. 1986) (Newman, J., concurring)); *see also* Gerber Garment Tech., Inc. v. Lectra Sys., Inc., 916 F.2d 683, 688 (Fed. Cir. 1990) (approving of the description of the purpose of § 121 set forth in concurring opinion in *Studiengesellschaft*). Prior to the enactment of section 121 in 1952, courts were aware of the unfairness that resulted when the Patent Office required restriction between claims in a patent application and then rejected a subsequent application on the basis of the first. *See Ex parte* Davis, 1904 C.D. 85, 86 (Comm'r Pat. 1904) ("[If] the present claims cover the matter required to be divided out . . ., the applicant is certainly entitled to very liberal consideration of them. . . . The Examiner should resolve any and all doubts in the applicant's favor, since the applicant should not be deprived of adequate protection by contradictory rulings by the Office.").

[A] The Safe Harbor Requires a Prior Restriction by the Examiner

To obtain the benefit of the safe harbor, claims must have been entered in the original application corresponding to the later divided claims before the examiner issues the restriction requirement.[1059] "[T]he earlier application must contain formally entered claims that are restricted and removed, and . . . claims to the second invention [must] reappear in a separate divisional application after the restriction."[1060]

[B] The Safe Harbor Requires Consonance Between the Restriction Requirement and the Later Claims in the Later Application

Section 121 "only applies to a restriction requirement that is documented by the PTO in enough clarity and detail to show consonance" between the divided claims and the restriction requirement.[1061] Courts apply "a strict test for application of § 121" because of the "potential windfall such patent term extension could provide to a patentee."[1062]

"Consonance requires that the line of demarcation between the 'independent and distinct inventions' that prompted the restriction requirement be maintained."[1063] In other words, the divisional application must satisfy the following requirements:

- it must be "filed as a result of a restriction requirement";
- it "may not contain claims drawn to the invention set forth in the claims elected and prosecuted to patent in the parent application"; and
- it "must have claims drawn only to the 'other invention.'"[1064]

1059. *See* Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1379, 1382 (Fed. Cir. 2003); Bristol-Myers Squibb Co. v. Pharmachemie B.V., 361 F.3d 1343, 1348–49 (Fed. Cir. 2004).

1060. *Geneva Pharm.*, 349 F.3d at 1379 ("The text of § 121 does not suggest that the original application merely needs to provide some support for claims that are first entered formally in the later divisional application.").

1061. *Id*. at 1382 (interview summary lacks sufficient clarity to support section 121 protection).

1062. *Id*.

1063. Gerber Garment Tech., Inc. v. Lectra Sys., Inc., 916 F.2d 683, 688 (1990).

1064. *Id*. at 687.

If the consonance requirement is violated, the safe harbor provision in "[s]ection 121 does not apply."[1065] Several cases serve to illustrate this requirement.[1066]

A restriction requirement does not obligate the applicant to obtain all of the unelected subject matter in a single divisional in order to receive the protection of the safe harbor even if the examiner fails to impose a separate restriction requirement in each of the divisional applications.[1067] Furthermore, an applicant is not barred from seeking claims within a single divisional to inventions that the examiner determined to be separate and distinct when issuing the restriction requirement in the original application.[1068]

[C] The Safe Harbor Requires Filing of a Subsequent Application Denominated a "Divisional"

The safe harbor provision refers to a "divisional application." The Federal Circuit rejected the argument that a continuation-in-part or

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1065. *Id*. at 688.

1066. *See, e.g.*, *Geneva Pharm.*, 349 F.3d at 1382 (no section 121 protection because the original application "did not contain the 'method of use claims' that later appeared in the '720 patent" and because "the examiner did not issue a formal restriction requirement relating to the claims at issue in any document in the record"); Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc., 98 F.3d 1563, 1577 (Fed. Cir. 1996) (safe harbor unavailable because "the claims as amended during prosecution of the divisional application crossed the examiner's precise and unambiguous line of demarcation"); *Gerber*, 916 F.2d at 989 ("After numerous amendments, Gerber incorporated as a limitation the cutting blade of elected claim 23 of the [parent] patent and thereby rendered claims 15 and 16 non-consonant with those not elected in its response to the restriction requirement.").

1067. *Boehringer*, 592 F.3d at 1353 n.3 ("According to the dissent, because the restriction requirement did not explicitly require the applicant to carve out the child application (the '671 application) from the parent application (the '197 application) and the examiner did not impose a separate restriction in the parent application, the child application fails to satisfy the 'as a result of' requirement. Dissenting Op. at 9–10. We believe that this interpretation of the 'as a result of' requirement is too narrow. The child application was 'due to the administrative requirements imposed by the Patent.'").

1068. *Id*. ("None of the inventions claimed as between the '374 original patent, the '086 division, and the '812 division of the division, crosses the examiner's lines of demarcation of inventions identified in the restriction requirement. Thus, consonance is met and the '086 patent cannot be used as a reference against the '812 patent any more than if both patents had issued from direct divisions from the application in which the restriction requirement was made.").

even a continuation without any intervening divisional can obtain the benefit of the safe harbor—even if all of the other requirements are satisfied.[1069] Moreover, a patentee cannot regain the protection of the safe harbor by transforming a continuation-in-part into a divisional through a reissue[1070] or reexamination.[1071] The Federal Circuit also rejected the argument that a continuation patent not denominated as a divisional during prosecution qualifies as a divisional.[1072] However, in order to fall within the scope of the safe harbor, a patent must have been "issued on" a divisional application: "[f]or a challenged patent to receive safe harbor protections, the application must be properly designated as a divisional application, at the very latest, by the time the challenged patent issues on that application."[1073] A patent "cannot retroactively become, for the purposes of § 121, a 'patent issued on' a divisional application after it already issued on a CIP application."[1074]

On the other hand, if the applicant subsequently files "a divisional of a divisional of the application in which a restriction requirement was entered" prior to issuance of the first divisional, the applicant can obtain the benefits of the section 121 safe harbor if its other requirements are satisfied.[1075] This is true even if there is no copendency

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1069. Amgen Inc. v. F. Hoffman-La Roche Ltd., 580 F.3d 1340, 1353 (Fed. Cir. 2009) ("the § 121 safe harbor protects patents descending from divisional applications, but not from continuation applications exclusively"); Pfizer, Inc. v. Teva Pharm. USA, Inc., 518 F.3d 1353, 1362 (Fed. Cir. 2008) (holding that the safe harbor did not apply to a CIP derived from an earlier application); *In re* Janssen Biotech, Inc., 880 F.3d 1315, 1321 (Fed. Cir. 2018) ("[P]atents issued on CIP applications are not within the scope of § 121. Nor are patents issued on continuation applications.") (citations omitted).

1070. G.D. Searle LLC v. Lupin Pharm., Inc., 790 F.3d 1349, 1351 (Fed. Cir. 2015).

1071. *Janssen Biotech, Inc.*, 880 F.3d 1315.

1072. *Amgen*, 580 F.3d at 1354 (rejecting argument that because "continuation applications could have been filed as divisional applications, we should treat them as such for purposes of § 121" where the applicant "denominated [its] applications continuations [and] checked the continuation application box on the submitted form"); *cf.* Transco Prods. Inc. v. Performance Contracting, Inc., 38 F.3d 551, 556 (Fed. Cir. 1994) (terms such as "'continuation,' 'divisional,' and 'continuation-in-part' are merely terms of administrative convenience").

1073. *Janssen Biotech, Inc.*, 880 F.3d at 1323.

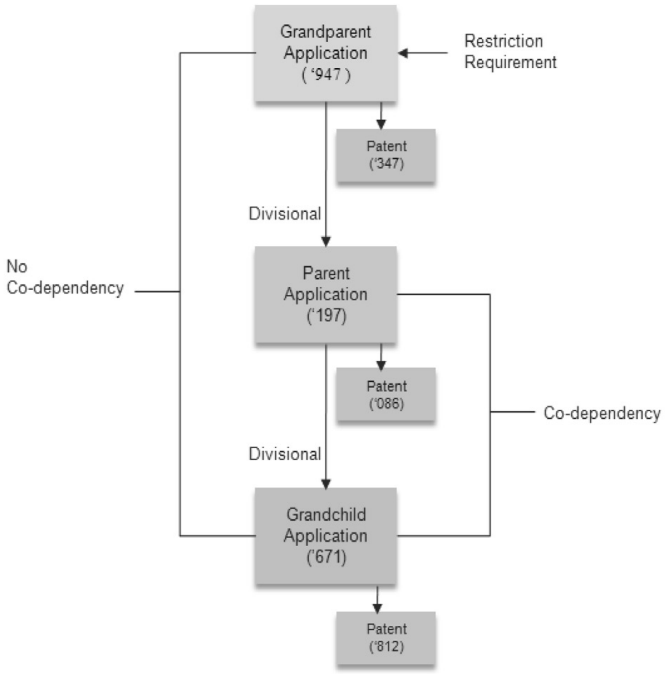
1074. *Id*.

1075. *Boehringer*, 592 F.3d at 1352 ("We see no reason why § 121 would not likewise extend to a divisional of a divisional."); *see also* Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1378 (Fed. Cir. 2003) (if the challenged patent and the reference patent "trace their lineage back

between the original application and the divisional of the divisional as depicted in Fig. 5-2.[1076]

Fig. 5-2

Safe Harbor May Apply in the Absence of Co-Pendency Between Restricted Application and Challenged Patent or Application



to a common parent which was subject to a restriction requirement, then § 121 intervenes to prevent [an obviousness-type] double patenting rejection."); Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569, 1580 (Fed. Cir. 1991) (applying safe-harbor to a continuation patent from a divisional); Amgen Inc. v. F. Hoffman-La Roche Ltd., 580 F.3d 1340, 1354 (Fed. Cir. 2009) ("[I]ntervening continuation applications do not render a patent ineligible for § 121 protection so long as they descended from a divisional application filed as a result of a restriction requirement.").

1076. *Boehringer*, 592 F.3d at 1340 (holding that the safe harbor applies despite the lack of copendency between the '947 parent, which was subject to a three-way restriction requirement, and the '671 grandchild filed as a divisional of a divisional of the parent).

§ 5:8.7 *Double Patenting Issues in Pharmaceutical Patents*[1077]

[A] Structural Obviousness-Type Double Patenting

Structural obviousness applies to obviousness-type double patenting where the reference patent discloses a structurally similar compound to the challenged claims, but its application differs in at least one important respect from traditional structural obviousness analysis. When considering structural obviousness in the context of obviousness-type double patenting, unlike traditional structural obviousness, there is no requirement that the reference compound qualify as a lead compound.[1078] The challenger, however, must still provide evidence that the prior art "supplied a motivation to modify the earlier claimed compound . . . . which in the chemical context requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success."[1079] In *Otsuka*, the challenger failed to provide evidence that the challenged aripiprazole compound was an obvious variant of the unsubstituted butoxy reference compound because nothing taught that the "chlorine substituents and the 2 and 3 positions of" aripiprazole's phenyl ring would result in antipsychotic activity in view of the "high degree of unpredictability in antipsychotic drug discovery as of the priority date."[1080]

[B] Method Patents over Prior Compound Patents

Courts can find obviousness-type double patenting where the same patentee claims compounds in one patent and methods to use those

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1077. See discussion of Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989 (Fed. Cir. 2009), in section 7:2.2[A][2][b][ii] for an example of structural obviousness analysis in the context of obviousness-type double patenting.

1078. *See* Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1297 (Fed. Cir. 2012) ("[W]hen analyzing obviousness-type double patenting in cases involving claimed chemical compounds, the issue is not whether a skilled artisan would have selected the earlier compound as a lead compound. That is so because the analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, lead compound or not.").

1079. *Id*.

1080. *Id*. at 1298; *see also* Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 689 F.3d 1368, 1378 (Fed. Cir. 2012) ("a complicated compound such as the '608 [reference] Compound provides many opportunities for modification, but the district court did not find that substituting a phenyl group into the aryl position was the one, among all the possibilities, that would have been successfully pursued").

compounds in a later patent if the only use disclosed in the compound patent is the method claimed by the later patent.[1081] "Our predecessor court recognized that a claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use."[1082]

[C] Examples

Eli Lilly & Co. v. Barr Laboratories, Inc.[1083]

Claims:	A method of blocking the uptake of serotonin in animals by administering fluoxetine hydrochloride. vs. Administration of fluoxetine or its pharmaceutically acceptable salts to treat anxiety in a human.
Differences:	(1) blocking uptake of serotonin limitation vs. treating anxiety; (2) administration to animals vs. human; (3) fluoxetine hydrochloride vs. fluoxetine or its pharmaceutically acceptable salts.
Ruling:	Finding obviousness-type double patenting because: (1) blocking the uptake of serotonin was "an inherent characteristic of the administration of fluoxetine hydrochloride for any purpose, including the treatment of anxiety."; (2) treatment of the human species was anticipated by an earlier claim directed to treatment of the animal genus; (3) person of ordinary skill in the art would have recognized that fluoxetine hydrochloride was a pharmaceutically acceptable salt of fluoxetine.

1081. *Geneva Pharm.*, 349 F.3d at 1385 (method of using clavulanic acid as lactamase inhibitor invalid over prior patent claiming clavulanic acid with a sole disclosed utility as lactamase inhibitor).

1082. *Id.* at 1385–86 ("It would shock one's sense of justice if an inventor could receive a patent upon a composition of matter, setting out at length in the specification the useful purposes of such composition, manufacture and sell it to the public, and then prevent the public from making any beneficial use of such product by securing patents upon each of the uses to which it may be adapted.") (citing *In re* Byck, 48 F.2d 665, 666 (C.C.P.A. 1931)).

1083. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955 (Fed. Cir. 2001).

Geneva Pharmaceutical, Inc. v. GlaxoSmithKline PLC[1084]

Claims: "A method of effecting β-lactamase inhibition in a human or animal in need thereof . . . which comprises administering . . . a β-lactamase inhibitory amount of clavulanic acid or a pharmaceutically acceptable salt thereof."

vs.

"Potassium clavulanate . . ."

Differences: Method of administering compound vs. compound claim.

Ruling: Method claim invalid as obviousness-type double patenting over compound claim because a person of ordinary skill reviewing the compound "patent would recognize a single use for potassium clavulanate, administration to patients to combat bacteria that product β-lactamase."

Perricone v. Medicis Pharmaceutical Corp.[1085]

Claims: Method for "treating sunburn" comprising applying an ascorbyl fatty acid ester "effective to solubilize in the lipid-rich layers of the skin an amount effective to scavenge free radicals . . . ." (prior patent).

vs.

Method for treatment of certain skin disorders comprising applying "an effective amount of an ascorbyl fatty acid ester" using a certain type of "fat-penetrating" carrier (invalidated patent).

Differences: (1) treating sunburn vs. certain skin disorders; (2) an amount effective to scavenge free radicals vs. an effective amount; (3) no carrier vs. a "fat-penetrating" carrier.

1084. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1385 (Fed. Cir. 2003); *see also* Pfizer, Inc. v. Teva Pharm. USA, Inc., 518 F.3d 1353, 1362 (Fed. Cir. 2008) (finding method of treatment claim invalid for obviousness-type double patenting based on reference claim to compound required in the treatment claim).

1085. Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1373 (Fed. Cir. 2005).

Ruling: (1) "Sunburn is a species of skin damage" and therefore "renders the later genus claims invalid under non-statutory double patenting"; (2) affirming finding that the claimed effective amount in the later claim "falls within the ranges of effective amounts in the" earlier claim; (3) based on the specification, the court found the "'effective to solubilize language' . . . means the same thing as the 'carrier' language" in the later claim.

Research Corp. Technologies Inc. v. Gensia Laboratories, Inc.[1086]

Claims: Therapeutic composition comprising an amount of a class of compounds (genus that includes species used in method claim of prior patent) "protected from light" and "suitable for therapeutic administration by injection" and "dissolved in a stabilizing effective amount of a saline or buffer solution."

vs.

Method of treating tumor cells comprising "parenterally administering . . . a solution containing" a specified compound "administered in a saline salt-containing buffer solution."

Differences: (1) genus of compounds vs. species within genus; (2) composition claim vs. method; (3) inclusion of "protected from light" vs. no limitation in prior claim; inclusion of "suitable for therapeutic administration by injection" and "*stabilizing effective amount* of saline or buffer solution" vs. no such limitation in prior claim.

1086. Research Corp. Techs., Inc. v. Gensia Labs. Inc., 10 F. App'x 856, 859 (Fed. Cir. 2001) (unpublished).

Ruling: Obviousness-type double patenting because (1) the composition of the later claim "when there are two chloride and two ammonia ligands . . . is the same as the composition used in the claims in the method patents"; (2) "there is no nonobvious variation between the claimed compositions and the composition to be used in the claimed methods"; (3) "We do not agree that a complex 'suitable for *therapeutic* administration' requires a degree of purity greater than that already required by the claims of the method patents. . . . Similarly . . . 'dissolved in a stabilizing effective amount of a saline or buffer solution,'" does not distinguish "over the claims in the method patents reciting that the platinum compound is 'administered in a saline salt-containing buffer solution.'"

In re Metoprolol Succinate Patent Litigation[1087]

Claim: "Metoprolol Succinate"

vs.

composition including one or more of several active ingredients (including metoprolol succinate) with another weak acid or salt, and an inner and outer layer coating.

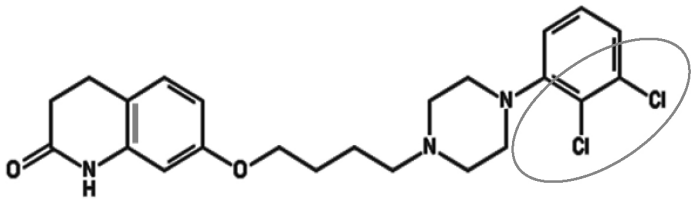
Differences: The reference claim disclosed a genus of active ingredients that included metoprolol succinate, and inner and outer layer coatings, whereas the later claim was limited to metoprolol succinate.

Ruling: Affirming double patenting determination because "it would have been an obvious variation . . . to omit the inner layer (B) and outer layer (C)."

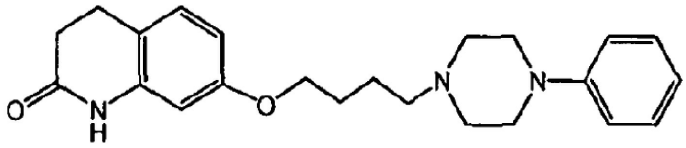
1087. *In re* Metoprolol Succinate Patent Litig., 494 F.3d 1011 (Fed. Cir. 2007).

Otsuka Pharmaceutical v. Sandoz[1088]

Claimed compound (aripiprazole):



Reference compound:



"unsubstituted butoxy"

Differences: The aripiprazole had two chlorine substituents that the reference compound lacked.

Ruling: The challenger failed to provide evidence that the challenged aripiprazole compound was an obvious variant of the unsubstituted butoxy reference compound because nothing taught that the "chlorine substituents and the 2 and 3 positions of" aripiprazole's phenyl ring would result in antipsychotic activity in view of the "high degree of unpredictability in antipsychotic drug discovery as of the priority date."

§ 5:9 Inequitable Conduct*

§ 5:9.1 Introduction

A patent that is otherwise valid may be rendered unenforceable if the applicant, prosecuting attorneys, or other persons substantively involved in the prosecution of the patent application are guilty of "inequitable conduct" during prosecution of the patent. "Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of 'candor, good faith and honesty.'"[1089] "Inequitable conduct includes affirmative misrepresentations of material facts, non-disclosure of

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1088. Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1298 (Fed. Cir. 2012).

* Written by Richard G. Greco.

1089. Warner-Lambert Co. v. Teva Pharm. USA, Inc., 418 F.3d 1326, 1342 (Fed. Cir. 2005) (citation omitted).

material information, or submission of false material information, coupled with an intent to deceive."[1090]

Charges of inequitable conduct are ubiquitous in patent litigation, and are often raised in pharmaceutical patent cases. The inherent difficulty in determining the "materiality" of information submitted or withheld, the circumstantial nature of "intent" evidence, the uncertain teachings of Federal Circuit precedents, and the profits to be gained by overcoming pharmaceutical patents provide strong incentives to patent challengers to make the allegation.

Some time ago, the Federal Circuit noted that inequitable conduct charges were getting out of hand. In *Burlington Industries, Inc. v. Dayco Corp.*,[1091] the court stated: "[T]he habit of charging inequitable conduct in almost every major patent case has become an absolute plague. Reputable lawyers seem to feel compelled to make the charge against other reputable lawyers on the slenderest grounds. . . ."[1092]

In May 2011, in *Therasense, Inc. v. Becton, Dickinson & Co.*,[1093] the Federal Circuit, sitting en banc, similarly expressed the following concerns about the inequitable conduct doctrine:

> [I]nequitable conduct charges cast a dark cloud over the patent's validity and paint the patentee as a bad actor. Because the doctrine focuses on the moral turpitude of the patentee with ruinous consequences for the reputation of his patent attorney, it discourages settlement and deflects attention from the merits of validity and infringement issues.[1094]

> [C]harging inequitable conduct has become a common litigation tactic. One study estimated that eighty percent of patent infringement cases included allegations of inequitable conduct. Inequitable conduct "has been overplayed, is appearing in nearly every patent suit, and is cluttering up the patent system." "[T]he habit of charging inequitable conduct in almost every major patent case has become an absolute plague. Reputable lawyers seem to feel compelled to make the charge against other reputable lawyers on the slenderest grounds, to represent their client's interests adequately, perhaps."[1095]

1090. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 2006 U.S. App. LEXIS 31748, at *26 (Fed. Cir. Dec. 26, 2006) (citation omitted).
1091. Burlington Indus., Inc. v. Dayco Corp., 849 F.2d 1418 (Fed. Cir. 1988).
1092. *Id*. at 1422.
1093. Therasense, Inc. v. Becton, Dickinson & Co., 99 U.S.P.Q.2d 1065 (Fed. Cir. 2011).
1094. *Id*. at 1071.
1095. *Id*. at 1072 (citations omitted).

> Left unfettered, the inequitable conduct doctrine has plagued not only the courts but also the entire patent system. Because allegations of inequitable conduct are routinely brought on the "the slenderest grounds," patent prosecutors constantly confront the specter of inequitable conduct charges. With inequitable conduct casting the shadow of a hangman's noose, it is unsurprising that patent prosecutors regularly bury PTO examiners with a deluge of prior art references, most of which have marginal value.[1096]
>
> While honesty at the PTO is essential, low standards for intent and materiality have inadvertently led to many unintended consequences, among them, increased adjudication cost and complexity, reduced likelihood of settlement, burdened courts, strained PTO resources, increased PTO backlog, and impaired patent quality.[1097]

In an effort to rein in the overuse of inequitable conduct allegations, the *Therasense* court "tighten[ed] the standards for finding both intent and materiality in order to redirect a doctrine that has been overused to the detriment of the public."[1098]

§ 5:9.2 Inequitable Conduct Requires Proof of Materiality and Intent

A party prosecuting an application before the PTO has a duty of candor, and is obligated to disclose (and not to misrepresent) facts that are material to the prosecution of the patent.[1099]

Inequitable conduct occurs when a party substantively involved in the patent prosecution fails to disclose, or misrepresents, a material fact with the intent to deceive the PTO.[1100] A party challenging a patent as unenforceable bears the burden of proving both elements, materiality, and culpable intent, by clear and convincing evidence.[1101]

§ 5:9.3 The Materiality Requirement

[A] Standard for Materiality Before *Therasense*

For many years, PTO Regulations defined materiality in a manner analogous to that applied in other types of fraud cases. Specifically,

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1096. *Id*. (citations omitted).
1097. *Id*.
1098. *Id*.
1099. 37 C.F.R. § 1.56 (2007).
1100. Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1379 (Fed. Cir. 2002).
1101. Purdue Pharma L.P. v. Endo Pharm., Inc., 438 F.3d 1123, 1128 (Fed. Cir. 2006); Allied Colloids, Inc. v. Am. Cyanamid Co., 64 F.3d 1570, 1578 (Fed. Cir. 1995); N. Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 939 (Fed. Cir. 1990).

PTO rules stated that information is "material" when "there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent."[1102] This standard is objective, based on what a "reasonable examiner" would have done rather than what the actual examiner concluded. Much of the inequitable conduct case law was developed using this standard.

In 1992, the Patent Office undertook a major revamping of the rules of disclosure and also revised the definition of materiality. The changed standard was not intended to make a major substantive revision.[1103]

The revised standard for materiality stated that information was material if it constituted a prima facie case of unpatentability (even if the responsive evidence may overcome the prima facie case) or was inconsistent with a position the applicant took in opposing an argument of unpatentability relied on by the Patent Office or in asserting an argument for patentability.[1104] The purpose of the change was said to be an effort to make the standard of materiality "clearer and more objective."[1105]

The Federal Circuit, in reviewing the evolution of materiality standards from "but for," through "important to a reasonable examiner," to "make a *prima facie* case or contradict an argument for patentability," held that a fact is material if it satisfies any of these standards. In *Digital Control, Inc. v. Charles Machine Works*,[1106] the Federal Circuit made clear that all of the prior formulations of materiality could be used:

> Even though the PTO's 'reasonable examiner' standard became the dominant standard invoked by this court, in no way did it supplant or replace the case law precedent. Rather, it provided an additional test of materiality, albeit a broader and all-encompassing test. Similarly, the PTO's recent adoption of an arguably narrower standard of materiality does not supplant or replace our case law.

1102. 37 C.F.R. § 1.56(a) (1991).

1103. Hoffmann-LaRoche, Inc. v. Promega Corp., 323 F.3d 1354, 1368 n.2 (Fed. Cir. 2003).

1104. *See* 37 C.F.R. § 1.56(b) (2003). It is unclear from the face of the language whether the post-1992 standard, at least to the extent that it considers information material if it contradicts an argument in favor of patentability, requires that the information also be important to a reasonable examiner. A contradiction on an unimportant issue, theoretically, could fall within the post-1992 materiality definition, if it is applied literally.

1105. Dig. Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1316 (Fed. Cir. 2006).

1106. *Id*.

> Rather, it merely provides an additional test of materiality. That is, if a misstatement or omission is material under the new Rule 56 standard, it is material. Similarly, if a misstatement or omission is material under the 'reasonable examiner' standard or under the older three tests, it is also material.[1107]

The standard of materiality did not require the court to find that the patent would not have issued, or would have issued in a different form, if the information had been disclosed or not misrepresented.[1108] It was not a "but for" standard.[1109]

Indeed, in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*,[1110] the examiner actually considered an omitted reference in a later reissue proceeding, and issued the claims over the reference. The court nonetheless held that the reference was material because a "reasonable examiner" would have wanted to know the information.[1111]

The Federal Circuit at times appeared to allow flexibility in a district court's determination of materiality. In one case, the inventor submitted a declaration to the PTO stating that in a comparative test, the invention showed a statistically significant lower C_{Max} than the prior art formulation, but the inventor admitted at trial that she had never analyzed the statistical significance of the reported data, and also that statistical significance could not be shown.[1112] The district court held that the misstatement satisfied the definition of materiality under 37 C.F.R. § 1.56(b). Nonetheless, the court concluded that the statement was not material to patentability because the claims did not require statistical significance, the data was before the Examiner, and there was in fact a difference between the invention and the prior art. The Federal Circuit did not comment on the district court's finding of no materiality notwithstanding satisfaction of the section 1.56 definition, but upheld the finding that there was no inequitable conduct, because the weighing of materiality of the statement and absence of evidence of intent to deceive demonstrated no abuse of discretion.

1107. *Id*.
1108. PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1322 (Fed. Cir. 2000); A.B. Dick Co. v. Burroughs Corp., 798 F.2d 1392, 1397 (Fed. Cir. 1986).
1109. Merck & Co. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989).
1110. Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226 (Fed. Cir. 2003).
1111. *Id*. at 1234–35.
1112. Abbott Labs. v. Sandoz Inc., 544 F.3d 1341 (Fed. Cir. 2008).

[B] The Materiality Standard Under *Therasense*

In *Therasense*, the Federal Circuit heightened the materiality standard, stating that "as a general matter, the materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art."[1113]

The Federal Circuit explained that "in assessing the materiality of a withheld reference, the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference."[1114] The court commented that, "[a]s an equitable doctrine, inequitable conduct hinges on basic fairness. . . . [A]s a general rule, this doctrine should only be applied in instances where the patentee's misconduct resulted in the unfair benefit of receiving an unwarranted claim."[1115]

The *Therasense* court did recognize an exception to the but-for materiality standard "in cases of affirmative egregious misconduct."[1116] The Federal Circuit noted that this exception "incorporates elements of the early unclean hands cases before the Supreme Court, which dealt with 'deliberately planned and carefully executed scheme[s]' to defraud the PTO and the courts.'"[1117] The court stated that "[w]hen the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material."[1118] According to the Federal Circuit, "[b]ecause neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references in an affidavit constitutes affirmative egregious misconduct, claims of inequitable conduct that are based on such omissions require proof of but-for materiality."[1119] The court observed that "[b]y creating an exception to punish affirmative egregious acts without penalizing the failure to disclose information that

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1113. Therasense, Inc. v. Becton, Dickinson & Co., 649 F.3d 1276, 1291 (Fed. Cir. 2011) (en banc).
1114. *Id*.
1115. *Id*. at 1292.
1116. *Id*.
1117. *Id*. (quoting Hazel-Atlas Glass Co. v. Hartford-Empire Co., 322 U.S. 238, 245 (1944)).
1118. *Id*.; *see also* Ohio Willow Wood Co. v. Alps S., LLC, 735 F.3d 1333 (Fed. Cir. 2013) (reversing summary judgment of no inequitable conduct and finding disputed material facts to support the kind of egregious misconduct needed to demonstrate materiality where the patentee argued repeatedly in a reexamination that there was no corroboration for the testimony of a witness describing the prior art, when the patentee knew of such corroboration).
1119. *Therasense*, 649 F.3d at 1292–93.

would not have changed the issuance decision, this court strikes a necessary balance between encouraging honesty before the PTO and preventing unfounded accusations of inequitable conduct."[1120]

§ 5:9.4 The Intent Requirement

[A] Actual Intent Required; Negligence Not Enough

The Federal Circuit has held that inequitable conduct requires an actual intent to deceive the Patent Office by misrepresenting or withholding a material fact.[1121] Negligence, oversight, erroneous or poor judgment, or even gross negligence are not sufficient to establish inequitable conduct.[1122] "A patentee's oversights are easily magnified out of proportion by one accused of infringement. . . . Given the ease with which a relatively routine act of patent prosecution can be portrayed as intended to mislead or deceive, clear and convincing evidence . . . sufficient to support an inference of culpable intent is required."[1123]

[B] There Must Be a Specific Intent to Deceive

To satisfy the intent requirement of inequitable conduct, there must be a specific intent to deceive.[1124]

In *In re Harita*,[1125] the Federal Circuit made clear that the intent must be a conscious effort to deceive, not merely an intention to withhold information that was in fact material. There, the Federal Circuit rejected the Patent Office's finding of inequitable conduct when a Japanese patent agent knew of prior art references, knew that the prior art references fully anticipated certain claims asserted, but did not disclose the references to the Patent Office because he did not realize that there was a U.S. requirement for such disclosure. The Federal Circuit held:

1120. *Id*.

1121. Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 872 (Fed. Cir. 1988) (en banc).

1122. *Id*. at 872–73; N. Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 939 (Fed. Cir. 1990).

1123. N. Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 939 (Fed. Cir. 1990) (internal quotation marks omitted).

1124. *Molins PLC*, 48 F.3d at 1181 ("[C]lear and convincing evidence must prove that an applicant had the specific intent to accomplish an act that the applicant ought not to have performed, *viz.*, misleading or deceiving the [Patent Office]."); Allen Organ Co. v. Kimball Int'l, Inc., 839 F.2d 1556, 1567 (Fed. Cir. 1988); FMC Corp. v. Manitowoc Co., 835 F.2d 1411, 1415 (Fed. Cir. 1987); *Kingsdown Med. Consultants*, 863 F.2d at 872–73.

1125. *In re* Harita, 847 F.2d 801 (Fed. Cir. 1988).

> 'Inequitable conduct' is not, or should not be, a magic incantation to be asserted against every patentee. Nor is that allegation established upon a mere showing that the art or information having some degree of materiality was not disclosed. To be guilty of inequitable conduct, *one must have intended to act inequitably*. Thus, one who alleges a 'failure to disclose' form of inequitable conduct must offer clear and convincing proof of: . . . (3) failure of the applicant to disclose art or information *resulting from an intent to mislead the PTO*. That proof may be rebutted by showing that: . . . (d) . . . applicant's failure to disclose art or information *did not result from an intent to mislead the PTO*.[1126]

[C] The Intent Requirement Under *Therasense*

In *Therasense*, the Federal Circuit stated, consistent with prior case law, that "[t]o prevail on a claim of inequitable conduct, the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO."[1127] "[T]he accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it."[1128]

[C][1] Proving Intent Before Therasense

The Federal Circuit has repeatedly emphasized that intent is a separate element to be proven by clear and convincing evidence, separate and distinct from the element of materiality. "'Materiality does not presume intent, which is a separate and essential component of inequitable conduct.'"[1129] An "[i]ntent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent."[1130]

Nonetheless, the requirement that there be proof of specific intent to deceive separate from proof of materiality was sometimes relaxed in practice. Thus, for example, the Federal Circuit held that the failure to

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1126. *Id*. at 808 (citing *FMC Corp.*, 835 F.2d at 1415) (emphasis and alteration in original).

1127. Therasense, Inc. v. Becton, Dickinson & Co., 99 U.S.P.Q.2d 1065, 1072 (Fed. Cir. 2011).

1128. *Id*.

1129. Aventis Pharma S.A. v. Amphastar Pharm., Inc., No. 05-1513, 2006 WL 925278, at *5 (Fed. Cir. Apr. 10, 2006) (citing to GFI, Inc. v. Franklin Corp., 265 F.3d 1268, 1274 (Fed. Cir. 2001)); *see also* Braun, Inc. v. Dynamics Corp. of Am., 975 F.2d 815, 822 (Fed. Cir. 1992) (intent cannot be inferred from knowledge of material prior art).

1130. Hebert v. Lisle Corp., 99 F.3d 1109, 1116 (Fed. Cir. 1996); *see also* Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552 (Fed. Cir. 1990).

disclose highly material information could by itself lead to an inference of intent.[1131]

[C][1][a] *Ferring B.V. v. Barr Laboratories, Inc.*

In *Ferring B.V. v. Barr Laboratories, Inc.*,[1132] the Federal Circuit affirmed summary judgment of inequitable conduct. The patent examiner had rejected claims over prior art, and the inventor submitted a declaration regarding the meaning of the term "peroral" administration in a prior art reference. The examiner, in an oral interview, had requested declarations on the subject from persons other than the inventors. After an appeal to the Board and return to prosecution, four years later, the applicant submitted four declarations of non-inventors who were well-known scientists in the field. Three of the declarants had prior connections to the licensee of the applicant (Ferring), which were not disclosed in the declaration. One of the past affiliations was that Ferring had provided some equipment used by the declarant in a clinical trial, another declarant worked for a foundation that in the past had received research grants from Ferring, and a third declarant had been a paid consultant prior to submitting the declaration. The inventor knew of one of the past affiliations.[1133]

The Federal Circuit found that the omission of the past relationships with Ferring from the declarations was highly material, interpreting the first examiner's request for declarations from non-inventors to be a request for declarations from "disinterested" persons. Notwithstanding the fact that none of the declarants were compensated and none had any financial interest in the award of the patent, the court found the connections of the declarants to the applicant's exclusive licensee of the patent were material to the credibility of the declarations.[1134] The court then inferred the intent to deceive from the failure of the inventor to disclose the affiliations of the declarant:

> [S]ummary judgment is appropriate on the issue of intent if there has been a failure to supply highly material information and if the summary judgment record establishes that (1) the applicant knew of the information; (2) the applicant knew or *should have known of* the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding.[1135]

1131. Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253 (Fed. Cir. 1997).
1132. Ferring B.V. v. Barr Labs., Inc., 437 F.3d 1181 (Fed. Cir.), *reh'g denied*, 2006 U.S. App. LEXIS 10765 (Fed. Cir. Apr. 10, 2006).
1133. 437 F.3d at 1184–85.
1134. *Id*. at 1189–90.
1135. *Id*. at 1191 (emphasis added).

Judge Newman wrote in dissent that the court's "positive inference of wrongdoing" seems at odds with prior statements that intent cannot be inferred solely from a failure to disclose a material fact, but requires proof in addition to materiality.[1136] Here, the court strung together several inferences: that the examiner's request for "non-inventor" declarations meant, and was understood to mean, that any declarants must be disinterested, that the one past relationship with Ferring known to the inventor would have been sufficient to make the inventor believe the declarant was not disinterested, that the inventor believed that the prior affiliation was material, and that he intentionally omitted the information (as opposed to having forgotten it or never giving it thought one way or the other) in order to deceive the Patent Office.

The court in *Ferring* put great weight on the absence of declaration evidence from the inventor explaining that he did not intend to deceive.[1137] The importance of a plausible explanation in avoiding an inference of intent to deceive is shown by *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*,[1138] where the court reversed an award of summary judgment of inequitable conduct where the applicant had offered some evidence that a misleading statement was made inadvertently. The court contrasted the case with *Ferring*, where a summary judgment of inequitable conduct was affirmed in the absence of an explanation for the failure to disclose.[1139]

On the other hand, in *Cargill Inc. v. Canbra Foods, Ltd.*,[1140] the Federal Circuit affirmed an inferred intent to deceive from failure to disclose certain test data in spite of an explanation by applicant that the nondisclosed tests were performed under unusual circumstances that made them inappropriate for comparison with other data.

Judge Newman observed the cases are not easily reconciled. She explained in the *Ferring* dissent that there are cases requiring proof of intent separate from materiality, and there are cases holding that intent may be inferred from a failure to disclose material information.[1141]

[C][2] Proving Intent After Therasense

Citing prior Federal Circuit case law, the *Therasense* court stated that "to meet the clear and convincing evidence standard, the specific intent to deceive must be 'the single most reasonable inference

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1136. *Id*. at 1196–97.
1137. *Id*. at 1191–93.
1138. Aventis Pharma S.A. v. Amphastar Pharm., Inc., No. 05-1513, 2006 WL 925278 (Fed. Cir. Apr. 10, 2006).
1139. *Id*. at *6.
1140. Cargill Inc. v. Canbra Foods, Ltd., 476 F.3d 1359 (Fed. Cir. 2007).
1141. Ferring B.V. v. Barr Labs., Inc., 437 F.3d 1181, 1201–03 (Fed. Cir. 2006).

able to be drawn from the evidence.'"[1142] The court departed from prior precedent in directing that "[a] district court should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a strong showing of materiality."[1143] Moreover, in the words of the Federal Circuit, "a district court may not infer intent solely from materiality. Instead, a court must weigh the evidence of intent to deceive independent of its analysis of materiality."[1144] Thus, "[p]roving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive."[1145]

[C][3] Whether the Actual Intent Standard Requires That at Least One Individual Have the Requisite Culpable State of Mind

Actual intent to deceive should logically require that at least one real person possessed both the actual knowledge of the facts not disclosed or misstated, and the actual knowledge of materiality, and either misstated or withheld the material facts with an intent to deceive.[1146] To prove an actual, specific intent to deceive, it should not be sufficient to show that one employee knew of the facts, but not the materiality, and that a different employee understood the materiality, but did not know the facts. As the MPEP acknowledges, the duty to disclose attaches to individuals substantially involved in the patent prosecution, but not to organizations as such.[1147]

1142. Therasense, Inc. v. Becton, Dickinson & Co., 99 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2011) (quoting Star Sci. Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1366 (Fed. Cir. 2008)).

1143. *Id*.

1144. *Id*.; 1st Media, LLC v. Elec. Arts, Inc., 694 F.3d 1367 (Fed. Cir. 2012) (reversing finding of inequitable conduct where the record contained no affirmative evidence of a deliberate decision to withhold the material references and defendant relied solely on the inability of the inventor and prosecution counsel to supply a good-faith basis for failing to submit them).

1145. *Therasense, Inc.*, 99 U.S.P.Q.2d at 1073.

1146. *See* FMC Corp. v. Hennessey Indus., Inc., 836 F.2d 521, 525 n.5 (Fed. Cir. 1987) ("One attempting to prove inequitable conduct must prove by clear and convincing evidence that the conduct of the person *charged* was inequitable.").

1147. *See* M.P.E.P. § 2001.01 (2006).

§ 5:9.5 Categories of Inequitable Conduct

[A] References

[A][1] Non-Disclosed References

Perhaps the most frequent inequitable conduct allegation is that the applicant for the patent failed to disclose a material reference to the PTO. However, a court will consider whether a non-disclosed reference was merely cumulative of other references that were before the examiner. A cumulative reference is not material.[1148]

[A][2] References Before the Examiner

If a reference is before the examiner during prosecution, it is irrelevant whether it was found by the examiner or cited by the applicant. As the Federal Circuit explained in *Molins PLC v. Textron, Inc.*:[1149]

> When a reference was before the examiner, whether through the examiner's search or the applicant's disclosure, it cannot be deemed to have been withheld from the examiner.[1150]

The examiner is presumed to have read and considered all references that were before him.[1151]

The court has been willing to take account of the fact that an examiner knew of a reference from related patent files, even if not cited in the particular application at issue.[1152]

1148. *See supra* section 5:9.3.

1149. Molins PLC v. Textron, Inc., 48 F.3d 1172 (Fed. Cir. 1995) (citations omitted).

1150. *Id*. at 1185 (citations omitted).

1151. *In re* Portola Packaging, Inc., 110 F.3d 786, 790 (Fed. Cir. 1997), *superseded by statute*, 35 U.S.C. § 303, Pub. L. No. 107-273, § 13105, 116 Stat. 1758, 1900, as recognized in *In re* Bass, 314 F.3d 575 (Fed. Cir. 2002).

1152. *See, e.g.*, Allen Organ Co. v. Kimball Int'l, Inc., 839 F.2d 1556, 1568 (Fed. Cir. 1988) (no inequitable conduct where prior art reference was cited in the specification of one of two co-pending applications filed by the same attorney and which were examined by same examiner); FMC Corp. v. Hennessy Indus., Inc., 836 F.2d 521, 526 (Fed. Cir. 1987) (court presumed knowledge by examiner of reference disclosed in prosecution of another application belonging to same applicant and "pending before the same examiner at the very same time"); Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1457 (Fed. Cir. 1984) (when same examiner handled two applications, he is presumed to be aware of both).

[A][3] Disclosure Only of Abstracts

Disclosure of an abstract or summary of a reference may be sufficient, but will invite the accusation that the abstract was misleading because it omitted some information that appeared in the article. In *Atofina v. Great Lakes Chemical Corp.*,[1153] the Federal Circuit reversed a finding of the district court that there was inequitable conduct resulting from the failure of the applicant to provide a full English translation of a Japanese reference, although an English language Derwent Abstract was provided. The district court had found that there were material facts in the full reference that were not disclosed in the abstract. The Federal Circuit disagreed with the district court's interpretation of the reference, and found that the applicant's arguments about the reference were not inconsistent with the full translation.[1154] Note, however, that the court did not dismiss out of hand the notion that one could be guilty of inequitable conduct by providing only an English language abstract of a foreign language reference when a full translation of the reference is available.

[A][4] Potential Double-Patenting References

Failure to cite a non-prior-art earlier-issued patent can constitute inequitable conduct if it supports a double-patenting or provisional double-patenting rejection.[1155]

[A][5] Argument About a Reference

If a reference is before the examiner, an incorrect argument about that reference generally will not form the basis for finding inequitable conduct.[1156] It also does not constitute inequitable conduct to advocate, in good faith, a reasonable interpretation of the prior art even

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1153. Atofina v. Great Lakes Chem. Corp., 441 F.3d 991 (Fed. Cir. 2006), *reh'g denied*, 2006 U.S. App. LEXIS 14354 (Fed. Cir. May 16, 2006).

1154. 441 F.3d at 1001–03.

1155. McKesson Info. Sols., Inc. v. Bridge Med., Inc., 487 F.3d 897 (Fed. Cir. 2007) (affirming inequitable conduct finding based on failure to cite non-prior-art earlier-issued patent—issued by the same examiner handling the pending application—because it was potentially the basis for a double-patenting rejection); *see also* Golden Valley Microwave Foods, Inc. v. Weaver Popcorn Co., 837 F. Supp. 1444, 1476 (N.D. Ind. 1992) (finding inequitable conduct for deliberately withholding "the existence of the '723 application and prosecution history").

1156. Norian Corp. v. Stryker Corp., 363 F.3d 1321 (Fed. Cir. 2004); Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1581 (Fed. Cir. 1997) (inequitable conduct contention rejected where arguments about a cited reference were "overstatements" and "exaggerations," and examiner had reference and could consult it while examining arguments).

though the applicant suspects that interpretation may be incorrect.[1157] However, where an applicant knows that an interpretation is incorrect and makes false statements to support that interpretation, he crosses "the line from legitimate advocacy to genuine misrepresentation of material facts."[1158]

[B] Descriptions of Data and Experiments

Inequitable conduct attacks are often made based on an applicant's description of experiments or experimental data. The experiments underlying the statements made by the applicant in the patent specification or in declarations are scrutinized, and experts are brought in to criticize aspects of the experiments. The applicant is then accused of fraud for either providing false results or failing to disclose the nature of the alleged defects in the experiments.

Inequitable conduct has been found where an experiment described in the specification was not actually conducted as described, even though the results of the experiment reported were true. In *Hoffmann-La Roche, Inc. v. Promega Corp.*,[1159] the Federal Circuit affirmed a finding of inequitable conduct based on the manner in which an example in the patent specification was worded. The example described the purification of the claimed enzyme in the past tense, suggesting that all steps of the experiment were actually performed in sequence, as described. In fact, the steps of the described purification had been performed in two separate experiments. Although there was no finding that the reported *results* were in fact untrue or misleading, the court held that the example was misleading because testimony established that the order in which the steps were performed could affect the result.[1160]

In *Aventis Pharma SA v. Amphastar Pharmaceuticals, Inc.*,[1161] the district court granted summary judgment finding a patent unenforceable for inequitable conduct. The patent applicant had supported its

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1157. Apotex Inc. v. UCB, Inc., 763 F.3d 1354, 1361–62 (Fed. Cir. 2014) ("To be clear, we agree with Apotex that Dr. Sherman had no duty to disclose his own suspicions or beliefs regarding the prior art. There is nothing wrong with advocating, in good faith, a reasonable interpretation of the teachings of the prior art.") (footnote omitted).

1158. *Id*. (finding that the applicant's statements to the examiner about the absence of moexipril magnesium in a prior art reference were not the advocacy of a preferred interpretation, but instead set forth facts about the reference that the applicant knew were false).

1159. Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354 (Fed. Cir. 2003).

1160. *Id*. at 1365.

1161. Aventis Pharma SA v. Amphastar Pharm., Inc., 176 F. App'x 117 (Fed. Cir.), *reh'g denied*, 2006 U.S. App. LEXIS 14778 (Fed. Cir. June 7, 2006).

claim to patentability of a compound by showing that it had a greater half-life than a prior art compound. The comparison, however, was made with different dosage amounts; and the applicant had undisclosed data showing that when the two compounds were compared at the same dosage, the difference between the compounds was much smaller. The Federal Circuit affirmed the finding of materiality, but found an issue of fact remained on intent because the inventors offered a plausible reason why the disclosed comparison was reasonable and asserted that the failure to disclose was inadvertent.[1162]

In *Cargill Inc. v. Canbra Foods, Ltd.*,[1163] inequitable conduct was found when applicant failed to disclose test data showing that the difference between the claimed composition and one cited as a basis for obviousness was not as great as the applicant asserted. The court rejected the applicant's explanation that the nondisclosed experiments had been done under unusual conditions and were not a proper basis for comparison.

In *Apotex Inc. v. UCB, Inc.*,[1164] the Federal Circuit affirmed a finding of inequitable conduct where the applicant's arguments and representations to the examiner about a prior art reference were contradicted by the applicant's undisclosed testing. The Federal Circuit found that such representations were factual and known to be false and, as such, did not qualify as the legitimate advocacy of a reasonable interpretation of the prior art.

[C] Representations Regarding Inventorship

Prior to *Therasense*, a misrepresentation about inventorship, including a misrepresentation of inventorship by the named inventors with deceptive intent, can be a ground for a finding of inequitable conduct that renders the patent unenforceable.[1165]

In *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*,[1166] a district court found that there were five misstatements concerning the relationship between the named inventors and another laboratory that had supplied materials from which the invention was made. The Federal Circuit affirmed the finding of inequitable conduct, even though the issued patent correctly named the inventors of the allowed claims.[1167]

1162. *Id*. at 122–23.
1163. Cargill Inc. v. Canbra Foods, Ltd., 476 F.3d 1359 (Fed. Cir. 2007).
1164. Apotex Inc. v. UCB, Inc., 763 F.3d 1354, 1361–62 (Fed. Cir. 2014).
1165. PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1322 (Fed. Cir. 2000).
1166. *Id*.
1167. *Id*. at 1321–23.

A contrary result was reached on similar facts in *Board of Education v. American Bioscience, Inc.*,[1168] where the failure to disclose a prior working relationship with scientists not named as inventors was held not to be material, because the scientists who were not named as inventors did not conceive the invention.

The *PerSeptive Biosystems* case and the contrasting *Board of Education* case illustrate the benefit of making disclosure beyond what one may believe is material to avoid giving a patent challenger the opportunity to argue that material facts were withheld. It is difficult if not impossible to predict how a court will rule in any given case.

[D] Related Proceedings

[D][1] Related Patent Office Proceedings

The Federal Circuit has affirmed inequitable conduct findings for failure to give to one examiner an office action from the U.S. Patent Office that had issued in a "similar" application prosecuted by the same attorney at the same time before another examiner despite the fact that the co-pending application (but not the office action) was cited.[1169] Patent Office interpretations involving a "substantially similar claim" can be material even if the relevant reference has been disclosed because it is necessary to properly understand its meaning:

> Patent disclosures are often very complicated, and different examiners with different technical backgrounds and levels of understanding may often differ when interpreting such documents. Although examiners are not bound to follow other examiners' interpretations, knowledge of a potentially different interpretation is clearly information that an examiner could consider important when examining an application.[1170]

Although now, under *Therasense*, the standard for materiality is "but for," not the "reasonable examiner" standard, if an office action rises to this level of materiality, it should be disclosed. In addition, prior rejections of substantially similar claims may be material because

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1168. Bd. of Educ. v. Am. Bioscience, Inc., 333 F.3d 1330 (Fed. Cir. 2003).

1169. McKesson Info. Sols., Inc. v. Bridge Med., Inc., 487 F.3d 897, 919–25 (Fed. Cir. 2007); Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1368 (Fed. Cir. 2003) ("We hold that a contrary decision of another examiner reviewing a substantially similar claim meets" the materiality test (prior to *Therasense*).).

1170. *Dayco*, 329 F.3d at 1368.

they may contradict the applicant's assertion of patentability for the pending application.[1171]

It is unclear whether the same standard applies to foreign patent office proceedings. In an earlier decision prior to *McKesson* and *Dayco* (referenced above), the Federal Circuit held that an application was not "required to submit the documents relating to" a disclosed reference, including an international search report and a report applying that reference to the corresponding PCT application.[1172] "[I]t is the reference itself, not the information generated in prosecuting foreign counterparts, that is material to prosecution in the United States."[1173]

[D][2] Related Litigations

The MPEP imposes a duty to disclose litigation involving the subject matter of any pending patent application and "other material information" from the litigation including, for example, "evidence of possible prior public use or sales, questions of inventorship, prior art, allegations of 'fraud,' 'inequitable conduct,' and 'violation of duty of disclosure'" and "any assertion that is made during litigation which is contradictory to assertions made to the examiner."[1174] Contrary assertions made during litigation which are material should be disclosed even if they were made by another party.[1175]

[E] Miscellaneous Types of Inequitable Conduct

Inequitable conduct can be based on almost any omission or misrepresentation about the invention or the patent prosecution, and not

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1171. *Id*. ("When prosecuting claims before the Patent Office, a patent applicant is, at least implicitly, asserting that those claims are patentable. A prior rejection of a substantially similar claim refutes, or is inconsistent with the position that those claims are patentable.").

1172. ATD Corp. v. Lydall, Inc., 159 F.3d 534, 547 (Fed. Cir. 1998).

1173. *Id*.

1174. M.P.E.P. § 2001.06(c); *see also* Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1259 (Fed. Cir. 1997) (holding patent unenforceable due to inequitable conduct because the patentee "failed to disclose the ongoing litigation in the reissue proceedings" in violation of M.P.E.P. § 2001.06(c)); Golden Valley Microwave Foods, Inc. v. Weaver Popcorn Co., 837 F. Supp. 1444, 1477 (N.D. Ind. 1992) ("It is the 'material information' and not the mere existence of a lawsuit that needs to be brought to the attention of the examiner with regard to related litigation. If material information, such as supporting test data, prior art, etc. comes to an applicant's attention as a result of assertions in the lawsuit, then there is an obligation to disclose that to the examiner.").

1175. *Golden Valley Microwave Foods*, 837 F. Supp. at 1466 ("James River's assertions against [patentee] Golden Valley were material, though not necessarily acknowledged by Golden Valley, and these material assertions should have been brought to the attention of Examiner Bell.").

just those that relate to the substantive issue of whether the invention is patentable.

[E][1] Application for Expedited Treatment

In *General Electro Music Corp. v. Samick Music Corp.*,[1176] prior to *Therasense*, a patent was held unenforceable due to inequitable conduct where the applicant had applied for an expedited treatment of the patent application, but misrepresented that a prior art search had been done by the applicant as required for such treatment. The applicant did not perform a formal search, but only asked others in the industry and reviewed his own files of prior art. Although the alleged misstatement did not relate to whether or not the patent should issue, the Federal Circuit affirmed the finding of inequitable conduct.[1177]

[E][2] Payment of Maintenance Fees

In *Ulead Systems, Inc. v. Lex Computer & Management Corp.*,[1178] prior to *Therasense*, the district court granted summary judgment finding inequitable conduct because the patent applicant had paid the "small entity fee" to maintain the patent; a license of the patent to a larger entity required the payment of the higher fee. The Federal Circuit agreed that maintenance fee payments could be the subject of an inequitable conduct finding and that payment of the incorrect fee was material. However, it reversed as it found that there were genuine issues of fact concerning intent.

In *Nilssen v. Osram Sylvania*,[1179] the Federal Circuit expanded the scope of inequitable conduct for payment of the wrong fee to the improper payment of a small-entity maintenance fee which was due only after the patent had issued. There the pro se patent applicant was found to have committed inequitable conduct when he paid a small-entity maintenance fee when a license to the patent arguably took it out of small-entity status.

[E][3] Disclosure of Relationships Between Declarant and Applicant

The *Nilssen* court, prior to *Therasense*, expanded the scope of the duty, announced in *Ferring B.V. v. Barr Laboratories, Inc.*,[1180] to disclose relationships between declarants supporting the patent application and

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1176. Gen. Electro Music Corp. v. Samick Music Corp., 19 F.3d 1405 (Fed. Cir. 1994).
1177. *Id*. at 1411.
1178. Ulead Sys., Inc. v. Lex Comput. & Mgmt. Corp., 351 F.3d 1139 (Fed. Cir. 2003).
1179. Nilssen v. Osram Sylvania, 304 F.3d 1223 (Fed. Cir. 2007).
1180. Ferring B.V. v. Barr Labs., Inc., 437 F.3d 1181 (Fed. Cir. 2006).

the applicant. In *Nilssen*, the court found that the failure to disclose an economic interest of a declarant was inequitable conduct, although, unlike *Ferring*, the examiner had never asked for declarations from persons who were not inventors. The court stated that "it is material to an examiner's evaluation of the credibility and content of affidavits to know of any significant relationship between an affiant and applicant . . . failure to disclose that relationship violated Nilssen's duty of disclosure."[1181]

[E][4] Notes About a Presentation

In *Monsanto Co. v. Bayer Bioscience N.V.*,[1182] a scientist's handwritten notes about a poster presentation she attended were deemed material, although the abstract related to the poster was disclosed to the PTO. The notes contradicted an argument made by the prosecuting attorney to distinguish the abstract. The court rejected the attorney's explanation that he could not decipher the notes and that the note taker's recollection of them was not clear because the note taker's deposition testimony reflected a good understanding of the notes.

[E][5] Concealment of Best Mode

The concealment of a "best mode" has also been a basis for inequitable conduct.[1183]

[E][6] Litigation Misconduct

Litigation misconduct which obfuscates prosecution misconduct can be considered in determining inequitable conduct.[1184]

1181. *Nilssen*, 304 F.3d at 1230.

1182. Monsanto Co. v. Bayer Bioscience N.V., 514 F.3d 1229 (Fed. Cir. 2008).

1183. *See* Old Town Canoe Co. v. Confluence Holdings Corp., 448 F.3d 1309, 1321–22 (Fed. Cir. 2006); Consol. Aluminum Corp. v. Foseco Int'l Ltd., 910 F.2d 804 (Fed. Cir. 1990).

1184. Regeneron Pharm., Inc. v. Merus N.V., 864 F.3d 1343, 1364 (Fed. Cir. 2017) (affirming judgment of patent unenforceability for inequitable conduct because the patentee "failed to disclose documents directly related to its prosecuting attorneys' mental impressions of the Withheld References during prosecution of the '018 patent" and engaged in other "widespread litigation misconduct," and the challenger "proved the remaining elements of inequitable conduct").

§ 5:9.6 *Late and Corrected Disclosures*

[A] Late Disclosures

Late disclosure should not create a basis for inequitable conduct, as long as the reference was before the examiner prior to the patent being issued.[1185]

[B] Correcting a Disclosure During Prosecution

Sometimes, an incorrect statement made during the prosecution of a patent is corrected prior to the issuance of the patent. The question then becomes whether the correction is sufficient to prevent a finding of inequitable conduct.

In *Rohm & Haas Co. v. Crystal Chemical Co.*,[1186] a patent was held unenforceable for inequitable conduct because of misrepresentations regarding experimental data. There, a comparison was made between the claimed herbicide, which was tested in May and June, and a prior art compound, which was tested in December. The applicants knew that the time of year had a significant impact on the resistance of plants to herbicide, and that when the compounds were compared at the same time, there was no difference between the invention and the prior art. In addition, some data submitted to the PTO had been falsified. However, the district court found there was no inequitable conduct, because the applicant had submitted the actual data later in the prosecution.[1187]

The Federal Circuit reversed. The court held that inequitable conduct cannot be cured by subsequently disclosing large amounts of data without pointing out precisely where the prior misrepresentation occurred and the nature of the misrepresentation. To cure a prior intentional misrepresentation, the applicant must

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1185. Under the current rules of practice, prior art cited in an Information Disclosure Statement "shall be considered by the Office" when submitted prior to the Notice of Allowance, although a fee may be required. 37 C.F.R. § 1.97(c) (1996). *E.g.*, Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc., 30 U.S.P.Q.2d (BNA) 1967 (N.D. Cal. 1994) (no inequitable conduct where prior art reference was not cited in initial application and citation was delayed until continuation application), *aff'd*, 1996 U.S. App. LEXIS 33588 (Fed. Cir. Dec. 16, 1996); Libbey-Owens-Ford Co. v. BOC Grp., 655 F. Supp. 897, 916–17 (D.N.J. 1987) (in finding no inequitable conduct, court rejected argument that patentee had delayed submission of prior art references until "just prior to the grant of the patent . . . when the examiner had the 'mind-set' to issue the patent" because "in order to accept [these] theories, I would need to believe that the examiner did not properly discharge his duties").

1186. Rohm & Haas Co. v. Crystal Chem. Co., 722 F.2d 1556 (Fed. Cir. 1983).

1187. *Id*. at 1560.

(1) expressly advise the PTO of the misrepresentation and show where it resides;

(2) inform the PTO of the actual facts and suggest that further examination in light of the actual facts may be needed if the PTO based any of its actions on the misrepresentation; and

(3) show patentability in light of the actual facts.

Moreover, if the patentee made intentional misrepresentations during prosecution, it bears the burden of proving that the misrepresentation was sufficiently cured by clear and convincing evidence.[1188]

The *Rohm & Haas* rules for correcting intentional misrepresentations have been applied narrowly to affirmative, false statements deliberately made. The rigorous criteria have not been required where a non-disclosure of material information is later cured by disclosure. As noted above, a disclosure of a previously non-disclosed reference prior to patent issuance normally precludes a finding that the reference was withheld.

In *Kao Corp. v. Unilever U.S., Inc.*,[1189] a patent owner narrowly avoided a finding of inequitable conduct. There, the claim related to a polymer for removing kertotic plugs from skin pores. Data were provided showing that the polymer of the invention removed 23.3% of the plugs, while a prior art composition removed only 3.7%. The inventor's declaration did not disclose that another polymer within the invention had removed only 14.4% and that the margin of error was 7.1%. While the district court found the omission material, it held that there was no inequitable conduct because of a lack of intent to deceive. Important to that finding of lack of intent was the later disclosure to the PTO of the lower results (but not the margin of error). The Federal Circuit affirmed the finding, although it suggested that it might have come out differently if it were deciding the issue de novo.[1190]

[C] Disclosure in Reissue Proceedings

As set forth earlier,[1191] inequitable conduct ordinarily does not arise if the disclosure in question was made prior to issuance of the patent. However, disclosure in reissue proceedings is too late: it does not cure a failure to disclose in the original prosecution. In *Bristol-Myers*

1188. *Id*. at 1572.
1189. Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963 (Fed. Cir.), *reh'g denied*, No. 05-1038, 2006 U.S. App. LEXIS 14543 (Fed. Cir. May 31, 2006).
1190. *Kao Corp.*, 441 F.3d at 971–72.
1191. *See supra* section 5:9.6[A].

Squibb Co. v. Rhone-Poulenc Rorer, Inc.,[1192] a reference that was not prior art, but which was found to be material to enablement, was not disclosed in the original patent prosecution, but was disclosed during a reissue. The reissue disclosure was held insufficient and the patent, including the patent as reissued, was held unenforceable. The disclosure of the reference in the reissue proceeding at the direction of the accused patent agent did not convince the court that he lacked intent to deceive when the reference was not disclosed in the original prosecution.

§ 5:9.7 Practical Problems in Pharmaceutical Patent Prosecution

Given that Hatch-Waxman Act litigation typically takes place prior to the launch of the generic product, a generic manufacturer has relatively little to risk, and much to gain, from a broad challenge to patent validity and enforceability. Because of the strong incentives created by the statutory scheme, inequitable conduct charges are frequently raised. To what extent *Therasense* changes that remains to be seen.

Opportunities for alleging inequitable conduct are generated by the way that patents are typically prosecuted. A traditional scenario for patent prosecution of a new drug will commence with the discovery of a promising candidate, often one of a number of compounds that have at least minimal activity. The inventors provide the chemical structure and usually the data that got their attention to the company's patent department, and the patent attorney drafts an application, including a generic formula that encompasses not only the lead compound but others that are structurally related and show some activity. Usually, examples are provided, including the preliminary test results that sparked interest in the compound.

The inventors sign the application and, for U.S. applications, sign a lengthy declaration that in fine print warns the applicant, among other things, of the duty to disclose material information to the PTO.

Because most compounds that are the subject of an application fail for one or another reason and ultimately have no commercial importance, the mere preparation of a patent application is not always a significant event. While quite a large number of applications are filed by pharmaceutical companies, most never result in commercial products. As a result, once the application is filed, the inventors may not remain in close communication with the patent attorney; often they

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1192. Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226 (Fed. Cir. 2003).

will have no further communications with the attorney unless they are specifically asked for further information.

While the patent application is pending, however, a large amount of work will be ongoing respecting a drug candidate that ultimately becomes successful. There will be, of course, testing on animals, preparation of an Investigational New Drug application to start clinical trials, and often at least Phase I and II clinical trials in humans. Process development scientists will experiment with ways to make the compound more efficiently, and express preferences about the synthesis methods. Even if the inventors are not directly involved in these activities, they may be copied on reports relating to them, and therefore, may appear to have knowledge of them.

The inventors or their associates may be asked to submit additional data in response to an Office Action later in the prosecution, often long after the initial information was provided for the patent application. The busy scientist, often with only small quantities of the new compound at his disposal and many demands on those resources for regulatory testing, often does not have the luxury of devoting substantial time and resources to conduct a definitive experiment of peer review quality in the time available. Therefore, it is not uncommon for a scientist to respond to a patent attorney's request by providing relevant existing data previously obtained in experiments that were conducted for purposes other than responding to the specific PTO Office Action. However, the type of experiments done in normal research, and therefore often used in responding to the PTO, are designed to give practical information in a reasonable time, and may not be performed to a level of perfection that precludes criticism.

Moreover, the scientist, who often has not been following the progress of the patent application and who may have little knowledge or understanding of the arguments made by the attorney to support patentability, may respond by providing what is requested without considering how other data, unknown to the patent attorney, might be relevant. And in the communications between patent attorneys and inventors, some information can be easily lost in translation and misunderstood, particularly as to details of experiments or test methods. It is not hard to assert that any such errors are intentional, particularly when the declarant swears to the declaration that contains them.

For a pharmaceutical that reaches market and becomes the subject of patent litigation, there is bound to be a vast amount of data generated concerning the compound, much of it known (or at least copied) to the inventors or others involved in the patent prosecution. In addition, the party challenging the patent will therefore usually obtain a large body of information concerning the product from discovery, much more than what would be reasonable to include in a patent

application or to disclose during prosecution. A little creativity can often find something that one could argue should have been disclosed but was not, or which might be argued to be inconsistent with something said or implied in the course of the prosecution. In addition, criticisms of experimental methods and results are often transformed by patent challengers into allegations of fraud.

§ 5:9.8 *Practical Advice for Defeating Inequitable Conduct Allegations*

Good faith and honesty during the patent prosecution will not guarantee a patentee that no charge of inequitable conduct will be made. Furthermore, unfortunately, good faith and honesty may not be sufficient to prevail against a charge of inequitable conduct, given both the imprecise definitions of materiality and the willingness of a court to infer intent.

Nonetheless, a patent applicant can take some steps to increase the likelihood that inequitable conduct will not be found. To do so, one must think beyond the formal legal standards of materiality and intent, and instead think defensively to disclose all information and exercise great care in making statements in the patent specification and prosecution. A high degree of paranoia is helpful.

None of the following suggestions should be understood as required by the duty of disclosure. This is practical advice to reduce the chance that a patent challenger can make innocent conduct appear to be intentional deception.

[A] Disclosure of References

Pharmaceutical patent applications are typically filed throughout the world, or at least in the European Union and Japan, as well as the United States. Examination of the patent application in foreign jurisdictions will produce search reports of prior art that may include additional or different references than were disclosed by the applicant in the United States.

It is important to any prosecution program that there be a routine means of collecting all foreign search reports and disclosing to the U.S. PTO the reports themselves as well as the references cited. No effort should be made to evaluate the materiality of references cited in foreign prosecutions to determine what shall be provided to the U.S. PTO; rather, they should be disclosed as a matter of course. Disclosing any such reference is less time-consuming, and far better protection, than the most compelling analysis showing the reference

is not material. PTO regulations specifically encourage applicants to pay close attention to foreign search reports.[1193]

The failure to disclose a reference cited in a foreign search report will result in charges that the reference was intentionally concealed. Even if the allegation is defeated, litigation costs and risk will be incurred, which could be avoided by routinely disclosing all foreign search reports and their cited references.

[B] Disclosure of Experimental Details

No experiment is immune from criticism, so attacks will be made regardless of the degree of care in design and execution. The best that an applicant can do to prevent such attacks from succeeding is to make sure that there are accurate, complete and detailed descriptions of the experiment disclosed to the PTO. Actual lab notebooks or instrument readings should be disclosed when possible to minimize the ability of the patent challenger to argue that the experiment was mischaracterized or that important limitations of the method were not disclosed. While the methodology can still be subject to criticism, a detailed disclosure of the experimental methods and results gives the applicant the opportunity to argue that the examiner was aware of the methods used.

In providing descriptions of experimental methods, a prudent attorney should obtain from the scientists and disclose to the PTO the actual documentation for the experiments, printouts from instruments, lab notebook entries, and the like. It is not safe to rely on oral recollections of what was done, or on assumptions based on what is usually done. If one provides the source material, there will be less room for errors and omissions.

One need not clutter patent specifications or declarations with excess detail of experimental procedures to achieve adequate disclosure. If declarations are supplied, the detailed descriptions or actual lab notebook pages can be attached as exhibits. If the test descriptions will appear in the application's specification, the raw data and descriptions may be provided to the PTO in an Information Disclosure Statement.

[C] Disclosure of Experimental Data

To minimize exposure to charges of inequitable conduct, a prudent patent attorney should be as comprehensive as possible in his submission of data to the PTO. In this regard, a common pitfall is to focus only on data regarding the lead compound—the compound

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1193. *See* 37 C.F.R. § 1.56(a)(1) (2007).

being commercially developed—to demonstrate unexpectedly superior results as compared to prior art compounds. If the patent application contains generic claims that encompass other compounds as well, and data has been generated for those other compounds, those data should be presented as well. Otherwise, if the advantageous qualities of the other compounds were somewhat less, the patentee will end up defending against charges of fraud, even if legally baseless—that the "bad" data was intentionally withheld.

The best practice is to include all data acquired about any compound within the scope of the patent in disclosures to the PTO, whether or not one considers the information material. In this age of computer-stored records, it might be possible to gather virtually all test data on compounds that fall within the generic formulae of a compound patent. Completeness is the best defense to the argument that negative data were withheld. However, to be complete, one must make a thorough inquiry and must update all disclosures at the end of the prosecution.

[D] Care in Patent Prosecution

One who is involved in a patent prosecution must approach the task with awareness that his actions may become the target of allegations of fraud, and that he needs to create as full and strong a record as possible to defeat any such claims. Inaccuracies and mistakes will almost always be painted by the patent's adversary as false statements made with intent to deceive.

While actual fraud is no doubt rare, mistakes in patent prosecution are surprisingly common. Mistakes often result from treating patent applications like products on an assembly line that must be produced in large quantities, and from allowing scientists to read applications and declarations in a cursory manner before signing them. While negligence is not enough to support a finding of inequitable conduct, the court may look at negligence and see intent.

Having inventors read the boilerplate recitation of their duty of candor in the inventor's declaration may not be sufficient to make them aware of their duty under 37 C.F.R. § 1.56.[1194] Rather, those involved in the prosecution of a patent application must be conscious of the degree of scrutiny that their work and statements will undergo

1194. The inventors' declarations will be used as proof of their knowledge of the duty to disclose. Thus, the attorney should make sure that the inventor actually understands that duty and is not signing the declaration as a matter of rote.

by people who are motivated to accuse them of fraud or failure to disclose material information. Sensitivity to the potential consequences of material misstatements and omissions will enhance the level of care and lower the chances of an inequitable conduct finding.

§ 5:9.9 *The Legal Effect of a Finding of Inequitable Conduct*

[A] Inequitable Conduct Renders a Patent Unenforceable

A finding of inequitable conduct as to any claim in a patent (even one that is not asserted in the infringement action) renders all claims of the patent unenforceable.[1195] In fact, a finding of inequitable conduct renders the entire patent unenforceable even if it does not relate to the substance of *any* particular claim.[1196] This is contrary to the usual "claim by claim" approach to patent enforcement where the invalidity of one patent claim does not disturb the validity of other claims in the patent.[1197]

If the inequitable conduct in one patent has '"an immediate and necessary relation"' to other patents, the inequitable conduct occurring in the prosecution of one patent may render the related patents unenforceable as well, even if there were no acts of inequitable conduct in their prosecution.[1198]

[B] Inequitable Conduct May Result in Assessment of Attorneys' Fees

A finding of inequitable conduct in prosecuting a patent is also sufficient reason to hold that a case is special under 35 U.S.C. § 285 and to support the award of attorneys' fees to the infringing defendant.[1199]

1195. Impax Labs., Inc. v. Aventis Pharm. Inc., 468 F.3d 1366, 1375 (Fed. Cir. 2006).

1196. *See, e.g.*, Gen. Electro Music Corp. v. Samick Music Corp., 19 F.3d 1405 (Fed. Cir. 1994) (inequitable conduct found respecting a petition for expedited treatment of an application).

1197. *See* 35 U.S.C. § 282 (2006) ("[E]ach claim of a patent . . . shall be presumed valid independently of the validity of other claims . . . .").

1198. *See* Consol. Aluminum Corp. v. Foseco Int'l Ltd., 910 F.2d 804, 810 (Fed. Cir. 1990) (citing to Keystone Driller Co. v. Gen. Excavator Co., 290 U.S. 240, 245 (1933)).

1199. Brooks Furniture Mfg., Inc. v. Dutailier Int'l, Inc., 393 F.3d 1378, 1381 (Fed. Cir. 2005); Cambridge Prods., Ltd. v. Penn Nutrients, Inc., 962 F.2d 1048, 1050–51 (Fed. Cir. 1992).

[C] Inequitable Conduct May Have Antitrust Consequences

Losing a patent on a major pharmaceutical because of inequitable conduct potentially may cause even greater problems than the loss of exclusive rights to the drug. If inequitable conduct is found to render a pharmaceutical patent unenforceable, antitrust class action suits may follow, seeking triple damages. The theory of such cases is that the patent was obtained by fraud, and the patentee's use of the patent to prevent the sale of generic versions was therefore an illegal exclusion of competition.

To show an antitrust violation, more than inequitable conduct must be shown. There must be a showing of actual fraud on the PTO, including a showing that the patent would not have issued but for the fraud.[1200] Inequitable conduct, by contrast, can be found even if the patent would have issued had the non-disclosed information been provided to the PTO.[1201]

Notwithstanding these differences, antitrust claims will often be filed after a finding of inequitable conduct that makes a pharmaceutical patent on a marketed drug unenforceable. Because triple damages are possible in antitrust cases, and the amounts involved in major pharmaceutical cases are large, the risk of damages is great. The expense of defending such suits alone can be a major burden.

§ 5:9.10 *Procedural Aspects*

[A] Inequitable Conduct Is an Issue of Equity Decided by the Court, Not a Jury

Inequitable conduct is an equitable defense and is generally for the court to decide, not the jury.[1202] The Federal Circuit held that there is no Seventh Amendment right to a jury trial on any of the issues underlying inequitable conduct, as it is entirely a matter of equity:

> As this court held upon extensive analysis in *Gardco Mfg., Inc. v. Herst Lighting Co.*, 820 F.2d 1209, 1211–13, 2 USPQ2d 2015, 2017–19 (Fed. Cir. 1987), the decision respecting inequitable conduct is a discretionary decision to be made by the judge on his or

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1200. Walker Process Equip., Inc. v. Food Mach. & Chem. Corp., 382 U.S. 172, 177 (1965); *see also* C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1364–65 (Fed. Cir. 1998).

1201. *In re* Spalding Sports Worldwide, Inc., 203 F.3d 800, 807 (Fed. Cir. 2000); Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059, 1070 (Fed. Cir. 1998).

1202. PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1318 (Fed. Cir. 2000).

> her own factual findings. Thus, a disputed finding of intent to mislead or to deceive is one for the judge to resolve, not the jury, albeit not on summary judgment if there is a genuine dispute. A patentee has no right to a jury trial respecting the factual element of culpable intent as part of the defense of inequitable conduct. *Id.*[1203]

[B] Standard of Review

A district court's factual findings as to materiality and intent may be overturned on appeal only if clearly erroneous.[1204] The district court's weighing of the equities—its ultimate determination of whether inequitable conduct has been committed—is reviewed by the Federal Circuit under an abuse of discretion standard.[1205]

1203. Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1190 (Fed. Cir. 1993).

1204. Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 971 (Fed. Cir.), *reh'g denied*, 2006 U.S. App. LEXIS 14543 (Fed. Cir. May 31, 2006).

1205. *Id.*; *accord* Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995).

Chapter 6. Biological Deposits

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Chapter 6

Biological Deposits

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§ 6:1 Introduction

Patents must describe and enable the claimed inventions. The person of ordinary skill, however, even if provided with the best written description an inventor could hope to author, cannot always make or find the biological materials needed to practice the invention. The difficulty lies not in the skilled artisan's lack of technical competence, nor in the inventor's lack of fluency, but rather in the nature of the biological material needed to practice the invention.[1] An inventor

1. *In re* Wands, 858 F.2d 731, 735 (Fed. Cir. 1988) ("Where an invention depends on the use of living materials . . . it may be impossible to enable" the invention solely by a written disclosure); *In re* Lundak, 773 F.2d 1216, 1220 (Fed. Cir. 1985) ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *In re* Argoudelis, 434 F.2d 1390, 1392 (C.C.P.A. 1970) ("[A] unique aspect of using microorganisms as starting materials is that a sufficient description of how to obtain the microorganism from nature cannot be given.").

may find a rare microorganism that makes antibiotics but lack the ability to ever find that microorganism again. No amount of written description by the inventor will ever teach the person of ordinary skill how to practice that invention. Satisfaction of the written description, enablement or best mode requirements may be impossible despite the conception of an otherwise patentable invention. The inability of words to teach what the law commands to satisfy the patent disclosure requirements forces the inventor to choose, and the law to accept, other means.[2] Biological deposits, referred to in the patent and made available to the public by the time a patent issues, solve this problem.[3] The skilled artisan can thereby read the patent and obtain samples of the biological deposit. Then, the biological materials can be replicated by known or disclosed means once a sample is in hand.

§ 6:2 The Evolution of Biological Deposits

"For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention. This practice arose out of the development of antibiotics, when microorganisms obtained from soil samples uniquely synthesized antibiotics which could not be readily prepared chemically or otherwise."[4] "The practice of depositing biological material arose primarily to satisfy the enablement requirement of § 112, ¶ 1."[5] The practice has also been applied without controversy to best mode.[6] In 2002, the Federal Circuit vacated its prior opinion and extended the practice to written description.[7]

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2. See *supra* sections 5:4 (written description), 5:5 (enablement), and 5:6 (best mode) for a discussion of these disclosure requirements.
3. Atl. Thermoplastics Co. v. Faytex Corp., 974 F.2d 1279, 1288 n.6 (Fed. Cir. 1992) ("Accommodation of the patent law to evolving technologies is not unusual. Another example is seen in the deposit law, whereby certain biological products may be described, in compliance with section 112, simply by making a sample publicly available."); *Lundak*, 773 F.2d at 1220 n.1 (discussing deposits, the court stated: "The PTO must continue to adapt its procedures to facilitate the advance of science and technology.").
4. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1210 (Fed. Cir. 1991) (citing *Argoudelis*, 434 F.2d 1390).
5. Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 965 (Fed. Cir. 2002).
6. *See infra* section 6:3.3.
7. *Enzo*, 323 F.3d at 965 ("While deposit in a public depository most often has pertained to satisfaction of the enablement requirement, we have concluded that reference in the specification to a deposit may also satisfy the written description requirement with respect to a claimed material."); *see also infra* sections 7:6.4[B][2] & [3] (discussing Federal Circuit's decisions in *Enzo I* and *Enzo II* where it changed its opinion on the availability of deposits to satisfy written description).

The requirements for making a deposit that qualifies as disclosure under section 112 evolved over the course of several decades. The Patent Office, in the 1950s, "established the requirement that physical samples" of materials that could not be reproduced "be made available to the public, as a condition of the patent grant."[8] Then, in 1970, the Court of Customs and Patent Appeals accepted a "procedure" followed by a particular applicant and "in accordance with" the then applicable Patent Office rule.[9] That acceptable procedure included the following steps:

(1) Applicant deposits material by the filing date "in a depository affording permanence" that is accessible by the public upon issuance and to the Patent Office during pendency of the application.

(2) Patent application identifies the deposit.

(3) Applicant provides "assurance of permanent availability" of the deposited material.[10]

Five years later, the court made clear that the procedure approved in *Argoudelis* for making deposits was sufficient but not mandatory,[11] leaving open the possibility that lesser or alternative procedures could still comply with section 112. The Patent Office has since developed a detailed set of rules and regulations governing biological deposits.[12]

§ 6:3 Biological Deposits Can Satisfy Disclosure Requirements

§ 6:3.1 Written Description

A biological deposit can be used to satisfy the written description requirement.[13] "Inventions that cannot reasonably be enabled by a

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8. *Lundak*, 773 F.2d at 1220–21 (citing Levy & Wendt, *Microbiology and a Standard Format for Infra-Red Absorption Spectra in Antibiotic Patent Applications*, 37 J. PAT. OFF. SOC'Y 855 (1955)).
9. *Argoudelis*, 434 F.2d at 1393.
10. *See* Feldman v. Aunstrup, 517 F.2d 1351 (C.C.P.A. 1975) (describing procedure followed by applicant and approved by the court in *Argoudelis*).
11. *See Feldman*, 517 F.2d at 1355.
12. *See* 37 C.F.R. §§ 1.801–1.809; M.P.E.P. §§ 2401–11 (9th ed. 2014); *infra* section 6:5.
13. Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004) ("[A]s long as an applicant has disclosed a '*fully characterized* antigen,' either by its structure, formula, chemical name, or physical properties, *or by depositing the protein in a public depository*, the applicant can then claim an antibody by its binding affinity to that described antigen.") (second emphasis added); *Enzo*,

description in written form in the specification, but that otherwise meet the requirements for patent protection, may be described in surrogate form by a deposit that is incorporated by reference into the specification."[14]

§ 6:3.2 Enablement

A biological "deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. § 112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required."[15]

§ 6:3.3 Best Mode

A biological deposit can be used to satisfy the best mode requirement.[16] "To satisfy the best mode requirement, an inventor must disclose the preferred embodiment of his invention . . . ."[16.1] "[T]he best mode requirement cannot be satisfied by the deposit of a non-preferred [embodiment]."[16.2]

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323 F.3d at 965 ("[A] reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of §112, ¶ 1."); Monsanto Co. v. Scruggs, 459 F.3d 1328, 1337 (Fed. Cir. 2006) ("The written description requirement was satisfied because the '605 patent incorporates by reference deposits with the American Type Culture Center, which are publicly available.").

14. *Enzo*, 323 F.3d at 965.

15. *Amgen*, 927 F.2d at 1210; Ajinomoto Co. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1345–46 (Fed. Cir. 2000) ("The deposit of biological organisms for public availability satisfies the enablement requirement for materials that are not amenable to written description or that constitutes unique biological materials which can not be duplicated."); *Wands*, 858 F.2d at 735 ("Where an invention depends on the use of living materials . . . it may be impossible to enable the public to make the invention (*i.e.*, to obtain these living materials) solely by means of written disclosure."); *Lundak*, 773 F.2d at 1220 ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *see also supra* section 5:5.9.

16. *Ajinomoto Co.*, 228 F.3d at 1346; *see also supra* section 5:6.6.

16.1. Ajinomoto Co. v. Int'l Trade Comm'n, 597 F.3d 1267, 1272 (Fed. Cir. 2010).

16.2. *Id*. at 1276 (finding that the patentee failed to satisfy the best mode requirement where the inventors' deposit was not the preferred embodiment).

§ 6:4 Biological Deposits Not Required If Disclosure Otherwise Adequate

If the disclosure is otherwise adequate, the applicant need not provide a biological deposit merely because it would be easier for the skilled artisan.[17] Nor is a deposit necessary simply because it is the only way to practice the invention in the exact same way as the inventor.[18] The mere fact that a patent contains a reference to a biological deposit does not constitute an admission that the deposit is needed to satisfy section 112.[19]

§ 6:5 Making and Maintaining Biological Deposits

Regulations specify how to make an acceptable biological deposit for purposes of patentability.[20] If an applicant relies on a deposit to satisfy a disclosure requirement, the patentee, according to the Patent Office, "takes the risk that the material may cease to be known and readily available. Such a defect cannot be cured by reissue after the grant of a patent."[21]

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17. Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1579 (Fed. Cir. 1991) (rejecting argument "that because of the laborious nature of the process of screening monoclonal antibodies, the inventors should have voluntarily placed in a depository and made available to the public the antibody . . . used by Scripps in carrying out the claimed invention"); *Amgen*, 927 F.2d at 1211 ("when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells"); *Feldman*, 517 F.2d at 1354 ("No problem exists when the microorganisms used are known and readily available to the public."); *Ex parte* Rinehart, 10 U.S.P.Q.2d (BNA) 1719 (B.P.A.I. 1989) (describing precise location of marine tunicates needed to practice claim satisfied enablement); 37 C.F.R. § 1.802(b) (no deposit needed if biological material "is known and readily available to the public or can be made or isolated without undue experimentation"); *cf. Ex parte* Humphreys, 24 U.S.P.Q.2d (BNA) 1255, 1258–59 (B.P.A.I. 1992) (biological deposit required because plasmids developed through UV mutagenesis of publicly available bacteria could not be made without undue experimentation).
18. *Amgen*, 927 F.2d at 1212 (rejecting argument that skilled artisans "were unable to duplicate" exactly the patentee's best mode cell strain where example 10 of the patent disclosed taught how to prepare a similar strain because "the issue is whether the disclosure is 'adequate,' not that an exact duplication is necessary").
19. 37 C.F.R. § 1.802(c) ("The reference to a biological material in a specification disclosure or the actual deposit of such material by an applicant or patent owner does not create any presumption that such material is necessary to satisfy 35 U.S.C. [§] 112 or that deposit in accordance with these regulations is or was required.").
20. 37 C.F.R. § 1.803; *see also supra* section 5:5.9.
21. M.P.E.P. § 2404.01.

Biological deposits raise several timing issues such as when must the material be deposited, when must it be available to the Patent Office and the public, and how long must it be made available. The following table sets forth answers:

Event	Time
Placing material in acceptable depository[22]	Upon patent issuance[23]
Willingness and ability to provide Patent Office a sample upon request	As of the filing date[24]

22. Regulations specify when and how replacement or supplementation can be accomplished without losing the deposit as a basis for satisfying the disclosure requirements. *See* 37 C.F.R. § 1.805. A private or foreign depository can be used. *See Feldman*, 517 F.2d at 1356 ("[W]e find no merit in Feldman's argument that Aunstrup's deposit was inadequate per se because CBS was a private institution in 1966."); 37 C.F.R. § 1.803(a)(2), (b) (setting forth requirements for "any other depository recognized to be suitable"); M.P.E.P. § 2405 (listing approved depositories; identity of newly recognized depositories "will be announced in the *Official Gazette*" of the PTO).

23. *Lundak*, 773 F.2d at 1222 ("§ 112, first paragraph, does not require the transfer of a sample of the invention to an independent depository prior to the filing date of the patent application."; "Lundak's deposit in his laboratory or in the laboratories of colleagues suffices to meet the requirements of 35 U.S.C. §§ 112 and 114 as they apply to pending patent applications."); *Feldman*, 517 F.2d at 1355 (enablement requires "assurance of access (to the micro-organism culture by the public upon issuance of a patent on the application) prior to *or during the pendency* of the application, so that, upon issuance of a patent on the application, 'the public will, in fact, receive something in return for the patent grant'") (emphasis added); 37 C.F.R. § 1.804(a) ("Whenever a biological material is specifically identified in an application for patent as filed, an original deposit thereof may be made at any time before filing the application for patent or, subject to Sec. 1.809, during pendency of the application for patent."); *cf.* M.P.E.P. § 2406.03 ("[W]hile the deposit of a biological material subsequent to the effective filing date of a United States application is sufficient to comply with 35 U.S.C. [§] 112, an applicant may not be able to rely on the filing date of such a U.S. application if a patent is sought in certain countries foreign to the United States.").

24. *See Lundak*, 773 F.2d at 1222 ("requirement that the deposited culture be available to the PTO during the pendency of the patent application is . . . satisfied by compliance with a request from the PTO to the applicant" even if the applicant maintains possession of the material "in his laboratory").

Event	Time
Making deposit available to the public[25]	Upon patent issuance[26]
Including reference to deposit in specification	Prior to issuance[27]
Length of time deposit must be available to public	>"30 years" >"5 years after the most recent request" and >"enforceable life of the patent"[28]

25. A properly made deposit does not become defective merely because its availability is subject to legal restrictions "imposed for safety, public health or similar reasons." 37 C.F.R. § 1.802; *see also* 37 C.F.R. § 1.808 (specifying what restrictions patentee may or may not place on access to the deposit).
26. *See* note 22, *supra*.
27. *See Lundak*, 773 F.2d at 1223 ("the insertion of depository data after filing is not new matter under 35 U.S.C. § 132").
28. 37 C.F.R. § 1.806. Regulations also specify how to provide an assurance that the deposit be "viable" during the term of the deposit. *See* 37 C.F.R. § 1.807.

Chapter 7. Types of Biological and Pharmaceutical Patents

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Chapter 7

Types of Biological and Pharmaceutical Patents

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§ 7:1 Research Tools*

Modern medical science yields thousands of new treatments for disease and injury. The Patent Act places few restrictions on the types of subject matter that can be patented, so long as the patentability requirements are satisfied.[1] An inventor may obtain a patent, according to the statute, for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" upon satisfying the requirements for patentability.[2] The patent statute does not generally define different types or categories of patents for any area of technology, including pharmaceuticals.

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* Written by Aaron Stiefel and Daniel L. Reisner.

1. See *supra* chapters 3, 4, and 5 for a description of the utility, inventorship, and other patentability requirements.
2. 35 U.S.C. § 101.

Nevertheless, it is both useful and common for the practitioner to place a biological or pharmaceutical patent of interest within one or more categories when analyzing legal and practical issues associated with these patents.

This chapter identifies several commercially significant categories of patentable subject matter and explores recurring legal issues associated with each of these categories. The purpose behind establishing these analytical categories is to help the practitioner think about the problems and opportunities presented by various types of patent claims, and provide a convenient means to organize the body of pharmaceutical and biotechnology patent law.

Each section begins with an explanation of a type of biological or pharmaceutical patent followed by sample claims and then various issues relevant to that category of patent rights. The categories are by no means exclusive. Many patent claims can easily fall within multiple categories. For example, a screening assay employing a nucleic acid sequence-based probe could be a research tool, medical diagnostic and a nucleic acid sequence patent. It may therefore be necessary to consult several sections when considering any particular biological or pharmaceutical patent.

§ 7:1.1 What Is a Research Tool Patent?

Traditionally, in seeking patent protection, drug researchers focused exclusively on patenting their drug discoveries. More recently, though, researchers have become aware that there may be value in obtaining patents covering the many innovative technological tools that are used in the process of finding new treatments. Such patents are commonly referred to as "research tool patents."

Research tool patents have far-reaching effects on the development of new medical treatments. They permit the marketplace to marry the inventions of basic researchers to the resources and skills of powerhouse drug developers. Academics who invent research tools can license patents on those tools to drug makers. Research tool patents may thus spur drug discovery research by making powerful new research tools widely available. On the other hand, research tool patents risk chilling drug discovery efforts given the difficulty and expense of obtaining necessary licenses.

The term "research tool" has appeared in the case law and in the literature.[3] According to the National Institutes of Health, research tools are "tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors,

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3. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 205 n.7 (2005); *In re* Fisher, 421 F.3d 1365, 1373 (Fed. Cir. 2005).

combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines."[4] The U.S. Supreme Court has distinguished between conducting research on a patented composition (not using a research tool) and using a patented composition to conduct research on something else (using a research tool).[5] The term "research tool" is descriptive, not determinative. In other words, labeling an invention a research tool does not determine patentability or the scope of any resulting claims.[6] Nevertheless, the term is useful in considering a variety of issues common to such patents.

Research tool patents come in many forms. They may cover anything from a new microscope to a cellular receptor that holds promise as a drug target. Thus, research tool patents cover, inter alia, methods for making cDNA libraries and gDNA libraries; machines used for synthesizing compounds; high throughput screening methods; immunological assays; and receptor and enzyme activity assays.

§ 7:1.2 Utility Requirement for Patenting Research Tools

Patents covering research tools must satisfy the patentability requirements common to all patents.[7] However, the utility requirement, as applied to research tool patents, deserves special attention.[8]

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4. Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, 64 Fed. Reg. 72,090, 72,092 n.1 (Dec. 23, 1999) (cited by Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 872 n.4 (Fed. Cir. 2003), *vacated on other grounds*, 545 U.S. 193 (2005); and by Integra Lifesciences I, Ltd. v. Merck KGaA, 496 F.3d 1334 (Fed. Cir. 2007)).
5. *Merck KGaA*, 545 U.S. at 205 n.7 ("Use of an existing tool in one's research is quite different from study of the tool itself.") (quoting 331 F.3d at 878 (Newman, J., dissenting)).
6. U.S. PATENT & TRADEMARK OFFICE, U.S. DEP'T OF COMMERCE, 2 MANUAL OF PATENT EXAMINING PROCEDURE § 2107.01 (8th ed. 2006) (hereinafter "M.P.E.P.") ("Labels such as 'research tool' . . . are not helpful in determining if an applicant has identified a specific and substantial utility for the invention."); *Integra Lifesciences*, 331 F.3d at 872 n.4 ("Regardless of whether one considers the RGD peptides to assume the label of a 'research tool,' the points discussed in relation to determining the value of the peptides during a hypothetical negotiation [for establishing a reasonable royalty] are valid.").
7. See *supra* chapters 3, 4 and 5 for a description of the patentability requirements. See *infra* sections 7:6 and 7:7 for research tools involving nucleic acid sequences or antibodies.
8. See *supra* chapter 3 for a general description of the utility requirement.

Although the threshold for utility is not high,[9] some research tools do not meet this requirement.

To satisfy the utility requirement a claimed invention must yield a "specific benefit . . . in currently available form."[10] The mere fact that an invention "may prove useful at some future date after further research" is not sufficient.[11] Nor does the mere fact that an invention is a research tool necessarily establish patentable utility.[12] A research tool, to be patentable, must enable the discovery of something of immediate value. The Patent and Trademark Office (PTO) distinguishes "between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm."[13]

A microscope, for example, inherently has sufficient utility because it "has the specific benefit of optically magnifying an object to immediately reveal its structure."[14] A microscope "can offer an immediate, real world benefit in a variety of applications."[15] The utility of the microscope thus extends far beyond the benefits that can be derived from magnifying any one sample.

On the other hand, a nucleic acid sequence that encodes a partial protein of unknown function does not have utility. Such a sequence, known as an expressed sequence tag (EST), "can only be used to detect the presence of genetic material having the same structure as the EST itself" without providing "any information about the overall structure let alone the function of the underlying gene."[16] Absent identification of "the function for the underlying protein-encoding genes," the claimed sequence has not been "researched and understood to the point of providing an immediate, well-defined, real world benefit to the public meriting the grant of a patent."[17]

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9. Juicy Whip, Inc. v. Orange Bang, Inc., 185 F.3d 1364, 1366 (Fed. Cir. 1999).
10. Brenner v. Manson, 383 U.S. 519, 534–35 (1966).
11. *In re* Fisher, 421 F.3d 1365, 1371 (Fed. Cir. 2005).
12. *See supra* note 6 and accompanying text.
13. *Fisher*, 421 F.3d at 1372 (quoting M.P.E.P. § 2107.01).
14. *Id*. at 1373; *see also* M.P.E.P. § 2107.01 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (for example, they are useful in analyzing compounds).").
15. *Fisher*, 421 F.3d at 1373.
16. *Id*.
17. *Id*. at 1376 ("The claimed ESTs themselves are not an end of Fisher's research effort, but only tools to be used along the way in the search for a practical utility.").

§ 7:1.3 Research Tools Used to Obtain Data for FDA Submissions: Section 271(e)(1)

Section 271(e)(1) of title 35 of the U.S. Code establishes a safe harbor protecting otherwise infringing conduct directed to developing information for federal agencies, such as the FDA, that regulate pharmaceutical drugs.[18] In many cases, an infringer seeks to test a patented composition to develop data for FDA approval to market that composition as a drug product. Section 271(e)(1) shelters such pre-marketing conduct from infringement. Consequently, a generic version of a patented drug can be developed and tested while the patent is in effect so that the drug is ready for marketing upon patent expiration.

What happens, however, when, instead of testing a patented composition to seek FDA approval for that composition, a drug developer uses a patented research tool in discovering or developing a drug that requires FDA approval?[19] Does section 271(e)(1) create a safe harbor that permits infringement of research tool patents when used to develop information for the FDA even though the tools are not themselves subject to FDA approval? Does section 271(e)(1) render inventions whose only use is in conducting research relating to drug development of no commercial value to the patentee because such patents can be infringed by researchers with impunity?[20]

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18. Section 271(e)(1) states:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

See *infra* section 8:1.8 for a more general description of 35 U.S.C. § 271(e)(1).

19. The Supreme Court has held that the "phrase 'patented invention' in § 271(e)(1) is defined to include all inventions, not drug-related inventions alone." Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 665 (1990). The Court, though, was not considering the applicability of the statute to research tool patents.

20. The Federal Circuit cautioned that a broad reading of section 271(e)(1) would "effectively vitiate the exclusive rights of patentees owning biotechnology tool patents." Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 867 (Fed. Cir. 2003), *vacated on other grounds*, 545 U.S. 193 (2005). The Supreme Court stated that "[t]he Court of Appeals also suggested that a limited construction of § 271(e)(1) is necessary to avoid depriving so-called 'research tools' of the complete value of their patents." *Id*. at 205 n.7. Because patented tools often facilitate both "general research to identify candidate drugs" as well as "downstream safety-related

The Supreme Court, in interpreting section 271(e)(1) in a case involving pre-clinical research on a patented product, specifically did not "express a view about whether, or to what extent, section 271(e)(1) exempts from infringement the use of 'research tools' in the development of information for the regulatory process."[21] On remand to the Federal Circuit, the court expressly avoided considering the issue of research tools, stating the issue "is outside the Supreme Court's mandate" and rejecting the dissent's argument that its decision casts a "'large shadow' on the subject of 'research tools.'"[22]

Subsequently, the Federal Circuit did address the applicability of section 271(e)(1) to research tool patents in two contradictory decisions.

In *Proveris Scientific Corp. v. Innovasystems, Inc.*,[23] the Federal Circuit addressed whether the safe harbor of section 271(e)(1) would protect the manufacture and sale of a patented device, which was not subject to FDA approval, used to generate test data required for FDA review of drug products. Proveris alleged that an Optical Spray Analyzer made and sold by Innova infringed a Proveris patent. Innova argued that its activities were immunized by section 271(e)(1) because the Analyzer was used by third parties solely to develop test data in support of applications for FDA approval of aerosol drugs. The Federal Circuit held that because the Analyzer was "not subject to FDA premarket approval, and therefore faces no regulatory barriers to market entry upon patent expiration, Innova is not a party who, prior to enactment of the Hatch-Waxman Act, could be said to have been adversely affected" by the "*de facto* extension of effective patent life at the end of the patent term [resulting] from FDA premarket approval requirements."[24] The court stated: "For this reason, we do not think Congress could have intended that the safe harbor of Section 271(e)(1) apply to [the Innova Analyzer]."[25]

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experiments on those new drugs," and because the "downstream clinical testing for FDA approval" would be exempt under section 271(e)(1), the Federal Circuit expressed concern that "these patented tools would only supply some commercial benefit to the inventor when applied to general research." 331 F.3d at 867. The court's view was that an expansive reading of section 271(e)(1) to encompass general research activities "would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions." *Id*.

21. *Merck KGaA*, 545 U.S. at 205 n.7.
22. Integra Lifesciences I, Ltd. v. Merck KGaA, 496 F.3d 1334, 1348 (Fed. Cir. 2007).
23. Proveris Sci. Corp. v. Innovasystems, Inc., 536 F.3d 1256 (Fed. Cir. 2008).
24. *Id*. at 1265.
25. *Id.; see also* Infigen, Inc. v. Advanced Cell Tech., Inc., 65 F. Supp. 2d 967 (W.D. Wis. 1999) (holding that section 271(e)(1) did not apply to the

Ignoring entirely the court's earlier *Proveris* decision, the Federal Circuit in *Momenta* held that use of a patent relating to methods of analyzing enoxaparin fell within the safe harbor.[26] The court held that post-approval testing of enoxaparin was protected under section 271(e)(1) because the FDA required the manufacturer to perform these tests and maintain records for the continued approval of its ANDA.[27]

§ 7:1.4 Off-Shore Development Work: Section 271(f) and (g)

Drug discovery often involves testing candidate compounds for a desired activity in one or more screening assays. Screening assays may be patented research tools. In an effort to avoid infringing those U.S. patents, some drug developers based in the United States have chosen to conduct aspects of their basic drug discovery work abroad. When screening compounds for activity using the patented assay of another, a U.S. drug maker may send the candidate compounds to a foreign country in which the assay is not patented. The screening assay is then used to identify compounds that exhibit the desired activity. The results of the assay are sent to the United States to be used in developing one or more of the candidate compounds into a new drug.

Section 271(f) and (g) of the patent statute were enacted to prevent companies from avoiding infringement by moving certain portions of their activities overseas. Under those provisions, the foreign activity, when combined with activity in the United States, may still constitute an infringement of U.S. patents.[32]

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use of a patented process for activating bovine oocytes (egg cells) for use in cloning, even though the accused infringers' ultimate goal was to produce genetically altered milk that would require FDA approval—explaining that "§ 271(e)(1) is to be read in conjunction with § 156"); *cf.* Bristol-Myers Squibb Co. v. Rhône Poulenc Rorer, S.A., 2001 WL 1512597 (S.D.N.Y. Nov. 28, 2001) (rejecting argument that patented intermediates used by BMS in designing drug candidates were not "patented invention[s]" within the meaning of section 271(e)(1) because the intermediates were not themselves drug products and granting summary judgment of noninfringement).

26. Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348, 1351 (Fed. Cir. 2012).
27. *Id*. at 1357–58.
28.–31. [Reserved.]
32. 35 U.S.C. § 271(f) & (g).

[A] Section 271(f)

[A][1] The Statute

Exporting from the United States the unassembled components of a patented invention covered for assembly outside of the United States may constitute infringement under 35 U.S.C. § 271(f), which provides:

> (1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.
>
> (2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.[33]

[A][2] Legislative History

Congress enacted section 271(f) in 1984 in response to a Supreme Court decision, *Deepsouth Packing Co. v. Laitram Corp.*[34] The accused infringer exported unassembled equipment to its foreign customers who could assemble a patented machine in under an hour.[35] The Supreme Court held that defendant's exporting scheme did not infringe because "[t]he statute makes it clear that it is not an infringement to make or use a patented product outside of the United States," and that "a combination patent can be infringed only by combination."[36] Congress, therefore, enacted section 271(f) to ensure that "when components are supplied for assembly abroad to circumvent a

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33. 35 U.S.C. § 271(f).
34. Deepsouth Packing Co. v. Laitram Corp., 406 U.S. 518 (1972); *see also* 130 Cong. Rec. H10525 ¶ 3 (Oct. 1, 1984); S. REP. NO. 98-663, at 2–3 (1984).
35. *Deepsouth Packing*, 406 U.S. at 523.
36. *Id*. at 527, 532.

patent, the situation will be treated the same as when the invention is 'made' or 'sold' in the United States."[37]

[A][3] Applying Section 271(f) to Research Tools

Section 271(f) thus covers the export of the "components of a patented invention" for "combination" abroad where the combination within the United States would be infringing. This provision apparently would not reach the export of compounds for testing outside of the United States using a research tool patented in the United States.

In *Union Carbide Chemicals & Plastics Technology Corp. v. Shell Oil Co.*,[38] though, the Federal Circuit held that when section 271(f) speaks of "the components of a patented invention," the statute encompasses components used in "method/process inventions."[39] At issue was a Union Carbide patent claim to an improved process for manufacturing ethylene oxide. The court held that section 271(f) "applies to Shell's exportation of catalysts (*i.e.*, a 'component') used in the commercial production of [ethylene oxide] abroad (*i.e.*, a 'patented invention')."[40]

[B] Section 271(g)

[B][1] The Statute

Importing into the United States products that are made abroad by a process claimed in a U.S. patent may constitute infringement under section 271(g), which provides:

> Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. . . . A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—

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37. S. REP. NO. 98-663, at 3 (1984).
38. Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co., 425 F.3d 1366 (Fed. Cir. 2005).
39. *Id*. at 1380.
40. *Id*. at 1379. A petition for rehearing the *Union Carbide* case, en banc, was denied. 434 F.3d 1357 (Fed. Cir. 2006). However, in a dissent that was joined by Judges Michel and Linn, Judge Lourie argued that "the whole tenor of [§ 271(f)] relates to physical inventions, *i.e.*, apparatus or compositions, not methods." Judge Lourie took the position that the *Union Carbide* decision was contrary to the Federal Circuit decisions in NTP, Inc. v. Research in Motion Ltd., 418 F.3d 1282 (Fed. Cir. 2005), and Standard Havens Prods., Inc. v. Gencor Indies, Inc., 953 F.2d 1360 (Fed. Cir. 1991). *See* 434 F.3d at 1358–59 (Lourie, J., dissenting).

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product.[41]

[B][2] Legislative History

The legislative history indicates that section 271(g) was intended "to provide protection to owners of United States process patents against foreign manufacturers who would use the processes outside the United States to make products that are then imported, used or sold in the United States."[42] "Congress was concerned with methods of manufacture and with manufactured goods destined to travel in the stream of commerce."[43]

[B][3] Applying Section 271(g) to Research Tools

In *Bayer AG v. Housey Pharmaceuticals, Inc.*,[44] the Federal Circuit addressed whether the importing into the United States of research results, which are generated abroad using a research tool that is patented in the United States, constitutes infringement under section 271(g). At issue were patents directed to methods of screening for substances that specifically inhibit or activate a particular protein. Housey claimed that both the importation of a pharmaceutical composition identified outside the United States by a patented process and the importation of information generated outside the United States by the patented process infringed under section 271(g).

The Federal Circuit rejected Housey's arguments that (1) the information produced by Bayer using the patented process was a "product which is made" by that process per section 271(g); and (2) that a pharmaceutical composition determined by Bayer to be an inhibitor or activator of a target protein using the patented process infringed under section 271(g).[45] As to the first argument, the court held that "in order for a product to have been 'made by a process patented in the United States' it must have been a physical article that was 'manufactured' and that the production of information is not covered."[46] As to the second argument, the court held that "the process must be

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41. 35 U.S.C. § 271(g).
42. British Telecomms. v. SBC Commc'ns, Inc., 2004 U.S. Dist. LEXIS 29772, at *8 (D. Del. Feb. 24, 2004).
43. *Id*.
44. Bayer AG v. Housey Pharm., Inc., 340 F.3d 1367 (Fed. Cir. 2003).
45. *Id*. at 1377–78.
46. *Id*. at 1377.

used directly in the manufacture of the product, and not merely as a predicate process to identify the product to be manufactured."[47]

In *NTP, Inc. v. Research in Motion, Ltd.*,[48] the Federal Circuit addressed section 271(g) in the context of claims directed to methods for the transmission of information in the form of email messages. The court held that "[b]ecause the 'transmission of information,' like the 'production of information,' does not entail the manufacturing of a physical product, section 271(g) does not apply to the asserted method claims in this case any more than it did in *Bayer*."[49] The court rejected the notion "that the transformation of data and the manipulation of addresses qualify the asserted processes for section 271(g) protection."[50] The court stated that "section 271(g) does not cover every patented process and its purported result."[51]

The Federal Circuit, in *Momenta Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*,[51.1] held that post-approval testing of enoxaparin batches did not satisfy the "made" requirement in section 271(g) because, although "[b]ased on the test performed on [a] sample, an enoxaparin batch from which the samples were extracted may be selected for incorporation into the finished product," the enoxaparin samples were not incorporated into the finished product, they were not imported into the United States and the tests did not "create or give new properties to the enoxaparin substance in batches that are selected for further processing."

§ 7:2 Patentability of Chemical Compounds*

The foundation for most pharmaceutical products is the active pharmaceutical ingredient (API). Since pharmaceutical research is often first directed to the discovery and identification of lead compounds for development and testing, patent applications claiming chemical compounds are usually the first applications to be filed for a drug product. Patents covering the active molecule for a drug product are generally among the most valuable and most difficult to design around.

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47. *Id*. at 1378; *see also* Classen Immunotherapies, Inc. v. King Pharm., Inc., 403 F. Supp. 2d 451, 455 (D. Md. 2005) (absent "evidence that Skelaxin is manufactured using a method patented by Classen . . . Classen's claim for patent infringement under § 271(g) fails for lack of evidence").
48. NTP, Inc. v. Research in Motion, Ltd., 418 F.3d 1282 (Fed. Cir. 2005).
49. *Id*. at 1323.
50. *Id*. at 1324.
51. *Id*.
51.1. Momenta Pharm., Inc. v. Teva Pharm. USA, Inc., 809 F.3d 610, 616–17 (Fed. Cir. 2015).

* Written by David K. Barr.

This section focuses on the principles governing the patentability of chemical compounds and compositions of matter in terms of satisfying the novelty and nonobviousness requirements of 35 U.S.C. §§ 102 and 103. Over time, courts created standards for determining the patentability of these chemical entities based on more general principles.[52] The standards that have evolved apply to small molecules as well as to nucleic acids, genes, and proteins.[53] The primary focus of this section is directed to small molecules. Nucleic acids and proteins are discussed in section 7:6, and antibodies are discussed in section 7:7.

As with all inventions, to be patentable, claims to chemical compounds must satisfy the statutory requirements of utility, novelty, and nonobviousness, and must be supported by a disclosure meeting the requirements of section 112.[54]

§ 7:2.1 Novelty of a Claim to a Chemical Compound Over the Prior Art: The Requirement That an Anticipating Reference Be Enabling

A claim to a specific chemical compound is rendered non-novel (that is, "anticipated") by a prior art description of that compound as long as the prior art enables one skilled in the art to make the compound.[55] Therefore, the mere depiction or naming in a prior art

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52. *In re* Mayne, 104 F.3d 1339, 1342 (Fed. Cir. 1997) ("Standards for the patenting of chemical entities have evolved.").

53. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it."); Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229 (Fed. Cir. 1994) ("DNA encoding a human protein [is] a chemical compound."); *see also* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 925 (Fed. Cir. 2004) (with respect to written description requirement of 35 U.S.C. § 112, the distinction between genetic and non-genetic materials is "irrelevant; the statute applies to all types of inventions").

54. *See* 35 U.S.C. §§ 102, 103. The general concepts of novelty and nonobviousness are discussed in *supra* sections 5:3 and 5:2. Chapter 3 covers the showing of utility needed to patent chemical entities. Sections 7:2.1 and 7:2.2, *infra*, cover whether a chemical compound or composition claim is novel and nonobvious. Section 7:2.3[C], *infra*, covers the written description required to support chemical entities. Enablement is covered more generally in *supra* section 5:5.

55. *In re* Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the

reference of a claimed compound will not anticipate unless it can also be shown that, based on the teachings of the prior art, one skilled in the art would have been able to make the compound without undue experimentation.[56] Accordingly, a prior art reference describing a claimed compound will anticipate if it also describes a method of making the claimed compound, or if a method of making the claimed compound is otherwise available to one of ordinary skill in the art.[57]

The enablement requirement for anticipation can be satisfied by the description of a process in a different prior art reference from the prior art reference that describes the compound at issue.[58] The requirement that an anticipatory reference be enabling is necessary to show that the prior art placed the public "in possession" of the claimed subject matter. Recourse to an additional prior art reference to demonstrate that the public was "in possession" of the invention does not shift the basis for unpatentability from anticipation to obviousness.[59]

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publication's description of the invention with his own knowledge to make the claimed invention.") (citations omitted).

56. Forest Labs., Inc. v. Ivax Pharm., Inc., 501 F.3d 1263, 1268 (Fed. Cir. 2007) (no anticipation because paper did "not enable the preparation of the (+)-enantiomer of citalopram"); *In re* Wiggins, 488 F.2d 538, 542–43 (C.C.P.A. 1973) (prior art reference naming of compounds "whose syntheses were unsuccessfully attempted" did not anticipate later claim to compounds).

57. *Donohue*, 766 F.2d at 533. Under *Donohue*, "[i]t is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement." The *Donohue* court distinguished *Wiggins*, in which no anticipation was found because in that case the prior art reference reported a *failure* to make the claimed compound: "Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling. By contrast, the fact that the author of a publication did not attempt to make his disclosed invention does not indicate one way or the other whether the publication would have been enabling." *Id. See also In re* Coker, 463 F.2d 1344, 1347–48 (C.C.P.A. 1972) (no anticipation when prior art reference naming the claimed compound described an unsuccessful attempt to make it, notwithstanding that the applicant used that same method to make the compound; the prior art "direct[ed] the public *away* from the only" way to make the compound by reporting that the method "*has not been successful*").

58. *In re* Sasse, 629 F.2d 675, 681 (C.C.P.A. 1980) (enablement of prior art compound described in one reference established in another reference describing method for making a required precursor compound).

59. *In re* Samour, 571 F.2d 559, 563 (C.C.P.A. 1978) ("Additional references cited in a rejection under 35 U.S.C. § 102(b) are not relied on for a suggestion or incentive to combine teachings to meet claim limitations (as in a rejection under 35 U.S.C. § 103), but, rather, to show that the

The additional prior art reference used to show enablement can be dated after the primary reference describing the chemical structure.[60] In other words, one can demonstrate anticipation of a claimed chemical compound with a prior art description of the compound and a subsequently dated prior art reference describing a method of making the compound as long as all of the information necessary to enable making the compound was in the prior art.[61]

§ 7:2.2 *Obviousness of a Claim to a Chemical Entity and the Impact of the Supreme Court's Decision in* KSR

Claims to novel chemical entities can still be challenged as obvious in view of the combined teachings of the prior art pursuant to section 103 of title 35. An obviousness challenge to a claimed compound is typically based on similarities between its chemical structure and the structures of prior art compounds.[62] The Federal Circuit has developed a body of case law holding that obviousness of a chemical compound is to be predicated on a showing that one skilled in the art would have been "motivated" to have made the changes to a prior art compound necessary to arrive at the claimed compound.[63] Under Federal Circuit authority, the motivation can be an expectation that the claimed compound will have useful properties similar to the prior art compound.[64] Numerous cases, however, observe that

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claimed subject matter, every material element of which is disclosed in the primary reference, was in possession of the public.").

60. *Id*. ("The critical issue under 35 U.S.C. § 102(b) is whether the claimed subject matter was in possession of the public more than one year prior to applicant's filing date, not whether the evidence showing such possession came before or after the date of the primary reference.").

61. See *infra* section 7:2.3[A] for a discussion of anticipation of a chemical genus by a prior art species and a chemical species by a prior art genus.

62. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 2001 WL 1397304, at *4 (S.D. Ind. Oct. 29, 2001) ("Chemical compounds present special issues of obviousness because of the limited number of elements, recurring groups or substituents in complex molecules, the structural similarities within classes of related compounds, and the ability of chemists to undertake systematic experiments modifying known compounds.").

63. *E.g.*, Yamanouchi Pharm. Co. v. Danbury Pharmacal Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) ("For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'") (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)).

64. *See Dillon*, 919 F.2d at 693 (holding that a prima facie case of obviousness can be made out if the prior art "provided the motivation to make the claimed compositions in the expectation that they would have

even small changes in chemical structure frequently result in unpredictable changes in biological activity.[65] Ultimately, the degree of predictability in any case depends on the skill and the teachings in the relevant prior art.

Accordingly, cases deciding the obviousness of a chemical entity have generally involved a comparison between (1) the structure and the activity of the claimed compound (or composition of matter), and (2) the structures and activities of prior art compounds and evidence of motivation to modify the prior art to achieve the claimed compound.[65.1] Over time, the Federal Circuit had articulated a test for obviousness that required a finding of a "teaching, suggestion, or motivation" to combine prior art teaching or to otherwise modify the prior

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similar properties"). For a detailed discussion of *Dillon*, see *infra* section 7:2.2[A][2][a] and 7:2.2[A][4][a].

65. Fujikawa v. Wattanasin, 93 F.3d 1559, 1564 (Fed. Cir. 1996) ("It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility."); *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) ("The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results."); *In re* Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995) ("minor changes in chemical compounds can radically alter their effects on the human body"); Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 943 (Fed. Cir. 1992) ("In the 1950s and early 1960s, when these compounds were being developed, one could not predict the effect of small structural changes on the biological activity of steroid hormones. Given the structure and properties of the components claimed in '081 and '909, there would have been no suggestion in the art (and, hence, it would not have been obvious) to modify those structures in order to achieve the compounds of '322 claims 5, 19, 40, and 43 having properties similar to those of '081 and '909") (citation omitted); *Eli Lilly*, 2001 WL 1397304, at *5 ("The unpredictable nature of chemical reactions is especially pronounced, of course, when dealing with medicinal chemistry, where the biological effects of chemical reactions may be exceedingly difficult to predict from the chemical structure of a compound.").

65.1. *See* Amgen v. Sandoz, 66 F.4th 952 (Fed. Cir. 2023) (affirming the district court's decision that Sandoz had failed to prove by clear and convincing evidence that claims 3 and 6 of the '638 patent were obvious over the cited prior art, because (1) there was no motivation for a skilled artisan to isolate apremilast from the racemic mixture, as the prior art taught away from thalidomide analogues due to safety concerns; and (2) there was no reasonable expectation of success in resolving the racemic mixture into its enantiomers, as the process was unpredictable and lacked specific guidance in the prior art).

art to achieve the claimed invention.[66] When this "TSM" test is met, the Federal Circuit stated that the claimed invention is "prima facie" obvious, requiring the patent owner or applicant to come forward with rebuttal evidence of nonobviousness.[67]

However, in *KSR International Co. v. Teleflex Inc.*,[68] the Supreme Court rejected what it called the Federal Circuit's "rigid approach" in its TSM test for obviousness.[69] *KSR* involved a patent claim directed to a mechanical invention, which was an automobile pedal assembly that combined an electronic sensor with an adjustable automobile pedal. The Federal Circuit had reversed a district court's grant of summary judgment that the claimed invention was obvious, concluding that the district court had improperly applied the TSM test. On certiorari, the Supreme Court reversed the Federal Circuit's decision.

While the Supreme Court acknowledged that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does,"[70] it held that a "rigid and mandatory" application of the TSM test "is incompatible with [its] precedents."[71] The Supreme Court admonished that "[g]ranting patent protection to

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66. *See* Teleflex, Inc. v. KSR Int'l, 119 F. App'x 282, 285 (Fed. Cir. 2005), *rev'd*, KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007) (citing Tec Air, Inc. v. Denso Mfg. Mich. Inc., 192 F.3d 1353, 1359–60 (Fed. Cir. 1999) and Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573 (Fed. Cir. 1996)).

67. *Teleflex*, 119 F. App'x at 285 (citing WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999)). The establishment of prima facie obviousness for chemical compounds and the rebuttal of a prima facie case are discussed in *infra* section 7:2.2[A] and [B].

68. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

69. *Id*. at 1739–41.

70. *Id*. at 1741. Similarly, the Supreme Court stated that "[o]ften, it will be necessary for a court to look at interrelated teachings of multiple patents; the effects of demands known in the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id*.

71. *Id*. Among its prior cases, the Court discussed its seminal decision on obviousness in Graham v. John Deere, 383 U.S. 1 (1966). (See *supra* section 5:3 for a general discussion of the law of obviousness.) The Supreme Court concluded that "[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs." *KSR*, 127 S. Ct. at 1741.

advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility."[72] Thus, the Supreme Court stated that "[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability."[73]

The Supreme Court criticized the Federal Circuit for "look[ing] only to the problem the patentee was trying to solve," because "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed."[74] Moreover, the Supreme Court held that the Federal Circuit erred in concluding that "a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'"[75] On the contrary, the Supreme Court held:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.[76]

The Court in *KSR* concluded by stating that "as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws."[77]

While the invention at issue in *KSR* was a mechanical apparatus, the Supreme Court's decision is generally applicable to the obviousness

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72. *KSR*, 127 S. Ct. at 1741.
73. *Id*. at 1740. In reviewing its precedent, the Supreme Court in *KSR* restated its "earlier instructions," which pre-dated the enactment of 35 U.S.C. § 103 and its *Graham* decision, "concerning the need for caution in granting a patent based on the combination of elements found in the prior art." *Id*. at 1739. Thus, the Supreme Court admonished that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id*. It remains to be seen how this principle will be applied post-*KSR* in the chemical and biotech fields in which the effects of changes to chemical compounds are generally considered to be unpredictable.
74. *Id*. at 1742.
75. *Id*.
76. *Id*.
77. *Id*. at 1746.

determination for all inventions, including chemical compounds. After a discussion of prima facie obviousness immediately below, this chapter provides a detailed analysis of Federal Circuit case law on chemical structural obviousness, with a focus on small molecules, both before and after the Supreme Court's *KSR* decision.[78]

[A] Prima Facie Obviousness

[A][1] An Evidentiary Mechanism

Prima facie obviousness is an evidentiary mechanism, usually applied in Patent Office proceedings after the examiner presents a threshold showing of obviousness that shifts the burden to the applicant to present evidence of nonobviousness.[79] While a finding of prima facie obviousness most often finds application in Patent Office proceedings, it is also used in patent infringement litigation when a court deems that a patent challenger has made a threshold showing of obviousness.[80] In infringement litigation, prima facie obviousness is viewed in the context of the statutory presumption of validity, which "'remains intact and [the burden of proof remains] on the challenger throughout the litigation, and the clear and convincing standard does not change.'"[81] Accordingly, the Federal Circuit has stated that

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78. See *supra* section 5:3.3[B][1] for a discussion of the Federal Circuit's post-*KSR* decision in *In re* Kubin, 561 F.3d 1351 (Fed. Cir. 2009), holding obvious a claim to polynucleotide sequences encoding a specific polypeptide where the prior art disclosed the same polypeptide and a method for obtaining cDNA encoding that polypeptide, including a monoclonal antibody specific for the polypeptide. Thus, although the prior art did not disclose the amino acid sequence of the polypeptide or the claimed polynucleotide sequences encoding the polypeptide, the court held, based on *KSR*, that the prior art provided motivation with a reasonable expectation of success to achieve the claimed polynucleotide sequences. *Id*. at 1361. The Federal Circuit declined to limit "*KSR* to the 'predictable' arts (as opposed to the unpredictable art of biotechnology)." *Id*. at 1360.

79. *In re* Piasecki, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984) ("The concept of *prima facie* obviousness in *ex parte* patent examination is but a procedural mechanism to allocate in an orderly way the burdens of going forward and of persuasion as between the examiner and the applicant.").

80. *See* Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 970–71 (Fed. Cir. 2006), *reh'g denied*, 2006 U.S. App. LEXIS 14543 (Fed. Cir. May 31, 2006); Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1375–76 (Fed. Cir. 2000); Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000); Pfizer Inc. v. Apotex, Inc., 480 F.3d 1348, 1359–60 (Fed. Cir. 2007).

81. *Pfizer*, 480 F.3d at 1359–60 (citation omitted). See *supra* section 5:1.1 for a discussion of the statutory presumption of patent validity under 35 U.S.C. § 282.

> once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence. . . . But, all that means is that even though a patentee *never* must submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity—what we call a prima facie case—the patentee "would be well advised to introduce evidence sufficient to rebut that of the challenger."[82]

The failure to rebut a proper prima facie case of obviousness results in the unpatentability (in the PTO) or invalidity (in infringement litigation) of the claim at issue.[83] Once an applicant presents sufficient rebuttal evidence, "the prima facie case dissolves, and the decision is made on the entirety of the evidence."[84] The failure to consider rebuttal evidence has been held to be reversible error.[85]

[A][2] Demonstrating Prima Facie Obviousness

In the case of chemical compounds, prima facie obviousness is generally based on a finding of structural similarity between the claimed compound and the prior art with a reason or suggestion in the art to make the claimed compound.[86] The reason or suggestion can arise from the existence "of a reference to a similar composition" that has some useful property, "the presumption being that similar compositions have similar properties."[87]

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82. *Pfizer*, 480 F.3d at 1360 (emphasis in original) (citations omitted).
83. *See In re* Dillon, 919 F.2d 688, 693 (Fed. Cir. 1990) (claim to compound held unpatentable because Patent Office established prima facie case of obviousness unrebutted by applicant). "Patentability" is used to refer to the determination of whether the PTO should grant a patent. "Patent validity" is used to refer to a determination made in an infringement litigation when the validity of a granted patent is at issue.
84. *In re* Kumar, 418 F.3d 1361, 1366 (Fed. Cir. 2005); *see also In re* Oetiker, 977 F.2d 1443, 1445–46 (Fed. Cir. 1992); M.P.E.P. § 2142.
85. *In re* Sullivan, 498 F.3d 1345, 1353 (Fed. Cir. 2007) ("By failing to consider the submitted [rebuttal] evidence, the Board thus committed error."); *Kumar*, 418 F.3d at 1369 ("[t]he entirety of the evidence must be reviewed in order to determine whether the claimed invention" would be invalid over prior art); *see also Oetiker*, 977 F.2d at 1445.
86. *See, e.g.*, *Yamanouchi*, 231 F.3d at 1343 ("For a chemical compound, a *prima facie* case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'") (emphasis added) (quoting *Dillon*, 919 F.2d at 692).
87. *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995); *see also Dillon*, 919 F.2d at 692 ("[s]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives

[A][2][a] Properties of Claimed and Prior Art Compounds

The properties of a claimed compound are important in determining nonobviousness over the prior art.[88] "There is no question that all evidence of the properties of the claimed compositions and the prior art must be considered in determining the ultimate question of patentability . . . ."[89]

[A][2][a][i] New Property Alone Does Not Defeat a Prima Facie Case

The mere fact, however, that "a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a prima facie case."[90] Thus, "it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from *the prior art* that the claimed compound or composition will have the same or a similar utility *as one newly discovered by the applicant*."[91] Accordingly, a prima facie case of obviousness can be made out if the prior art "provided the motivation to make the claimed compositions in the expectation that they would have similar properties."[92] This is not to say that the new properties of the claimed compound are irrelevant. They may be used to rebut prima facie obviousness.[93]

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reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, and that the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case"). As discussed below, "[s]uch rebuttal or argument can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *Id*. at 692–93.

88. *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963) ("a compound and all of its properties are inseparable").

89. *Dillon*, 919 F.2d at 693.

90. *Id*. ("[I]t is not correct that similarity of structure and a suggestion of *the activity of an applicant's compounds* in the prior art are necessary before a *prima facie* case is established."). *Id*. at 698.

91. *Id*. at 693. In reaching this conclusion, the Federal Circuit expressly overruled its prior decision in *In re* Wright, 848 F.2d 1216 (Fed. Cir. 1988).

92. *Dillon*, 919 F.2d at 693; *see also In re* Sullivan, 498 F.3d 1345, 1353 (Fed. Cir. 2007).

93. *See infra* section 7:2.2[B].

[A][2][a][ii] To Demonstrate Prima Facie Obviousness, a Prior Art Compound Must Suggest Some Useful Property

An obviousness rejection based on similarity in chemical structure and function is generally predicated on "the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."[94] Therefore, the existence of a prior art compound with no known utility having structural similarity to a claimed compound alone will not support a prima facie case of obviousness.[95]

[A][2][a][iii] In re Dillon

In *In re Dillon*,[96] the Federal Circuit, in an en banc opinion, attempted to clarify the law regarding prima facie obviousness. *Dillon* related to a claimed composition comprising a hydrocarbon fuel containing tetra-orthoester compounds in an amount sufficient to reduce particulate emissions. The prior art relied on by the patent examiner consisted, among other things, of a primary reference showing the use of tri-orthoesters to dewater hydrocarbon fuels and a secondary reference that showed the use of both tri-orthoesters and tetra-orthoesters as water scavengers in hydraulic (that is, nonhydrocarbon) fluids. The court concluded that the secondary reference showed an equivalency between tri-orthoesters and tetra-orthoesters. Moreover, the claims were directed to a composition, and were not limited to any particular use. Accordingly, the combination of prior art references rendered the claimed composition prima facie obvious: "The art provided the motivation to make the claimed compositions in the expectation that they would have similar properties."[97] Thus, the combination of prior art references rendered the claimed composition prima facie obvious because there was motivation in the art to make the claimed composition, although the motivation in the prior art (to use the tetra-orthoesters in hydrocarbon fuels as water scavengers) was

94. *In re* Payne, 606 F.2d 303, 313 (C.C.P.A. 1979).
95. *In re* Stemniski, 444 F.2d 581, 586 (C.C.P.A. 1971) (no obviousness based on similarity in structure alone where no use was described for prior art compounds; "[h]ow can there be obviousness of structure, or particularly of the subject matter as a whole, when no apparent purpose or result is to be achieved, no reason or motivation to be satisfied, upon modifying the reference compounds' structure?").
96. *In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990).
97. *Id*. at 693.

not the motivation of the patent applicant (to use the tetra-orthoesters to reduce particulate emissions in hydrocarbon fuels).[98]

In summary, as held in *Dillon*, "a *prima facie* case has been established . . . [when] [t]he art provided the motivation to make the claimed compositions in the expectation that they would have similar properties."[99]

[A][2][b] Prima Facie Obviousness Based on Similarity in Structure: "Structural Obviousness"

*[A][2][b][i] Pre-*KSR *Federal Circuit Decisions*

Obviousness attacks on claims to chemical compounds that are novel, but structurally similar to prior art compounds, are usually predicated on the assumption that activity can be predicted from knowledge of prior art chemical structures, creating an expectation that structurally similar compounds will have similar activities.[100] Thus, in pre-*KSR* decisions, the Federal Circuit stated that "'[s]tructural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties,'"[101] and that "[w]hen chemical compounds have 'very close' structural similarities and similar utilities, without more a *prima facie* case may be made."[102]

Patents directed to chemical compounds have generated many attempts to establish generalized rules governing when a claimed chemical structure is prima facie obvious in view of prior art chemical structures. Indeed, pre-*KSR*, the Federal Circuit observed that "[t]he question of 'structural similarity' in chemical patent cases has generated a body of patent law unto itself,"[103] and has noted the historical efforts of the courts to create categories of chemical structures that would be amenable to generalizations based on structure.[104]

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98. The applicant in *Dillon* did not attempt to rebut the prima facie case of obviousness. *Id*.
99. *Id*.
100. *Payne*, 606 F.2d at 313 ("An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.").
101. *In re* Merck & Co., 800 F.2d 1091, 1096 (Fed. Cir. 1986) (quoting *Payne*, 606 F.2d at 313).
102. *In re* Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985).
103. *In re* Jones, 958 F.2d 347, 349 (Fed. Cir. 1992).
104. The Federal Circuit in *Grabiak*, 769 F.2d at 731, noted prior cases finding prima facie obviousness with respect to "adjacent homologues and

Ultimately, however, the Federal Circuit has concluded that generalized rules and categories of structural obviousness are to be avoided. As the court stated in its pre-*KSR Grabiak* decision:

> Analysis of those circumstances in which a *prima facie* case has or has not been made in view of the degree of structural similarity or dissimilarity, or the presence or absence of similar utility between the prior art compound and that of the applicant, has inspired generations of applicants, courts, and scholars. Upon review of this history, we have concluded that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other.[105]

Accordingly, prima facie obviousness based on structural similarities between a claimed compound and prior art compounds is in general determined on a case-by-case basis by analyzing and comparing the structure and asserted activities of the claimed compound with the evidence presented on the prior art compounds.

The Federal Circuit's pre-*KSR* decision in *In re Merck & Co.*[106] is an example of a finding of prima facie obviousness of a claimed compound in view of a structurally related prior art compound.[107]

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structural isomers" (citing *In re* Wilder, 563 F.2d 457 (C.C.P.A. 1977)), "stereoisomers" (citing *In re* May, 574 F.2d 1082 (C.C.P.A. 1978)), and "acid and ethyl ester" (citing *In re* Hoch, 428 F.2d 1341 (C.C.P.A. 1970)). In its subsequent case of *Jones*, 958 F.2d at 350, the Federal Circuit repeated this list and added "tri-orthoesters and tetra-orthoesters" (citing *Dillon*, 919 F.2d 688). Other earlier cases attempted to create a rule of prima facie structural obviousness when a claimed compound was an "adjacent homologue" of a prior art compound. See *In re* Hass, 141 F.2d 122 (C.C.P.A. 1944), and *In re* Henze, 181 F.2d 196 (C.C.P.A. 1950), which together formed the so-called "Hass-Henze Doctrine" of structural obviousness for adjacent homologues. It should be noted that *Henze was* overruled by *In re* Stemniski, 444 F.2d 581, 586–87 (C.C.P.A. 1971), to the extent *Henze* held that a claimed compound could be rendered prima facie obvious by a structurally related prior art compound where "the prior art reference neither discloses nor suggests a utility for [the] described compounds." As the Federal Circuit commented in *Dillon*, 919 F.2d at 697, in such a case, "a presumption [of obviousness] is not created when the reference compound is so lacking in any utility that there is no motivation to make close relatives." However, the *Dillon* court nevertheless stated that "[t]he cases of *Hass* and *Henze* established the rule that, unless an applicant showed that the prior art compound lacked the property or advantage asserted for the claimed compound, the presumption of unpatentability was not overcome." 919 F.2d at 696.

105. *Grabiak*, 769 F.2d at 731.

106. *In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986).

107. *Id*. at 1096.

Merck related to a claim to a method of treating depression with the compound amitriptyline. While amitriptyline had been described in the art as having central nervous system activity, it was not known to be an antidepressant. The court relied on the prior art teaching that a compound with a closely related structure, imipramine, was an antidepressant and that the prior art suggested testing amitriptyline for antidepressant properties.[108] In reaching a conclusion of prima facie obviousness, the court stated:

> In view of these teachings, which show a close structural similarity and a similar use (psychotropic drugs) between amitriptyline and imipramine, one of ordinary skill in the medicinal chemical arts, possessed of the knowledge of the investigative techniques used in the field of drug design and pharmacological predictability, would have expected amitriptyline to resemble imipramine in the alleviation of depression in humans.[109]

In *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*,[110] the Federal Circuit rejected an argument that it would have been obvious to have made a claimed pharmaceutical compound by first combining different structural aspects of two "lead compounds" from the prior art and then chemically modifying the resulting intermediate. In concluding that a case of prima facie obviousness had not been presented, the court found an absence of reason or motivation in the prior art to take the complex series of steps needed to achieve the claimed compound.[111]

Yamanouchi involved an obviousness challenge to the H_2 antagonist famotidine, the active ingredient in the heartburn and ulcer medication Pepcid®. Famotidine has the following chemical structure (with the component parts of the structure labeled as depicted by the Federal Circuit):[112]

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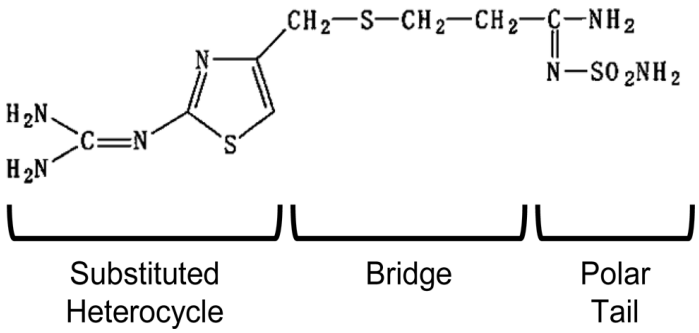
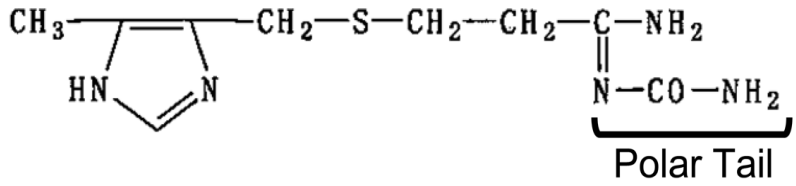
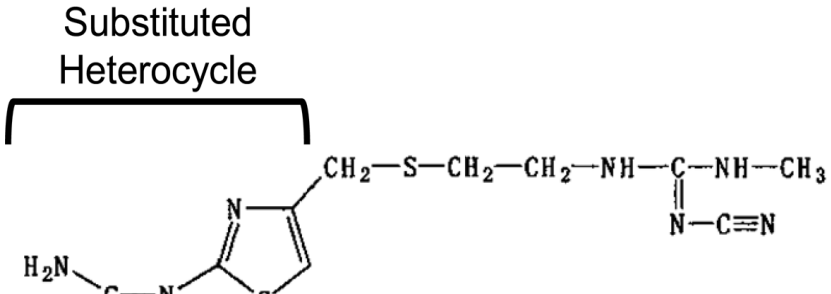
108. *Id*. at 1095.
109. *Id*. at 1097. The court rejected applicant's argument that it showed unexpected results sufficient to rebut the prima facie case of obviousness. The court concluded that "the alleged difference in properties [between the two compounds] is a matter of degree rather than kind." *Id*. at 1099. Thus, "[i]n the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case." *Id*.
110. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000).
111. *Id*. at 1344–45.
112. *Id*. at 1341.



The defendant argued that famotidine was prima facie obvious because one skilled in the art would have selected two prior art compounds as "leads" and modified those compounds to arrive at famotidine. First, the defendant asserted that example 44 from prior art U.S. patent 4,252,819 and the prior art compound tiotidine would have been selected as "leads for making famotidine" because "[t]hese compounds, respectively, are three and eleven times more active than cimetidine—the benchmark compound at the time of the invention."[113] The structures of these compounds are shown below:



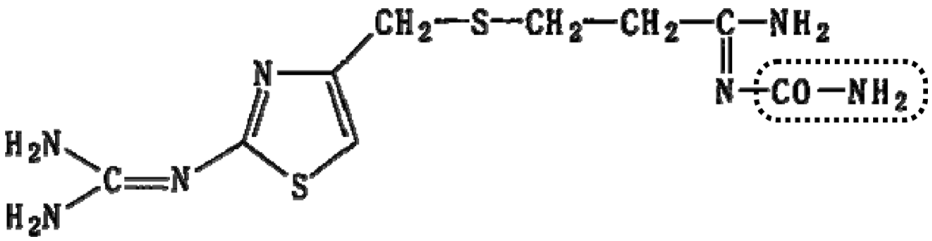
(Example 44 from U.S. Patent 4,252,819)



(Tiotidine)

The defendant argued that one skilled in the art would have combined the polar tail of example 44 with the substituted heterocycle of tiotidine to create the following intermediate:

113. *Id.* at 1343–44.



The defendant next argued that it would have been obvious to have substituted a sulfamoyl group (SO_2NH_2) for the carbamoyl group ($CONH_2$) of the intermediate to achieve famotidine.

The Federal Circuit characterized the defendant's position as "whether one of skill in this art would have found motivation to combine pieces from one compound in a prior art patent with a piece of another compound in the second prior art patent through a series of manipulations."[114] The court rejected the defendant's position and concluded that famotidine was not prima facie obvious.

First, the court rejected the argument that example 44 would have been selected as a lead compound based only on its activity, because there were other prior art compounds with activity up to ten times higher than cimetidine (the benchmark compound), which would have been "the obvious choices, not example 44," if activity was the sole criterion.[115] Second, the court found that there was no motivation to combine the prior art compounds in the way necessary to make famotidine. While the defendant argued that one skilled in the art would have expected the resulting compound "to exhibit the baseline level of H_2 antagonist activity," the court concluded that the success of famotidine was "not discovering one of the tens of thousands of compounds that exhibit baseline H_2 antagonist activity. Rather, the success was finding a compound that had high activity, few side effects, and lacked toxicity."[116] Moreover, the court concluded that "the prior art offers no suggestion to pursue the particular order of manipulating parts of the compounds . . . . Any deviation in the order of combination would have taught away from famotidine."[117]

The Federal Circuit followed the rationale of its *Yamanouchi* decision in rejecting a similar structural obviousness challenge presented in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*,[118] which

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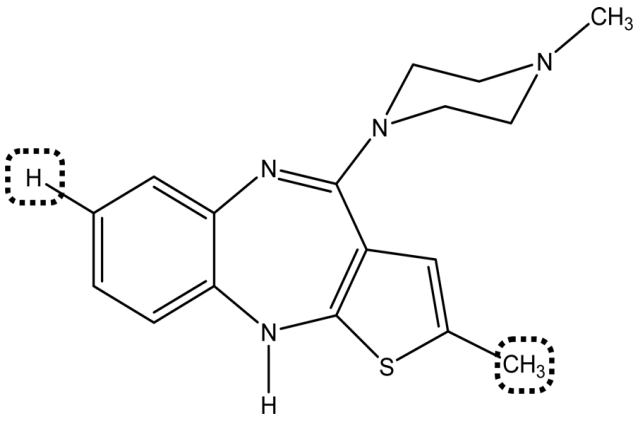
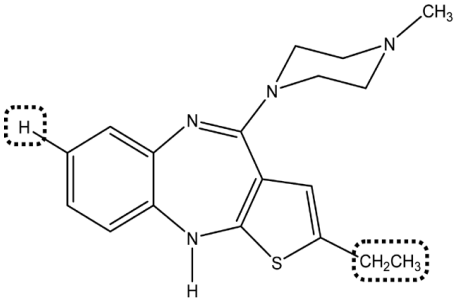
114. *Id.* at 1343.
115. *Id.* at 1345.
116. *Id.*
117. *Id.*
118. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369 (Fed. Cir. 2006), *cert. denied sub nom.* Dr. Reddy's Labs., Ltd. v. Eli Lilly & Co., 128 S. Ct. 288 (2007); Teva Pharm. USA, Inc. v. Eli Lilly & Co., 128 S. Ct. 146 (2007).

involved the claimed anti-schizophrenia drug, olanzapine, the active compound in the drug product Zyprexa®.

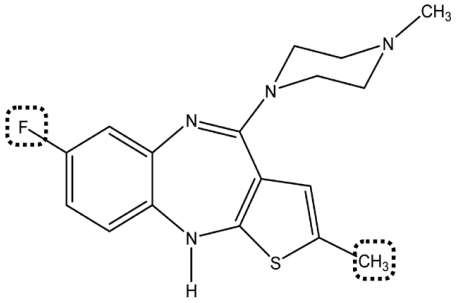
Olanzapine has the following chemical structure:[119]



Two prior art compounds asserted by the defendants, ethyl olanzapine (or "Compound '222") and flumezapine, have the following structures (with the key substituents highlighted):[120]



Ethyl olanzapine (Compound '222)



Flumezapine

The Federal Circuit rejected the position that Compound '222 would have been selected as a lead by one skilled in the art, or that one skilled in the art would have been motivated to modify either Compound '222 or flumezapine to obtain olanzapine.[121] The focus

119. *Eli Lilly & Co.*, 471 F.3d at 1374.

120. *Id.* at 1375.

121. Interestingly, the Federal Circuit noted that one of the defendants in *Eli Lilly* had argued that "the district court erred by erecting 'a threshold requirement that defendants establish a teaching or incentive to treat the closest prior art (*i.e.*, Compound '222) as a 'lead compound.'" *Id.* at 1377. The court's opinion does not elaborate on the specific basis for the asserted error or what alternative to the lead compound approach had been advocated by the defendant.

of the court's analysis was whether one skilled in the art would have been motivated to have made a compound that had a hydrogen atom instead of a fluorine or chlorine atom at the 7-position of the benzene ring.

First, the court concluded that the defendants had failed "to show that a person ordinarily skilled in this art would have selected Compound '222 as a lead compound because it contained hydrogen rather than fluorine or chlorine."[122] The court noted that the prior art taught that "the unfluorinated Compound '222 was less active than the benchmark compound clozapine."[123] Compound '222 was therefore not a proper lead compound because "at the time of the invention, the state of the art would have directed a person of ordinary skill in the art away from unfluorinated compounds like Compound '222."[124] Because the prior art "expressly taught that the addition of a fluorine or chlorine enhanced anti-psychotic activity . . . rather than providing the requisite motivation, the prior art taught away from selecting Compound '222 as a lead compound for further development."[125] Second, noting that flumezapine had negative side effects (it caused extra-pyramidal symptoms and an increase in liver and muscle enzymes), the court found that substantial evidence supported the conclusion that the prior art "would not have led a person of ordinary skill in the art to believe that flumezapine could be successfully modified with a hydrogen atom."[126] Moreover, the court concluded that "[b]eyond the non-obvious selection step, the prior art also did not suggest any of the other modifications necessary to reach olanzapine."[127]

Accordingly, the Federal Circuit held that "to establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention."[128] The court thus concluded that olanzapine was not prima facie obvious.[129]

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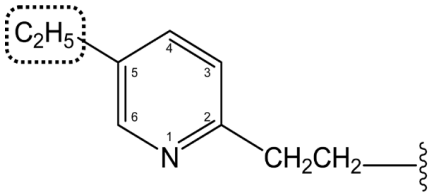
122. *Id*. at 1379.
123. *Id*.
124. *Id*.
125. *Id*.
126. *Id*. at 1380.
127. *Id*. at 1379.
128. *Id*.
129. *Id*. at 1380. The court, in the alternative, concluded that even if the claimed compound was prima facie obvious, such a finding was rebutted by "extensive secondary considerations." *Id*.

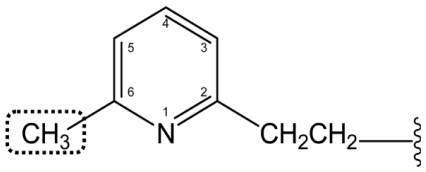
[A][2][b][ii] Post-KSR Federal Circuit Decisions

The Federal Circuit's first decision after *KSR* involving an obviousness determination for a chemical compound was *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*[130]

At issue in *Takeda* was the claimed antidiabetic drug compound pioglitazone which, critical to the case, differed from the closest prior art compound (called "compound b") in having a 5-ethyl substituted pyridyl ring instead of a 6-methyl substituted pyridyl ring:



Pioglitazone



Prior Art "compound b"

The remaining structures of both compounds are the same.

The Federal Circuit affirmed the district court's determination that the prior art compound b did not render pioglitazone prima facie obvious. The court concluded that "Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound"[131] and that the prior art "taught away" from the selection of compound b, which was described as having adverse, toxic properties.[132] Contrary to the facts of *KSR*, the Federal Circuit stated that in *Takeda*,

> [r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound.[133]

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130. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007).
131. *Id*. at 1360. The court defined a "lead" compound as "a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity." *Id*. at 1357.
132. *Id*. at 1358–60.
133. *Id*. at 1359.

Moreover, even if one skilled in the art would have selected compound b as a lead compound in developing an antidiabetic drug, the court concluded that the changes necessary to achieve the claimed pioglitazone compound were "unpredictable" and that there was no "reasonable expectation" that making those changes would reduce or eliminate the toxic properties of compound b.[134]

In reaching this conclusion, the Federal Circuit, while acknowledging *KSR*, reconfirmed its jurisprudence regarding a determination of prima facie obviousness based on a similarity in structure between a claimed compound and a prior art compound:

> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure.[135]

Takeda thus reconfirmed the Federal Circuit's pre-*KSR* case law that a prima facie case of obviousness based on a structural relationship between a claimed compound and the prior art is premised on "'the requisite motivation or suggestion to modify known compounds to obtain the new compounds'" and that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required."[136]

The Federal Circuit in *Takeda* maintained that *KSR* had not eliminated the teaching, suggestion, or motivation test for obviousness because, as the Supreme Court itself stated, "[a]s long as the test is not applied as a 'rigid and mandatory' formula, that test can provide 'helpful insight' to an obviousness inquiry."[137] Accordingly, the Federal Circuit stated that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[138] Thus, under *Takeda*, the body of Federal Circuit law on an obviousness determination for chemical compounds based on an asserted

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134. *Id*. at 1360–61.
135. *Id*. at 1356 (citations omitted).
136. *Id*. (quoting *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).
137. *Id*. at 1357.
138. *Id*.

structural similarity to prior art compounds remained largely intact following *KSR*.

Subsequently, in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*,[139] the Federal Circuit held the anticonvulsive compound topiramate nonobvious. Topiramate (the compound in the drug product TOPOMAX®) is an epilepsy drug that was discovered during a search for a reaction intermediate in the synthesis efforts directed to finding antidiabetic drugs. The Federal Circuit rejected Mylan's argument that, under *KSR*, it would have been obvious to have arrived at topiramate in the search for a diabetes drug:

> [T]he ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives) the exact route that produces topiramate as an intermediate. Even beyond that, the ordinary artisan in this field would have had to (at the time of invention without any clue of potential utility of topiramate) stop at that intermediate and test it for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes). In sum, this is clearly not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness.[140]

Moreover, the Federal Circuit rejected the obviousness challenge because it was based on "hindsight" which "simply retraced the path of the inventor."[141]

The "lead compound" analysis was the focus of the Federal Circuit's decision in *Eisai Co. v. Dr. Reddy's Laboratories, Ltd.*[142] In *Eisai*, the court affirmed a grant of summary judgment of nonobviousness of the compound rabeprazole, the sodium salt of which is the active ingredient in the drug product AcipHex®. Rabeprazole is a proton pump inhibitor approved for the treatment of duodenal ulcers, heartburn, and associated disorders. The structural obviousness challenge to rabeprazole was based on a combination of three prior art references, the principal argument being that the anti-ulcer compound lansoprazole, described in a prior art European patent, would have been selected by one skilled in the art as "a candidate for a lead compound in the search for anti-ulcer compounds."[143]

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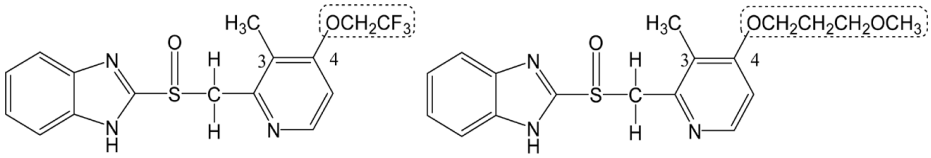
139. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358 (Fed. Cir. 2008).
140. *Id*. at 1364.
141. *Id*. The Federal Circuit also made clear its position that *KSR* did not reject the TSM test as long as the test is "flexibly applied." *Id*. at 1365.
142. Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353 (Fed. Cir. 2008).
143. *Id*. at 1358. The two other prior art references disclosed, respectively, the proton pump inhibitor omeprazole and a class of anti-ulcer compounds having a core structure shared by rabeprazole, lansoprazole, and

As shown below, lansoprazole differs structurally from the claimed rabeprazole compound only in the substitution at the 4-position of the pyridine ring. Whereas lansoprazole has a trifluroethoxy (OCH_2CF_3) substituent at that position, the claimed rabeprazole compound has a methoxypropoxy ($OCH_2CH_2CH_2OCH_3$) substituent.[144]



Rabeprazole **Lansoprazole**

The Federal Circuit concluded that lansoprazole, a prior art anti-ulcer compound, did not render prima facie obvious the claimed rabeprazole compound, which inhibits gastric acid. The court noted that the district court had "emphasized the differences between anti-ulcer action and gastric acid inhibition," including expert testimony that the level of acid secretion could not be determined from the data in the prior art reference describing lansoprazole.[145] Moreover, the prior art described the fluorinated substituent of lansoprazole as providing the advantage of lipophilicity[146] and the Federal Circuit concluded that the "record . . . shows no discernable reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property."[147] Thus, the court rejected the premise that one skilled in the art would have selected lansoprazole as a lead compound in the path to the discovery of rabeprazole.

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omeprazole. *Id*. at 1357. The Federal Circuit noted that "[a]lthough sharing the same basic structure, omeprazole is structurally farther afield from rabeprazole than is lansoprazole." *Id*. Interestingly, lansoprazole is the active ingredient in the proton pump inhibitor Prevacid®, which itself was challenged as structurally obvious in Takeda Pharm. Co. v. Teva Pharm. USA Inc., 542 F. Supp. 342 (D. Del.), *aff'd per curiam*, 2008 WL 4831469 (Fed. Cir. Nov. 7, 2008). As discussed *infra*, lansoprazole was also found not to be prima facie obvious over prior art compounds.

144. *Id*.

145. *Id*. at 1358.

146. *Id*. In reaching its decision, the Federal Circuit assumed that the prior art taught that "lansoprazole is twenty times superior to omeprazole for anti-ulcer action . . . ." *Id*. The court further stated that "[t]his court also assumes that lansoprazole has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight, that would have made it desirable to a skilled artisan." *Id*.

147. *Id*. at 1358–59.

In discussing *KSR*, the Federal Circuit concluded in *Eisai* that, "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."[148] Thus, the Federal Circuit held that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound."[149] On the facts of the case, there was a failure to show why one skilled in the art would have modified the prior art lansoprazole compound to achieve the claimed rabeprazole compound: "The record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution."[150]

Thus, *Eisai* appears to represent the establishment of the "lead compound" analysis as a general test for determining whether a claimed chemical compound is prima facie obvious. *Eisai* also reconfirms the Federal Circuit's determination that its jurisprudence on chemical structural obviousness is consistent with *KSR*.

In *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*,[151] the Federal Circuit affirmed a district court's judgment in rejecting an obviousness challenge to the claimed bisphosphonate compound risedronate, the sodium salt of which is the active ingredient in the osteoporosis drug Actonel®.[152] Defendant Teva's obviousness challenge was based on the bisphosphonate compound 2-pyr EHDP, a positional

148. *Id*. at 1359.

149. *Id*. The Federal Circuit may have found support for the lead compound concept in *KSR*: "*KSR* assumes a starting reference point or points in the art, prior to the time of the invention, from which a skilled artisan might identify a problem and pursue potential solutions." *Id*. A lead compound can be viewed as a "starting reference point" from which to "pursue potential solutions" to the problems presented by prior art compounds in terms of insufficient activity or unacceptable side effects.

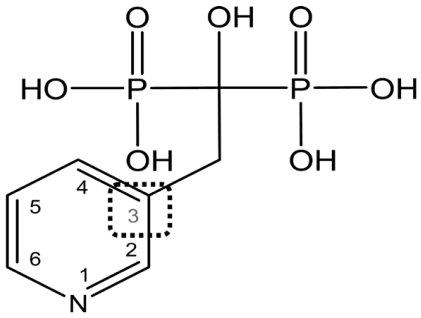
150. *Id*. "*KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound." *Id*.

151. Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989 (Fed. Cir. 2009).

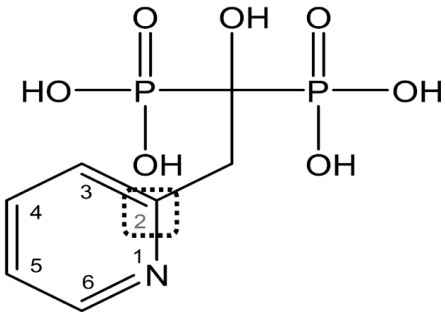
152. The district court decision is reported at 536 F. Supp. 2d 476 (D. Del. 2008).

isomer[153] of risedronate, which was disclosed in an expired prior art Procter & Gamble patent.[154]

As shown below, 2-pyr EHDP differs from risedronic acid only at the point of attachment of the pyridine ring.



Risedronic Acid: 3-pyr EHDP



Prior Art 2-pyr EHDP

The district court had concluded that the claimed compound was not prima facie obvious. First, after reviewing the prior art, the district court was "unpersuaded that a person of ordinary skill in the art would have selected 2-pyr EHDP as the 'lead compound' out of the numerous compounds disclosed in the [prior art] patent," including non-nitrogen-containing bisphosphonates.[155] Second, even if 2-pyr EHDP would have been selected as a lead compound, the court concluded that the necessary modification to obtain the claimed compound was not obvious based on the testimony of the "preeminent authority on bisphosphonates" that each bisphosphonate "exhibits its own physical-chemical, biological and therapeutic characteristics."[156]

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153. As the Federal Circuit noted, risedronate and 2-pyr EHDP are "positional isomers" because "they each contain the same atoms arranged in different ways." 566 F.3d at 995. The Federal Circuit further noted that "[b]ecause the nitrogen atom is in a different position in the two molecules, they differ in three dimensional shape, charge distribution and hydrogen bonding properties." *Id*.

154. The Federal Circuit rejected Procter & Gamble's challenge to the prior art status of its expired patent because one of the inventor's unwitnessed laboratory notebook entries was insufficient to corroborate a claim of an earlier conception date. *Id*. at 998.

155. 536 F. Supp. 2d at 495.

156. *Id*. (internal quotation marks omitted). The district court also concluded in the alternative that unexpected results and secondary considerations would have rebutted any finding of prima facie obviousness because risedronate was three times more active and three times less toxic than 2-pyr EHDP and because risedronate met a "long-felt but unresolved need." *Id*. at 495–96. The Federal Circuit agreed with the district court that unexpected results and secondary considerations would have supported a finding of nonobviousness of risedronate. 566 F.3d at 998.

In affirming, the Federal Circuit did not reach whether 2-pyr EHDP would have been selected as a lead compound in the treatment of osteoporosis, but instead concluded that risedronate was not prima facie obvious because the evidence did not establish that one skilled in the art would have found it obvious to modify 2-pyr EHDP to create risedronate.[157] In particular, the Federal Circuit noted that the trial evidence showed that the properties of bisphosphonate compounds could not be anticipated from their structure and that each bisphosphonate had to be considered on its own.[158] In this connection, the court noted that another positional isomer of risedronate, 4-pyr EHDP, had been tested by P&G and was not active in inhibiting bone resorption, despite its close relationship to potent compounds. The Federal Circuit also agreed with the district court's conclusion that there was an insufficient showing of a reasonable expectation that risedronate would be a successful compound.[159] Finally, the Federal Circuit stated that there was no credible evidence that the required structural modification was routine.[160]

In *Altana Pharma v. Teva Pharmaceuticals USA*,[161] the Federal Circuit affirmed the district court's denial of a preliminary injunction based on the defendant's raising a "substantial question" regarding the validity of the claimed compound pantaprazole, the active ingredient in the antiulcer drug product Protonix®. While in the context of a preliminary injunction, *Altana* marked the first post-*KSR* decision by the Federal Circuit crediting a position that a claimed chemical structure was prima facie obvious over a prior art compound.[162]

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157. 566 F.3d at 994–98.

158. *Id*. at 996.

159. *Id*. The Federal Circuit also affirmed the district court in rejecting Teva's obviousness-type double patenting challenge based on its conclusion that risedronate was not prima facie obvious in view of 2-pyr EHDP and because, while the patent-in-suit claimed the compound risedronate, the earlier P&G patent claimed a distinct invention, an intermittent dosing regimen for the treatment of osteoporosis with bisphosphonate compounds, including 2-pyr EHDP. *Id*. at 999.

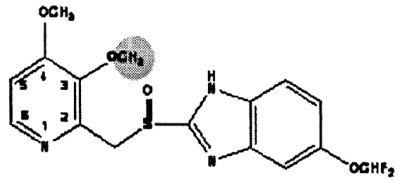
160. *Id*.

161. Altana Pharma v. Teva Pharm. USA, 566 F.3d 999 (Fed. Cir. 2009).

162. The Federal Circuit rejected Altana's argument that the district court had failed to take into account the defendants' burden at trial of proving invalidity by clear and convincing evidence, stating that "[t]he precedent of this court holds that if the accused infringer raises a 'substantial question' concerning validity . . . the preliminary injunction should not issue." *Id*. at 1006. The majority opinion, however, did not cite the U.S. Supreme Court's decision in Gonzalez v. O Centro Espirita Beneficente Uniao do Vegetal, 546 U.S. 418, 429 (2006), which was cited in Judge Newman's concurring opinion, for the proposition that "the burdens at the preliminary injunction stage track the burdens at trial." *Id*. at 1011.

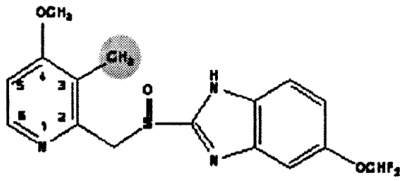
In denying plaintiffs' motion for a preliminary injunction, the district court found that defendants had raised a substantial question regarding the validity of pantaprazole, a proton pump inhibitor, in view of a prior art compound, which was also a proton pump inhibitor.[163] As shown below, the two compounds differ only at the 3-position of the pyridine ring.

Claimed compound
Pantoprazole
(methoxy at 3-position)



Proton Pump Inhibitor

Prior Art Compound
'518 patent, example 12
(methyl at 3-position)



Proton Pump Inhibitor

While emphasizing that decisions on preliminary injunction motions are based on less than a full record,[164] the Federal Circuit agreed that defendants had made a sufficient showing that the prior art compound of example 12 would have been selected as a lead compound and that there was a sufficient showing of a motivation to modify that compound to achieve pantoprazole to defeat the motion for preliminary injunction.

First, the Federal Circuit agreed that prior art compound 12, along with other compounds disclosed in the same prior art patent, were improvements over the first successful proton pump inhibitor, omeprazole.[165] Moreover, compound 12 was one of the more potent compounds described in that prior art patent.[166] The Federal Circuit rejected plaintiffs' argument that the prior art must point to only a single lead compound as too restrictive a view of the lead compound test—a view that "would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*."[167]

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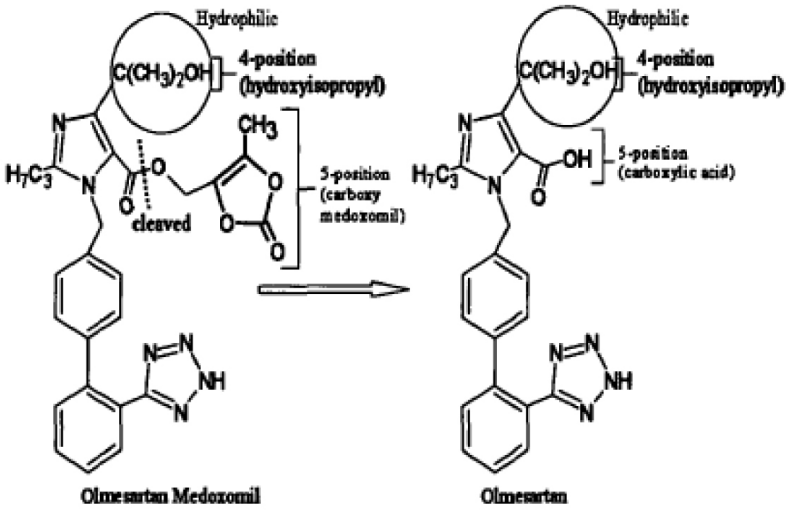
163. The district court's opinion in *Altana* is reported at 532 F. Supp. 2d 666 (D.N.J. 2007).
164. 566 F.3d at 1007.
165. *Id*.
166. *Id*. at 1007–08. The Federal Circuit also credited expert testimony presented to the trial court that the prior art patent describing example 12 (among eighteen exemplary compounds) was "on the cutting edge of PPI development" at the relevant time. *Id*. at 1008.
167. *Id*.

Second, the Federal Circuit agreed with the district court's general conclusion that the prior art provided a motivation to substitute a methoxy group for the methyl group at the 3-position of the pyridine ring in the prior art compound 12 because it would lower pKa and provide for better stability in the body.[168] While the district court did err in its technical understanding of a key prior art reference, it nevertheless correctly read that reference as to the relative pKa values for a methyl substitution versus a methoxy substitution at the 3-position.[169]

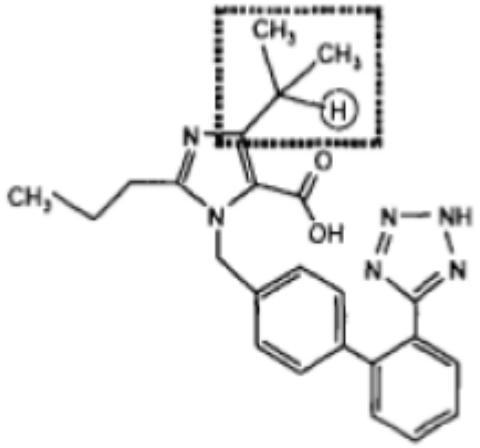
Because the Federal Circuit emphasized that in *Altana* it was reviewing the grant of a preliminary injunction for abuse of discretion on a necessarily preliminary record, it is difficult to draw any general conclusions as to whether the court's analysis is also applicable to a structural obviousness determination based on a full trial record.[170]

In *Daiichi Sankyo Co. v. Matrix Laboratories, Ltd.*,[170.1] the Federal Circuit affirmed the district court's application of the lead compound analysis in sustaining the validity of a patent claiming the compound olmesartan medoxomil, the active ingredient in the angiotensin receptor blocker (ARB) drug products Benicar®, Benicar HCT®, and Azor®. At issue was the alleged structural obviousness of olmesartan medoxomil, a prodrug that is cleaved after administration to a patient to provide olmesartan.



168. *Id*. at 1009.
169. *Id*. at 1009–10.
170. In a concurring opinion, Judge Newman stated that in her view, the evidence presented to the district court did not establish invalidity of the claimed pantoprazole compound. *Id*. at 1011.
170.1. Daiichi Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346 (Fed. Cir. 2010).

The Federal Circuit rejected defendant's argument that compounds structurally close to olmesartan that were disclosed in DuPont's U.S. Patent 5,137,902, including Example 6 depicted below, would have been selected by a person of ordinary skill in the art as a lead compound.



'902 Example 6

The Federal Circuit agreed with the district court's finding that "a medicinal chemist of ordinary skill would not have been motivated to select the '902 compounds over other second generation ARBs . . . because many of the latter ARBs demonstrated greater potency and all had been more thoroughly studied than the '902 ARBs."[170.2] The Federal Circuit rejected defendant's argument that "because the '902 ARBs are undisputedly the closest prior art, that 'should have been dispositive of the lead compound issue,'" finding that such an argument "runs contrary to our case law."[170.3] In particular, Federal Circuit noted that its cases "illustrate that it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention."[170.4] Importantly, "proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional

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170.2. *Id*. at 1353.
170.3. *Id*. at 1354.
170.4. *Id*.

properties and limitations of the prior art compounds. . . . Potent and promising activity in the prior art trumps mere structural relationships."[170.5]

The Federal Circuit also agreed with the district court that, even accepting that the '902 compounds would have been selected as lead compounds, a person of skill in the art would not have been motivated to modify those compounds to obtain olmesartan medoxomil.[170.6] In particular, the art taught "a clear preference for lipophilic groups at the 4-position of the imidazole ring" and that there would not have been a motivation to change the lipophilic alkyl groups that the '902 patent examples have at the 4-position with the hydrophilic hydroxyl-isopropyl group that olmesartan has at the 4-position.[170.7] Moreover, the defendant's argument relied on first selecting the '902 compounds as leads and then disregarding a distinguishing characteristic of those lead compounds, their increased lipophilicity at the 4-position as compared with prior ARBs.[170.8]

Because the Federal Circuit concluded that a prima facie case of obviousness had not been established, it did not address the issue of secondary considerations of nonobviousness.[170.9]

In *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*,[170.10] the Federal Circuit affirmed a district court bench trial verdict that claims to the compound entecavir, sold under the trademark Baraclude for the treatment of hepatitis B, were invalid as obvious over the prior art.

Citing its prior decisions in *Takeda* and *Eisai*, discussed above, the Federal Circuit reaffirmed that "[t]o establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound"[170.11] and that "[g]enerally, an obviousness inquiry concerning such 'known compounds' focuses on the identity of a 'lead compound.'"[170.12] In addition, citing *Altana*, the Federal Circuit also reaffirmed that a "lead compound is a compound in

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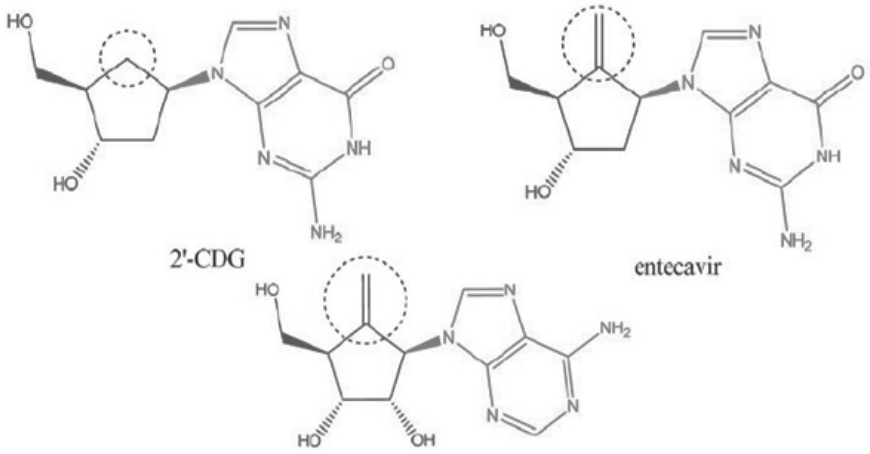
170.5. *Id*.
170.6. *Id*.
170.7. *Id*. at 1354–57.
170.8. *Id*. at 1357.
170.9. *Id*.
170.10. Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967 (Fed. Cir. 2014).
170.11. *Id*. at 973 (citing Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007)).
170.12. *Id*. (citing Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008)).

the prior art that would be 'a natural choice for further development efforts.'"[170.13]

The Federal Circuit agreed with the district court's conclusion that a person skilled in the art would have selected the prior art compound 2′-CDG as a lead compound and would have been motivated by another prior art compound, the "Madhavan compound 30" to have modified 2′-CDG to arrive at entecavir, the claimed compound.



In particular, the Federal Circuit concluded that during the late 1980s, research was being conducted and published on the antiviral activity of carboxylic nucleosides and 2′-CDG was a "'natural choice for further development.'"[170.14] The scientific literature available at the time that the application for the patent in suit was filed in October 1990 taught that 2′-CDG had "'excellent activity'" against hepatitis B and was thought to be nontoxic.[170.15] The Federal Circuit discounted evidence that 2′-CDG was later found to be toxic in the 1990s because,

> at the time of entecavir's invention, the Price [prior art] reference showed that 2′-CDG was generally understood to be safe and nontoxic, and other researchers were already using it as a lead compound. As the district court points out, in "October 1990, 2′-CDG was *not yet known* to have high toxicity," and BMS's expert, Dr. Schneller, agreed that researchers at the time treated 2′-CDG as a "promising compound."[170.16]

170.13. *Id*. (quoting Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009)).
170.14. *Id*. at 974.
170.15. *Id*. at 971, 976.
170.16. *Id*. at 974.

After concluding that evidence supported the selection of 2′-CDG as a lead compound, the Federal Circuit also concluded that "the record here amply supports the conclusion that one of ordinary skill in the art would have had a motivation to modify 2′-CDG's carbocyclic ring by substituting an exocyclic methylene group at the 5′ position to make the patented compound, entecavir."[170.17] In particular, the Federal Circuit credited expert testimony that it would have been a "natural decision" to have modified the carboxylic portion of 2′-CDG[170.18] and that it would have been obvious to have looked to the Madhavan 30 prior art compound and make an exocyclic methylene substitution at the 5′ position in order to improve antiviral activity.[170.19]

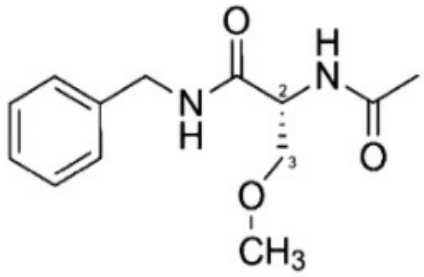
In summing up its conclusion on the structural obviousness of entecavir based on the prior art, the Federal Circuit stated that "[u]pon selecting 2′-CDG as the lead compound, the steps of deciding which bond to modify and how to modify that bond 'equate to a small, finite number of changes to try to [arrive at] the lead compound.'"[170.20]

Finally, the Federal Circuit concluded that the evidence of unexpected properties, commercial success, and long-felt need did not overcome the strong evidence of obviousness. In particular, the court concluded that (1) while entecavir's degree of effectiveness was unexpected, its effectiveness against hepatitis B without known toxicity was not unexpected, (2) entecavir's sales were "less dynamic" than BMS represented as the drug faced significant competition from other competitors, and (3) three other drugs for treating hepatitis B had been approved by the FDA before entecavir.[170.21]

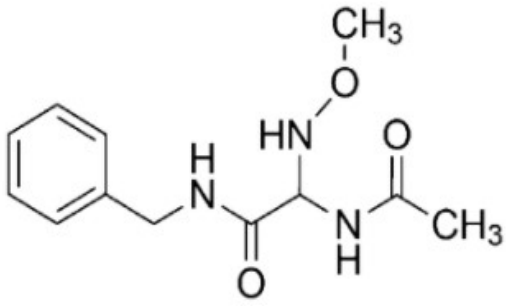
Mylan Pharmaceuticals Inc. v. Research Corporation Technologies, Inc.[170.22] concerned an appeal from the final written decision of the U.S. Patent Trial and Appeal Board in an inter partes review of a reissue patent directed to enantiomeric compounds useful in the treatment of epilepsy, including lacosamide. The Federal Circuit affirmed the PTAB's finding that the patent claims were not invalid as obvious because the appellants had failed to meet their burden to establish a motivation to modify their proposed lead compound.[170.23]

170.17. *Id*. at 974–75.
170.18. *Id*. at 975.
170.19. *Id*.
170.20. *Id*. at 976.
170.21. *Id*. at 978–79.
170.22. Mylan Pharm. Inc. v. Research Corp. Techs., Inc., 914 F.3d 1366 (Fed. Cir. 2019).
170.23. *Id*. at 1374.

At issue in the appeal were claims for the compound lacosamide, as well as compositions thereof and methods for use of those compounds in treating central nervous system disorders.[170.24] The chemical structure of lacosamide is:[170.25]



The petitioner put forward a structurally similar compound from the prior art, referred to as "compound 3*l*," in its lead compound analysis:[170.26]



The PTAB assumed without determining that the 3*l* compound was an appropriate lead compound, and the Federal Circuit did not disturb that assumption.[170.27]

The PTAB found that a person of ordinary skill in the art would not have had a motivation to modify the 3*l* compound to form lacosamide, and the Federal Circuit held that this finding was supported by substantial evidence.[170.28] Among the evidence considered was prior art suggesting that compounds without a methoxyimino or nitrogen-containing group at the α-carbon—present in the 3*l* compound but not in lacosamide—would have reduced activity.[170.29] The evidence

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170.24. *Id*. at 1368–69.
170.25. *Id*. at 1369.
170.26. *Id*. at 1370.
170.27. *Id*. at 1374.
170.28. *Id*. at 1376.
170.29. *Id*. at 1375.

also suggested that replacing the methoxyimino in compound 3*l* with the ethylene link in lacosamide would have yielded a different conformation, which may have affected interaction with receptors and altered biological activity.[170.30] Further, the PTAB rejected petitioner's theory that the bioisosterism of lacosamide was preferable to the 3*l* compound, as the record did not indicate why bioisosterism would have supported the modification of compound 3*l* in particular.[170.31] Given the "reductions in potency and the significant conformational changes that would have been expected" from modifying 3*l* to make lacosamide, the Federal Circuit affirmed the PTAB's finding that the patent was not invalid for obviousness.

The Federal Circuit in *Novartis Pharmaceuticals Corp. v. West-Ward Pharmaceuticals International Ltd.*[170.32] affirmed the district court's determination that patents directed to a method of using everolimus to treat advanced renal cell carcinoma (RCC) were not invalid as obvious. It did so on different grounds, however, holding that the district court had improperly applied the lead compound analysis.[170.33]

West-Ward's appeal arose after the district court required that West-Ward prove not just that a person of ordinary skill in the art (POSA) "would have been motivated to pursue everolimus as one of several potential treatment options for advanced solid tumors"—which West-Ward had established—but further that a POSA would have selected everolimus *over* other prior art treatment methods, such as temsirolimus.[170.34] The Federal Circuit rejected this heightened standard, chiefly because the asserted patent claimed *methods* of using everolimus as opposed to claiming the *compound* itself.[170.35] Therefore, the court reasoned, the lead compound analysis was inapposite.[170.36] Instead, the proper inquiry was whether a POSA would have been motivated to modify the prior art disclosing use of temsirolimus to treat advanced RCC with the prior art disclosing everolimus.[170.37]

Noting that the district court had found that a POSA would have been motivated to make this modification, the issue for the Federal Circuit then became whether a POSA would have had a reasonable

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170.30. *Id*.
170.31. *Id*. at 1376. Bioisosterism is a way to attenuate toxicity. *Id*. The Federal Circuit noted that compound 3*l* had low toxicity. *Id*.
170.32. Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd., 923 F.3d 1051 (Fed. Cir. 2019).
170.33. *Id*. at 1059–60, 1062–63.
170.34. *Id*. at 1059–60.
170.35. *Id*. at 1060.
170.36. *Id*.
170.37. *Id*.

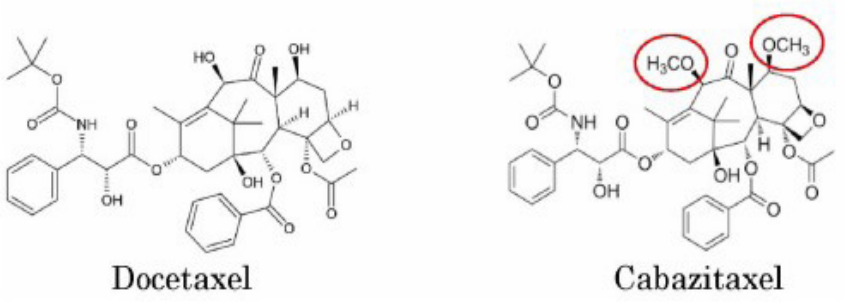
expectation of success in using everolimus to treat advanced RCC.[170.38] West-Ward argued there would be such an expectation as (1) RCC patients had shown responses to temsirolimus treatment in phase I clinical trials, (2) everolimus was an mTOR inhibitor that was available in oral formulations, and (3) inhibiting mTOR in prostate cancer cells inhibits HIF-1, which was hypothesized to inhibit tumor promoting angiogenesis.[170.39]

This did not satisfy the Federal Circuit, which affirmed the district court's finding that a POSA would not have a reasonable expectation of success in using everolimus.[170.40] Pointing to various fact findings of the district court, the Federal Circuit noted that temsirolimus phase I data resulted from small sample sizes in studies that were designed to test safety, not efficacy.[170.41] Further, everolimus and temsirolimus are pharmacologically different and had different elimination half-lives, and a POSA would not have expected the same efficacy for everolimus in light of these differences.[170.42] In addition, the roles of HIF-1 and mTOR in the molecular biology of advanced RCC were not fully understood as of the critical date, and there was evidence that inhibiting mTOR does not necessarily result in tumor growth inhibition.[170.43] Accordingly, the Federal Circuit held that, while the district court had erred in its motivation to combine analysis, the error was harmless because the district court did not clearly err in its finding regarding the lack of a reasonable expectation of success.[170.44]

In *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.*,[170.45] the Federal Circuit affirmed a holding by the district court that a patent directed toward the compound cabazitaxel was not invalid as obvious. In so doing, the Federal Circuit reiterated that, while it may be obvious to make a single chemical change to a lead compound where there are a "small, finite number of changes to try," the court's previous ruling in *Bristol-Myers Squibb* did not create a bright-line rule that small changes to a compound are necessarily prima facie obvious.[170.46]

170.38. *Id*.
170.39. *Id*. at 1060–61.
170.40. *Id*. at 1061.
170.41. *Id*. West-Ward's own expert stated that a POSA "would not make a determination or reasonable suggestion [of efficacy] simply based in isolation upon whether a drug enters phase II . . . ." *Id*.
170.42. *Id*.
170.43. *Id*. at 1061–62.
170.44. *Id*. at 1062–63.
170.45. Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367 (Fed. Cir. 2019).
170.46. *Id*. at 1380 (quoting *Bristol-Myers Squibb*, 752 F.3d at 975–76).

Sanofi marketed its patented cabazitaxel compound under the trade name Jevtana®, which was indicated to treat certain drug-resistant prostate cancers.[170.47] Cabazitaxel was one of hundreds of compounds that Sanofi had derived from docetaxel, a taxane that itself was used to treat drug-resistant tumors.[170.48] Specifically, two methoxy substitutions at C7 and C10 of docetaxel made the compound more lipophilic, which in turn improved its efficacy.[170.49] These substitutions are set forth below:



Finding that a person of ordinary skill in the art would have selected docetaxel as a lead compound, the district court then considered whether the person of ordinary skill in the art would have been motivated to replace the C7 and C10 hydroxyl groups of docetaxel with the methoxy groups to make cabazitaxel.[170.50] Ultimately, the district court found that modifications to docetaxel were considered at several positions and that it would not have been obvious to make simultaneous methoxy substitutions at C7 and C10 of docetaxel.[170.51]

The Federal Circuit affirmed. In reaching its determination, the court reasoned that no cited references supported that C7 or C10 methoxy-substituted taxanes have improved properties with respect to drug resistance.[170.52] While the prior art did suggest that a taxane analog with a methylthiomethoxy substitution at C7 had "promising qualities" against drug-resistant cell lines, the Federal Circuit noted that methylthiomethoxy groups differ from methoxy groups that were substituted to make cabazitaxel, and the district court found no evidence that the methoxy group would provide this similar benefit.[170.53]

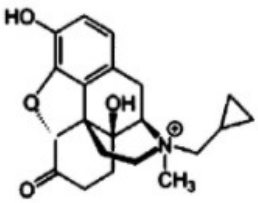
170.47. *Id.* at 1370–71.
170.48. *Id.* at 1371.
170.49. *Id.*
170.50. *Id.* at 1375.
170.51. *Id.* at 1377.
170.52. *Id.* at 1379.
170.53. *Id.* Methylthiomethoxy groups are structurally similar to methoxy groups but have sulfur. *See id.*

The Federal Circuit also took issue with appellants' characterization of *Bristol-Myers Squibb*.[170.54] Unlike in that case where there were a "small, finite number of changes to try," the district court found that there were numerous docetaxel modifications under investigation, and there was no showing that making individual or simultaneous methoxy substitutions at C7 and C10 improved activity against drug-resistant cells.[170.55] The court further stated that *Bristol-Myers Squibb* did not create a bright-line rule that small changes to a compound are necessarily prima facie obvious, as such a rule would be inconsistent with the "flexible analysis inherent to the highly contextual obviousness inquiry."[170.56]

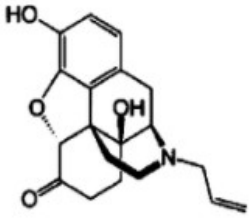
The Federal Circuit held in *Valeant Pharmaceuticals International, Inc. v. Mylan Pharmaceuticals Inc.*[170.57] that a POSA can expect compounds that share significant structural and functional properties to likewise share other related physical properties. In that case, the asserted patent claimed a stable pharmaceutical preparation comprising a solution of methylnaltrexone or a salt with a pH between about 3.0 and about 4.0, and a twenty-four-month stability period of that preparation. The district court granted summary judgment to the patent owner that the claimed preparation would not have been obvious, and the defendants appealed. While the case dealt with the obviousness of the claimed preparation, the Federal Circuit turned to its decisional law on the obviousness of chemical compounds.[170.58]

Methylnaltrexone, the compound recited in the claimed preparation, was known to be useful for reducing the side effects of opioids but was thought to be unstable in aqueous solution.[170.59] The inventors of the relevant patent-in-suit purportedly discovered that, when the pH of a methylnaltrexone solution is adjusted to between 3.0 and 3.5, the percentage of total degradants drops significantly.[170.60] Relatedly, the prior art taught that two similar compounds, naloxone and naltrexone, were useful as opioid antagonists.[170.61] The three compounds are shown below:

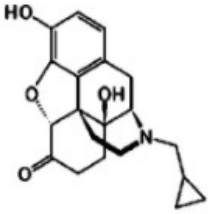
170.54. *Id*. at 1380 (citing *Bristol-Myers Squibb*, 752 F.3d at 975–76).
170.55. *Id*.
170.56. *Id*.
170.57. Valeant Pharm. Int'l, Inc. v. Mylan Pharm. Inc., 955 F.3d 25 (Fed. Cir. 2020).
170.58. *Id*. at 32.
170.59. *Id*. at 27.
170.60. *Id*.
170.61. *Id*. at 29.



Methylnaltrexone



Naloxone



Naltrexone

The prior art further taught that stable solutions of naloxone and naltrexone could be prepared using stabilizing agents.[170.62] In light of this, the defendants argued before the district court that, because methylnaltrexone bears significant structural and functional similarity to both naloxone and naltrexone, a person of skill in the art would seek to use prior disclosed pHs for naloxone and naltrexone when formulating solutions of methylnaltrexone.[170.63] The pH range, according to the defendants, was one of a finite number of options between pH 3 and pH 7 that a POSA would try based on the prior art. The district court disagreed because none of the prior art references explicitly taught methylnaltrexone formulations. It further reasoned that defendants' proposed pH range was "infinite, not finite."[170.64] It accordingly found that defendants had failed to make a prima facie case of obviousness and granted summary judgment in the patent owner's favor.

The Federal Circuit reversed and remanded. First, the court noted that there typically is a prima facie case of obviousness where the ranges of a claimed composition overlap or fell within the ranges disclosed in the prior art for the *same* claimed composition.[170.65] However, this appeal concerned whether there was a prima facie case for obviousness where the pH ranges of a claimed composition fell within the pH range of a structurally and functionally *similar*

170.62. *Id.*
170.63. *Id.* at 31.
170.64. *Id.* at 30.
170.65. *Id.* at 31.

compound.[170.66] The court concluded that they do, citing *Daiichi Sankyo* for the proposition that a prima facie case of obviousness "frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art."[170.67] Generally, the Federal Circuit held, "a person of skill in the art can expect that compounds with common properties are likely to share other related properties as well."[170.68] Thus, defendants set forth a prima facie case of obviousness sufficient to survive summary judgment.[170.69] The Federal Circuit further noted that the range of pH was not "infinite," as the record established only that pH was measured to two digits.[170.70]

Finally, the court cautioned that its "holding should not be misconstrued to mean that molecules with similar structure and similar function can always be expected to exhibit similar properties for formulation."[170.71] With respect to this case, the court noted that the patent owner could rebut the prima facie case for obviousness by establishing, by way of example, that the claimed pH range is critical or that the difference between the structures resulted in unexpected beneficial properties, or that the prior art teaches away from the claimed invention.[170.72] Accordingly, the court remanded for further consideration.[170.73]

[A][2][b][iii] Post-KSR District Court Decisions

This section addresses several post-*KSR* district court decisions on prima facie structural obviousness which either were not reviewed by the Federal Circuit or were affirmed by the Federal Circuit without a substantive opinion.

Bayer AG v. Dr. Reddy's Laboratories, Ltd.[171] involved an obviousness challenge to the claimed antibiotic moxifloxacin, the active ingredient in the drug product Avelox®. Dr. Reddy's had argued that one skilled in the art would have selected either of two prior art compounds as leads and modified them at the 7-position of the core structure to achieve moxifloxacin. As shown in the illustration, the

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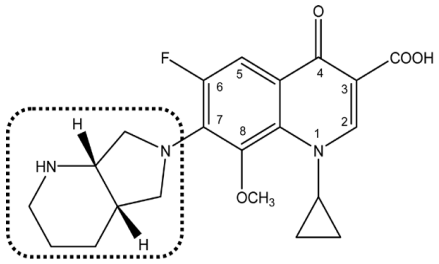
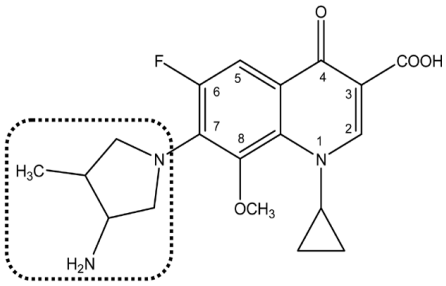
170.66. *Id*. at 32.
170.67. *Id*. (citing *Daiichi Sankyo*, 619 F.3d at 1352).
170.68. *Id*.
170.69. *Id*. at 33.
170.70. *Id*. at 34. That is to say that there are only eleven appreciable values in a pH range of 3.0 and 4.0 (3.0, 3.1, 3.2, etc.). *Id*.
170.71. *Id*. at 33.
170.72. *Id*.
170.73. *Id*. at 34. The parties settled after the court implemented the Federal Circuit's Mandate. *See* Valeant Pharm. Int'l, Inc. v. Mylan Pharm. Inc., 2:15-cv-08180-SRC-CLW (D.N.J. Dec. 28, 2020), ECF Nos. 420, 430.
171. Bayer AG v. Dr. Reddy's Labs., Ltd., 518 F. Supp. 2d 617 (D. Del. 2007).

only difference between the claimed moxifloxacin compound and the prior art Sankyo 1-130 compound was at the 7-position of the core structure.



Claimed Compound – Moxifloxacin



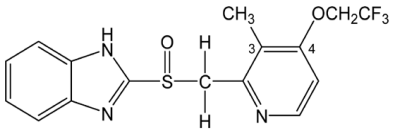
Prior Art EP241206 – "Sankyo 1-130"

The district court first rejected the selection of the asserted lead compounds: "[T]he court finds inadequate evidence to support Reddy's claim that a person of skill in the art would have been motivated to perform 7-position substituent modifications on [prior art compounds] AT-3295 or Sankyo 1-130 as compared to other prior art quinolones."[172] Second, the court rejected the argument that one skilled in the art would have been motivated to make the specific substitution to the asserted lead compounds necessary to achieve the claimed moxifloxacin compound: "[T]here is no indication that a person of ordinary skill in the art would have actually used the Bayer 5/5 bicycle [the claimed substituent]" at the 7-position.[173]

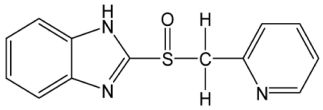
In *Takeda Pharmaceutical Co. v. Teva Pharmaceuticals USA Inc.*,[174] the Federal Circuit per curiam affirmed a district court's finding that the proton pump inhibitor lansoprazole, the active ingredient in Prevacid®, was not prima facie obvious over the prior art compounds timoprazole and omeprazole.[175]

172. *Id*. at 626–27.
173. *Id*. at 629.
174. Takeda Pharm. Co. v. Teva Pharm. USA Inc., 542 F. Supp. 342 (D. Del.), *aff'd per curiam*, 2008 WL 4831469 (Fed. Cir. Nov. 7, 2008).
175. Interestingly, lansoprazole was the compound asserted as prior art by the defendant in Eisai Co. v. Dr. Reddy's Labs. Ltd., 533 F.3d 1353 (Fed. Cir. 2008), discussed above, in the unsuccessful effort to argue that the claimed compound rabeprazole was prima facie obvious.

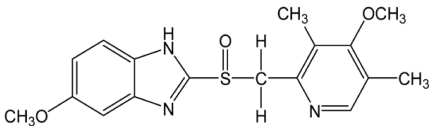
Claimed Compound
Lansoprazole (PPI)



Prior Art Compounds
Timoprazole (PPI)



Omeprazole (PPI)



While the district court agreed with Teva that "a person of ordinary skill in the art, seeking to make an improved PPI, would have started with timoprazole and focused on the four key locations on the skeleton, as evidenced by . . . omeprazole,"[176] it did not find a motivation to modify the prior art in the manner needed to achieve lansoprazole:

> What is lacking, however, is an indication that such a person would have been motivated to substitute the trifluoroethoxy substituent . . . onto the 4-position of the pyridine ring to form lansoprazole (while leaving [other positions] substituent free) or would have had a reasonable expectation of success in doing so.[177]

In particular, Teva did not identify a sufficient suggestion in the art for moving the 2,2,2-trifluoroethoxy group to the pyridine ring as required in the claimed compound.[178]

In *Novartis Pharmaceutical Corp. v. Teva Pharmaceuticals USA, Inc.*,[179] the district court denied a preliminary injunction based on the defendant's raising a "substantial question" regarding the validity of the claimed compound famciclovir, the active ingredient in the antiviral drug product Famvir®. Like *Altana*, discussed above, the issue of structural obviousness was addressed on a preliminary injunction record, rather than on a full record after trial.

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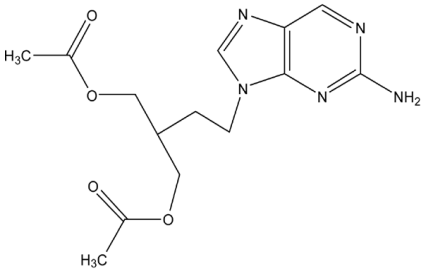
176. *Takeda Pharm. Co.*, 542 F. Supp. 2d at 357.
177. *Id*. at 357–58.
178. *Id*. at 358–59.
179. Novartis Pharm. Corp. v. Teva Pharm. USA, Inc., 2007 U.S. Dist. LEXIS 65792 (D.N.J. Sept. 6, 2007), *aff'd without opinion*, 2008 U.S. App. LEXIS 12299 (Fed. Cir. June 9, 2008).

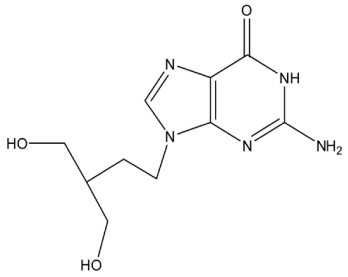
In denying plaintiffs' motion for a preliminary injunction, the district court found that the defendant had raised a substantial question regarding the validity of the compound famciclovir, which converts after ingestion to the prior art antiviral compound penciclovir. The main issue was whether the prior art would have motivated one skilled in the art to select penciclovir as a lead compound for an antiviral drug and modify it to make famciclovir as a "prodrug" for penciclovir.[180]

Claimed Compound – Famciclovir



Prodrug for Penciclovir

Prior Art Compound – Penciclovir



Anti-viral

The district court based its conclusion that the defendant had raised a substantial question about validity on a number of factual determinations. The court noted that the prior art penciclovir antiviral compound was "poorly absorbed when dosed orally,"[181] but "was one of only five known acyclic nucleosides to have strong activity and low toxicity."[182] Accordingly, the district court concluded that, unlike in *Takeda v. Alphapharm*, discussed above, where the prior art disclosed "'hundreds of millions,'" of potential lead compounds, in the instant case, "penciclovir was one of only a few compounds that would act as an effective lead compound."[183] In addition, the district court concluded that based on the art, one skilled in the art would have expected penciclovir to have poor oral bioavailability and would have been motivated to make pencivlovir into a prodrug.[184] Finally,

180. "Prodrugs are pharmaceutical compounds that do not have the desired activity (in this case antiviral effects), but are converted into the active compound when inside the body." 2007 U.S. Dist. LEXIS 65792, at *3.
181. *Id*. at *5.
182. *Id*. at *17.
183. *Id*.
184. *Id*. at *20–21.

the district court concluded that it would have been obvious from the prior art to make the particular modifications to penciclovir needed to achieve famciclovir.[185] The district court cited prior art which described making prodrugs of other acyclic nucleosides, including acyclovir, with the same modifications to improve oral bioavailability and concluded that the prior art "provided clear motivation" to make those modifications to penciclovir and achieve famciclovir.[186]

In *Pfizer, Inc. v. Mylan Pharmaceuticals Inc.*,[186.1] the district court rejected a structural obviousness challenge to patents claiming the sutinib malate active ingredient contained in the cancer treatment drug product Sutent®. The court rejected the defendant's proposed "lead compounds" from the prior art because the art taught away or because there was no data supporting the selection of the proposed compound.[186.2] The court also concluded that even if one skilled in the art would have selected a lead compound, it would not have been obvious to have made the modifications necessary to achieve the structure of sutinib.[186.3] The court also concluded that the selection of the malate salt form of sutinib was not obvious, citing evidence that malate was not a commonly used salt for pharmaceutical compounds and the "inherent unpredictability of acid salts" as acknowledged by both parties' experts.[186.4] Accordingly, the court concluded that the defendant had failed to make a prima facie showing of obviousness. Finally, the court concluded that even if a prima facie showing of obviousness had been made, "secondary considerations—unexpected properties, long-felt need, failure of others, commercial success, skepticism, and acceptance and praise—support a determination of non-obviousness."[186.5]

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185. *Id*. at *21–26.

186. *Id*. at *22–25.

186.1. Pfizer, Inc. v. Mylan Pharm. Inc., 71 F. Supp. 3d 458 (D. Del. 2014), *aff'd*, 628 F. App'x 763 (Fed. Cir. 2016).

186.2. *Id*. at 469–72.

186.3. *Id*. at 472–74.

186.4. *Id*. at 474. In finding the malate salt form nonobvious, the court distinguished the Federal Circuit's decision in Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007) and cited the later Federal Circuit decision in Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008), which upheld a district court's determination of the nonobviousness of the selection of a particular salt form.

186.5. *Id*. at 475. Other district court decisions have rejected structural obviousness challenges to patents directed to pharmaceutical compounds applying the "lead compound" analysis. Merck Sharp & Dohme Corp. v. Sandoz Inc., 2015 WL 5089543 (D.N.J. Aug. 27, 2015) (defendants' failed to establish sufficient motivation to select a lead compound and therefore did not establish prima facie obviousness, and even if prima facie obviousness had been established, secondary considerations supported

In *AstraZeneca AB v. Aurobindo Pharma Ltd.*,[186.6] the district court found that the defendant failed to establish by clear and convincing evidence that a person of ordinary skill in the art would have selected vildagliptin as a lead compound and then modified it to obtain saxagliptin.[186.7] The compound at issue, saxagliptin, is marketed as Onglyza® to treat adults with type 2 diabetes.[186.8] The chemical structure of saxagliptin is as shown:[186.9]

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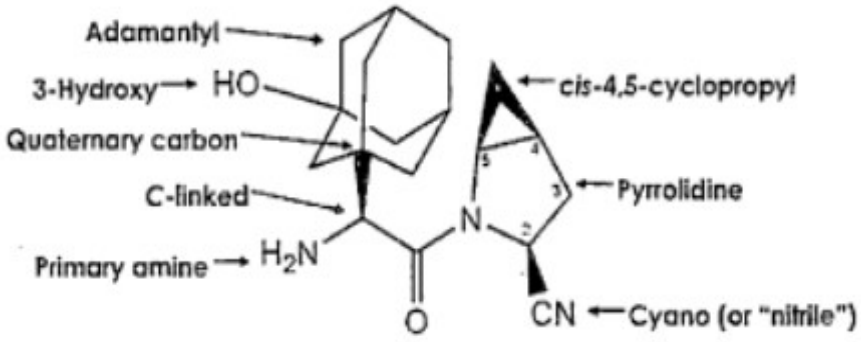
nonobviousness); Pfizer Inc. v. Sandoz Inc., 2016 WL 1611377 (D. Del. 2016) (court held that it would not have been obvious to have selected proposed lead compound to make a prodrug or to modify the proposed lead compound to arrive at the claimed prodrug compound). As of September 30, 2016, the following cases were on appeal to the Federal Circuit: Bayer Pharma AG v. Watson Lab., Inc., 2016 WL 2343488 (D. Del. May 2, 2016) (defendant failed to establish that a person of skill in the art would have selected its proposed lead compound, or that even if the proposed lead would have been selected, a person skilled in the art would have modified it to arrive at the claimed compound); UCB, Inc. v. Accord Healthcare, Inc., 2016 WL 4376346 (D. Del. Aug. 12, 2016), *aff'd* 890 F.3d 1313 (Fed. Cir. 2018) (defendants failed to establish that a person of skill in the art would have selected their proposed lead compounds, or that even if one of the proposed lead compounds would have been selected, a person skilled in the art would have modified it to arrive at the claimed compound); Vanda Pharm. Inc. v. Roxane Lab. Inc., 2016 WL 4490701 (D. Del. Aug. 25, 2016), *aff'd sub nom.* Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd., 887 F.3d 1117 (Fed. Cir. 2018) (rejecting defendants "lead compound" theory asserted against a claimed compound having atypical antipsychotic activity because one proposed lead (Compound A) was known to have tranquilizing activity, not antipsychotic activity, and the other proposed lead (Compound B), although having antipsychotic activity, had caused "serious cardiac side effects" in clinical trials, and further because defendant had failed to demonstrate that the modifications necessary to solve the adverse side effects of Compound B were known in the prior art); *In re* Depomed Pat. Litig., No. 13-4507, 2016 WL 7163647 (D.N.J. Sept. 30, 2016), *aff'd sub nom.* Grunethal GMBH v. Alkem Labs. Ltd., 919 F.3d 1333 (Fed. Cir. 2019) (defendants failed to clearly and convincingly show that (1) a POSA would have selected tramadol or its metabolites as lead compounds; and (2) the prior art motivated the modifications necessary to convert the tramadol to tapentadol hydrochloride with reasonable expectation of success).

186.6. AstraZeneca AB v. Aurobindo Pharma Ltd., 232 F. Supp. 3d 636 (D. Del. 2017). Defendants Aurobindo Pharma Ltd., Actavis Laboratories FL, Inc., Watson Laboratories, Inc., and Mylan Pharmaceuticals Inc. filed notices of appeal shortly after the judgment was entered in favor of the plaintiff on February 2, 2017. The appeals were either voluntarily dismissed or dismissed for failure to prosecute.

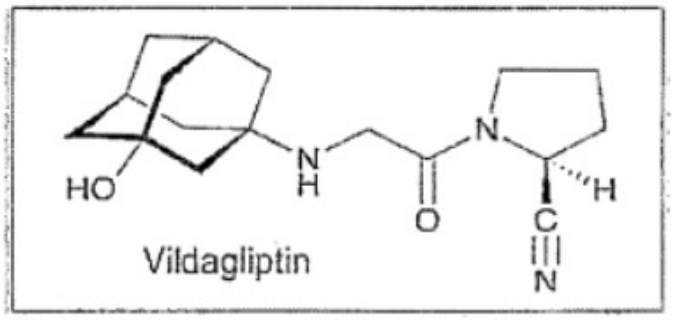
186.7. *Id*. at 649.

186.8. *Id*. at 641.

186.9. *Id*.



To establish a prima facie case of obviousness, the defendant had to show that a person of ordinary skill in the art would have selected vildagliptin as shown below[186.10] as the lead compound, a reason for selecting vildagliptin, and a reason to modify vildagliptin to saxagliptin.[186.11]



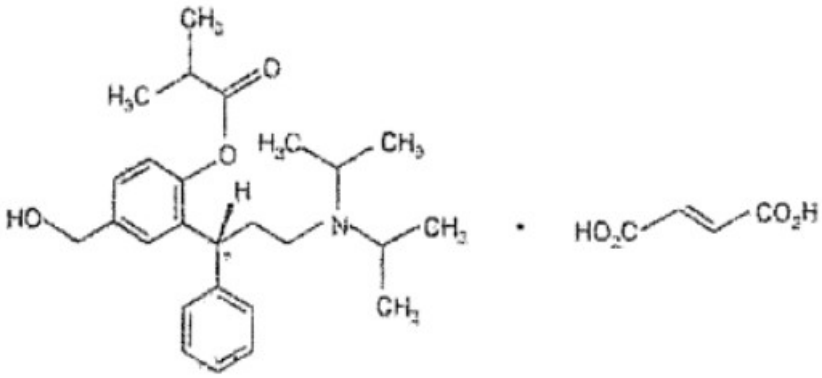
The district court found that a person of ordinary skill in the art would not have been motivated to select vildagliptin as a lead compound and that the defendant's expert had relied on hindsight bias.[186.12] In particular, the district court found that there were a number of other chemical compounds that could have been a natural lead.[186.13] For example, there were at least two more advanced compounds that had entered the clinic at the time.[186.14] The district court noted that the defendant's expert "did not perform an analysis of the art as a whole . . . [but] looked at the chemical structure of saxagliptin . . . [and] looked to a selection of prior art *handpicked* by Aurobindo's

186.10. *Id*. at 646.
186.11. *Id*. at 645.
186.12. *Id*. at 647.
186.13. *Id*. at 646–47.
186.14. *Id*. at 646.

counsel in order to select the compound for his obviousness analysis."[186.15] In addition, the district court found that the defendant had failed to show a motivation to modify vildagliptin to saxagliptin with a reasonable expectation of success.[186.16] First, the plaintiff showed that the prior art taught away from moving the hydroxyadamantyl group from the nitrogen of the glycine to the alpha-carbon of the glycine because such modification would reduce the stability of the chemical compound.[186.17] Second, the defendant had failed to show that a person of ordinary skill in the art would have been motivated to make a second modification: adding a cyclopropyl ring to address the stability problem.[186.18] The experts agreed that there was no way to predict from the prior art what the effect of cyclopropanation would have been and that there was no reasonable expectation of success in adding cyclopropyl.[186.19] For the foregoing reasons, the district court concluded that the asserted claims of the patent-in-suit are not invalid due to obviousness.[186.20]

In *Pfizer Inc. v. Mylan Pharmaceuticals Inc.*,[186.21] the district court determined that the defendant had failed to meet its burden to show that a person of ordinary skill in the art would have selected 5-hydroxymenthyl tolterodine (5-HMT) as a lead compound and, even further, modified 5-HMT to make its prodrug, fesoterodine.[186.22] The compound at issue, fesoterodine, is marketed as Toviaz® (fesoterodine fumarate extended-release tablets) to treat overactive bladder.[186.23] The structural formula of fesoterodine fumarate is as shown below:[186.24]

186.15. *Id*. at 647.
186.16. *Id*. at 649.
186.17. *Id*. at 647.
186.18. *Id*. at 648.
186.19. *Id*. at 649.
186.20. *Id*. at 650.
186.21. Pfizer Inc. v. Mylan Pharm. Inc., No. 15-79-GMS, 2017 WL 3412301 (D. Del. Aug. 9, 2017). In September 2017, the defendant appealed to the Federal Circuit. In January 2018, the Federal Circuit granted the defendant's motion to dismiss the appeal.
186.22. *See id*.
186.23. *Id*. at *1.
186.24. *Id*. at *2.



In determining the obviousness of a new chemical compound, the district court reviewed: (1) whether a chemist of ordinary skill would have selected 5-HMT as a lead compound for further development and (2) whether the prior art would have motivated a person of ordinary skill in the art to modify 5-HMT to make fesoterodine with a reasonable expectation of success.[186.25] First, the district court concluded that a person of ordinary skill in the art would have focused on antimuscarinic compounds at the time and had several lead compounds to consider in addition to 5-HMT.[186.26] For example, tolterodine is a compound that a person of ordinary skill would have also considered due to its similar benefits and limitations as 5-HMT.[186.27] Second, even if 5-HMT was selected as a lead compound, the court found that a person of ordinary skill in the art would not have been motivated to modify 5-HMT and create a prodrug.[186.28] In particular, the district court found that a person of ordinary skill in the art would not have had a reason to assume poor oral absorption associated with 5-HMT and modify it to improve its absorption.[186.29] The district court also agreed with the plaintiff that the prodrug approach is a "last resort."[186.30] Finally, assuming a person of skill in the art was motivated to create a prodrug of 5-HMT, the district court concluded that fesoterodine would not have been the obvious choice.[186.31] The district court found that the defendant had failed to prove that a person of ordinary skill in the art would have known to "(1) use an ester prodrug, (2) add the substituent to *only* the phenolic hydroxyl, and (3) use an isobutyryl substituent, *and* (4) that a person of ordinary

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186.25. *Id.* at *9 (citing Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1291–92 (Fed. Cir. 2012)).
186.26. *Id.* at *9–10.
186.27. *Id.* at *11.
186.28. *Id.*
186.29. *Id.* at *12.
186.30. *Id.*
186.31. *Id.* at *13.

skill would have had a reasonable expectation of success regarding the resulting compound's properties."[186.32] Further, the district court addressed the salt forms of fesoterodine claimed in one of the patents-in-suit and concluded that the salt formation process was highly unpredictable and, therefore, non-obvious.[186.33]

In *Onyx Therapeutics, Inc. v. Cipla Ltd.*,[186.34] the district court found that the defendant had failed to show that YU-101 would have been prima facie obvious over prior art compounds and further failed to prove that it was obvious to modify YU-101 to arrive at carfilzomib with a reasonable expectation of success.[186.35] The compound at issue, carfilzomib, is marketed as Kyprolis® to treat multiple myeloma.[186.36] To determine the obviousness of carfilzomib, the district court applied the two-part inquiry of the "lead compound" analysis as described previously.[186.37] First, the district court found that a person of ordinary skill in the art would not have selected YU-101 as a lead compound.[186.38] YU-101 is an irreversible inhibitor, which the industry had a strong aversion to at the time due to its potential catastrophic side effects.[186.39] Instead, a person of ordinary skill in the art would have chosen bortezomib, or other known reversible inhibitors, as a lead compound based on its human potency data and FDA approval for treating cancer at the time.[186.40] Second, even if a person of skill in the art would have selected YU-101 as a lead compound, the district court concluded that a person of skill in the art would not have had a reason to modify YU-101's N-terminus with a morpholino methylene.[186.41] The district court found that YU-101 had solubility problems and that "adding morpholino moieties was one of many known options for potentially increasing solubility."[186.42] However, the defendant had failed to show that a person of ordinary skill in the art "would have been motivated *specifically* to place a morpholino methylene on the N-terminus."[186.43] Moreover, the defendant

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186.32. *Id*.
186.33. *Id*. at *14.
186.34. Onyx Therapeutics, Inc. v. Cipla Ltd., No. 16-988-LPS, 2020 WL 2214443 (D. Del. May 4, 2020), *aff'd*, 839 F. App'x 545 (Fed. Cir. 2021).
186.35. *See id*.
186.36. *Id*. at *2.
186.37. *Id*. at *23.
186.38. *Id*. at *24.
186.39. *Id*.
186.40. *Id*. at *24–25.
186.41. *Id*. at *28.
186.42. *Id*. at *29.
186.43. *Id*. at *28 (emphasis added).

had failed to show that there was a reasonable expectation of success that this modification would work for its intended result.[186.44] The district court also found that the plaintiff had proved long-felt unmet need and industry skepticism.[186.45]

[A][2][c] Reason to Combine[187]

In the absence of a sufficient structural similarity between a prior art and a claimed compound to give a reason to the skilled artisan to make the claimed compound, one may attempt to demonstrate prima facie obviousness by combining multiple references describing different portions of the compound if there is sufficient reason or motivation to combine the references.[188] Several cases illustrate finding prima facie obviousness based on a suggestion in the art to combine references.[189] The mere fact that different prior art compounds, if combined, yield the claimed compound does not make a prima facie case of obviousness.[190] In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, the Federal Circuit stated that even after *KSR*,

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186.44. *Id*. at *29.

186.45. *Id*. at *30.

187. As discussed previously, the Supreme Court's expected decision in KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007), rejected what it called the Federal Circuit's "rigid" application of the TSM test for obviousness, which requires a teaching, suggestion, or motivation to combine the teachings of the prior art to make the changes needed to achieve the claimed invention. The effect of *KSR* on Federal Circuit law regarding chemical obviousness remains to be seen.

188. *See Yamanouchi*, 231 F.3d at 1343 ("At the heart of this validity dispute is whether one of skill in this art would have found motivation to combine pieces from one compound in a prior art patent with a piece of another compound in the second prior art patent through a series of manipulations."); Eli Lilly & Co. v. Teva Pharm. USA, Inc., 2004 WL 1724632, at *35 (S.D. Ind. July 29, 2004) ("Teva must point to 'the specific sources of the motivation to combine prior art references' in order to prevail on this theory.") (quoting Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1374 (Fed. Cir. 2000)).

189. *In re* Zenitz, 333 F.2d 924, 925 (C.C.P.A. 1964) (noting board affirmance of obviousness based on reference that "discloses compounds identical to those claimed except for a chloro (Cl) substituent in place of the trifluoromethyl (CF_3) substituent in the claimed compounds" and references that establish "the substitution of Cl and CF_3 potentiating groups in phenothiazines analogous to those now claimed"); *In re* Herr, 304 F.2d 906, 909 (C.C.P.A. 1962) (claimed testosterone derivative obvious over prior art disclosing same compound without "a methyl group in the 17 position" and "two compounds used as standards in the art hav[ing] exactly the same structural difference").

190. *See Yamanouchi*, 231 F.3d at 1345 ("Danbury also does not show the motivation to combine the polar tail of example 44 with the

"it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound."[191] If the prior art fails to suggest the precise changes required to obtain the claimed compound, the prior art should not provide a motivation to combine.[192] The fact that any changes to the steps required to modify the prior art into the claimed compound yield compounds with inferior activity can show the modification was not obvious.[193]

[A][3] Nonobviousness Where Prior Art Teaches Away from Claimed Compound

An assertion that a chemical compound is obvious can be negated by a showing that the prior art "taught away" from the claimed compound. For example, in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*,[194] the generic challenger argued that the claimed pharmaceutical compound was obvious in view of a structurally related prior art compound. The Federal Circuit rejected the challenge and concluded that the claimed compound was not prima facie obvious because, among other things, the prior art taught away from the use of the structurally related prior art compound because of its adverse side effects.[195] Similarly, a finding that the prior art taught away from nonhalogenated compounds was held in *Eli Lilly and Company v. Zenith Goldline Pharmaceuticals, Inc.*[196] to support the non-obviousness of the compound olanzapine, which had a hydrogen atom at the relevant position instead of a halogen (fluorine or chlorine) atom as taught by the prior art. Also, in *In re Baird*,[197] the

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substituted heterocycle of tiotidine, then to substitute the carbamoyl with a sulfamoyl.").

191. Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

192. *Yamanouchi*, 231 F.3d at 1345 ("[T]he prior art offers no suggestion to pursue the particular order of manipulating parts of the compounds. Danbury's proposed obvious course of invention requires a very specific series of steps.").

193. *Id*. ("Any deviation in the order of combination would have taught away from famotidine. If, for instance, the sulfamoyl group were substituted for the carbamoyl group on example 44 without attaching the substituted heterocycle from tiotidine, the evidence showed that the resulting compounds would have 1/100th the activity of cimetidine [the prior art standard drug].").

194. *Takeda Chem. Indus., Ltd.*, 492 F.3d 1350.

195. *Id*. at 1358–59.

196. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1377–80 (Fed. Cir. 2006).

197. *In re* Baird, 16 F.3d 380 (Fed. Cir. 1994).

Federal Circuit concluded that a claimed bisphenol A chemical compound that was encompassed by a broad prior art genus of more than 100 million different diphenol compounds was not obvious where the prior art taught away "from the selection of bisphenol A by focusing on more complex diphenols."[198]

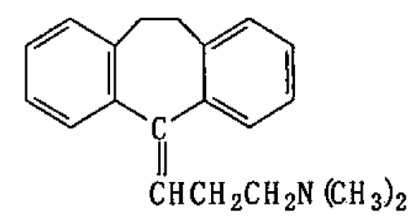
Accordingly, evidence that the prior art would have led a person of ordinary skill in the art away from, rather than toward, a claimed compound can support patentability.

*[A][4] Examples from Pre-*KSR *Decisions*

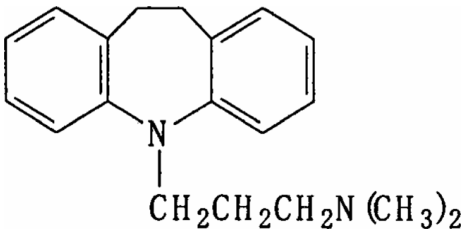
[A][4][a] Finding Structural Obviousness

In re Merck & Co.[199]

Claim: Method of treating depression in humans by the oral administration of amitriptyline.



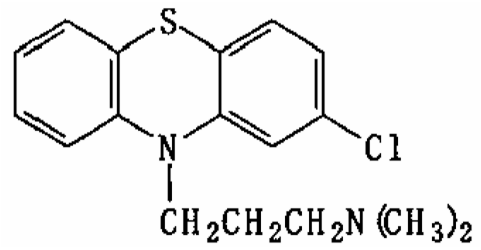
Prior Art: (a) The compound imipramine



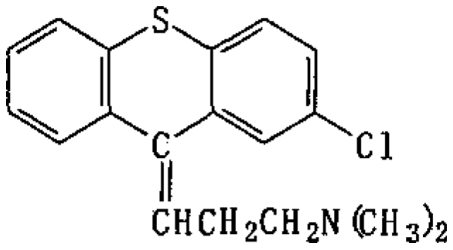
and its use as an antidepressant in humans.

(b) The theory of "biosterism", where the substitution of one atom or group of atoms for another atom or group of atoms having similar size, shape and electron density provides molecules having the same type of biological activity and a teaching that the interchange of the nitrogen atom in the central ring of chlorpromazine

198. *Id*. at 382.
199. *In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986).



for an unsaturated carbon atom as in the compound chlorprothiazine



does not change the strong tranquillizing activity of the compound.

(c) A suggestion that amitriptyline, based on its structural relationship to imipramine, should be tested for alleviation of depression.

Holding: The claim was prima facie obvious because the prior art teachings "show a close structural similarity and a similar use (psychotropic drugs) between amitriptyline and imipramine, one of ordinary skill in the medicinal chemical arts . . . would have expected amitriptyline to resemble imipramine in the alleviation of depression in humans."[200]

In re Dillon[201]

Claim: A composition comprising a hydrocarbon fuel and a sufficient amount of a tetra-orthoester to reduce particulate emissions from the combustion of the hydrocarbon fuel.

Prior Art: (a) The use of tri-orthoesters to dewater hydrocarbon fuels.

(b) The use of tri-orthoesters and tetra-orthoesters to dewater hydraulic (non-hydrocarbon) fuels.

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200. *Id*. at 1097.
201. *In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990).

Holding: Claimed composition was prima facie obvious because prior art would have motivated one skilled in the art to have made the claimed composition using tetra-orthoesters, albeit for a different purpose (dewatering) from the purpose recited in the claim (reduction of particulate emissions). The claim recited a composition and was not limited to any particular use.

In re Mayne[202]

Claim: A fusion protein comprising a polypeptide sequence linking an enterokinase cleavage site to either human growth hormone (HGH) or bovine growth hormone (BGH).

Met-Phe-Pro-Leu-$(Asp)_4$-Lys (HGH or BGH)

The enzyme enterokinase recognizes the cleavage site to produce mature HGH or BGH; "Met necessarily results from translation of RNA into proteins."

Prior Art: (a) The prior art taught fusion proteins having the sequence X-$(Asp)_4$-Lys-Y, where X is an enterokinase cleavage site and Y is the desired protein.

(b) The sequences for HGH and BGH and a motivation to link an enterokinase cleavage site to create a fusion protein.

(c) Enterokinase cleavage sites, including Phe-Pro-Ile.

Holding: Claimed polypeptide sequence was prima facie obvious; the amino acids Leu and Ile are isomers with the same number of hydrogen and carbon atoms and both are nonpolar, hydrophobic amino acids. "The structure of Leu and Ile alone suggest their functional equivalency." Therefore, the prior art disclosure of Phe-Pro-Ile rendered Phe-Pro-Leu obvious.

Pfizer v. Sanofi[202.1]

Claim: An immunogenic composition comprising a *Streptococcus pneumoniae* serotype 22F glycoconjugate, wherein the glycoconjugate has a molecular weight of between 1000 kDa and 12,500 kDa and comprises an isolated capsular polysaccharide from *S. pneumoniae* serotype 22F and a carrier protein, and wherein a ratio (w/w) of the polysaccharide to the carrier protein is between 0.4 and 2.

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202. *In re* Mayne, 104 F.3d 1339 (Fed. Cir. 1997).

202.1. Pfizer Inc. v. Sanofi Pasteur Inc., Nos. 2019-1871, -1873, -1875, -1876, -2224, 2024 U.S. App. LEXIS 5221 (Fed. Cir. Mar. 5, 2024).

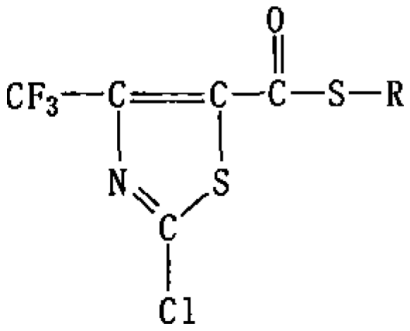
Prior Art:
- GSK-711 discloses Streptococcus pneumoniae serotype glycoconjugates having molecular weights within the range of approximately 1303 kDa to 9572 kDa.
- GSK-711 discloses that "saccharide conjugate vaccines retaining a larger size of saccharide can provide a good immune response against pneumococcal disease."
- GSK-711 and Merck-086 disclose that known methods and techniques could be used to isolate the polysaccharide from the bacteria and to couple it to a carrier protein.

Holding: Pfizer's patent claims were obvious based on the teachings of the prior art and the reasonable expectations of a person skilled in the field. Although the prior art did not explicitly mention the molecular weight range specified in Pfizer's claims, it did discuss similar ranges for other serotypes. A person skilled in the art would have been motivated to optimize molecular weight to improve stability and immune response.

[A][4][b] Finding No Structural Obviousness

In re Grabiak[203]

Claim: A compound that protects crops against herbicides (also known as a "safener") having the structure:



having a sulfur atom in the ester moiety.

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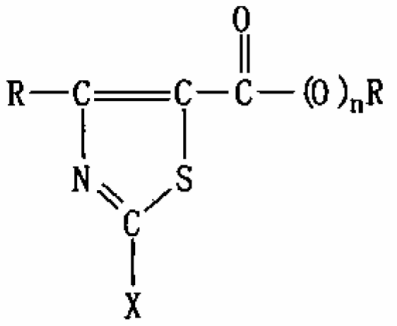
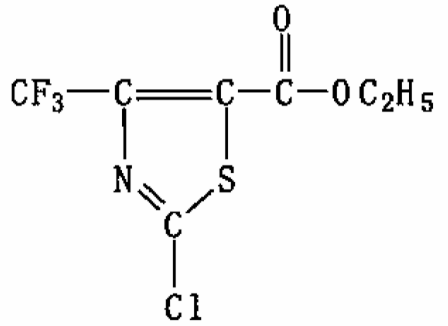
203. *In re* Grabiak, 769 F.2d 729 (Fed. Cir. 1985).

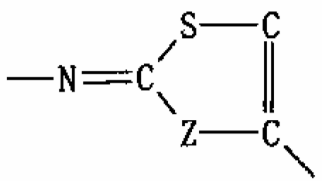
Prior Art: (a) A primary reference (Howe) showing safener compounds having the general structure:



Having an oxygen in the ester moiety, and describing the following specific compound:



(b) A secondary reference (Bollinger) showing safener compounds having the structure

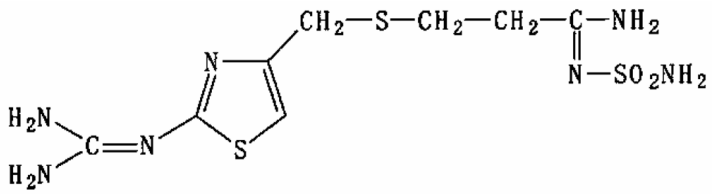


that the examiner argues showed the interchangeability of sulfur and oxygen in safener compounds.

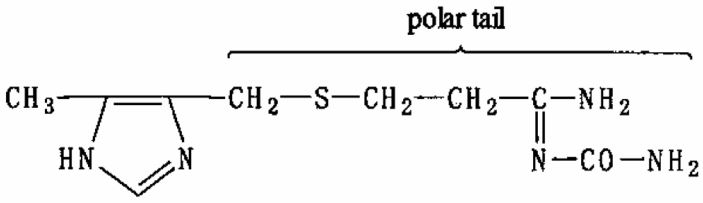
Holding: No prima facie based on structural similarities. The teaching of substitutability of sulfur for oxygen in the ring of the structure of the secondary reference does not suggest substituting sulfur for oxygen in the ester moiety of the primary reference. There is no teaching of the predictability of making the change required to achieve the claimed compound.

Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.[204]

Claim: The compound famotidine, useful for treating heartburn and ulcers, having a structure:

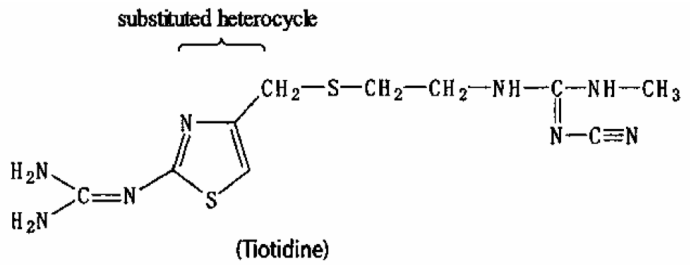


Prior Art: Defendant argued it would have been prima facie obvious to have made famotidine by combining the polar tail from:



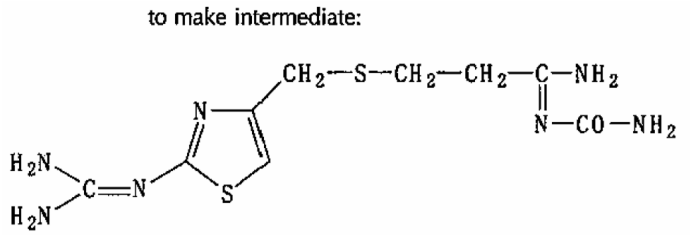
(Example 44 from U.S. Patent 4,252,819)

with the substituted heterocycle from:



(Tiotidine)

to make intermediate:



204. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000).

and then to substitute a sulfamoyl group (SO_2NH_2) for the carbamoyl group (CON H_2) of the intermediate to achieve famotidine.

Defendant argued that it would have been obvious to select Example 44 and tiotidine as "leads for making famotidine" because "[t]hese compounds, respectively, are three and eleven times more active than cimetidine—the benchmark compound at the time of the invention."[205]

Holding: Famotidine is not structurally obvious; defendant's argument was a hindsight reconstruction of the claimed compound; no suggestion to select the lead compounds or to manipulate them in the precise way to arrive at famotidine.

[B] Rebutting a Prima Facie Case of Obviousness

A prima facie case of obviousness shifts the burden to the applicant to come forward with evidence or argument in rebutta1.[206] It is well settled that "a compound and all of its properties are inseparable" and that the properties of a compound are to be considered in determining obviousness.[207] "A prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties."[208] Unexpected results are used

> to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would

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205. *Id*. at 1343–44.
206. *Mayne*, 104 F.3d at 1343; *In re* Soni, 54 F.3d 746, 749 (Fed. Cir. 1995); *In re* Rijckaert, 9 F.3d 1531, 1532 (Fed. Cir. 1993).
207. *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963) (close structural similarity between a claimed compound and a prior art compound, such as between homologs, does not prove obviousness in the face of proof that a claimed compound has "an advantageous pharmacological property shown not to be possessed by the prior art compound"); *id.* at 383, 387.
208. *In re* Payne, 606 F.2d 303, 315–16 (C.C.P.A. 1979); *see also In re* Merck & Co., 800 F.2d 1091, 1098 (Fed. Cir. 1986) ("A prima facie case of obviousness can be rebutted by evidence of unexpected results."); *In re* Mehta, 347 F.2d 859, 864 (C.C.P.A. 1965) ("The similarity of properties of a reference compound as compared with a claimed compound gives rise to an even stronger inference of obviousness than that of structural similarity alone, and conversely, where the properties are different, they imply nonobviousness, when they are unexpected."). In addition, a prima facie case of obviousness can be rebutted by the so-called "secondary indicia" of nonobviousness. *See supra* section 5:3.7.

> not have been obvious. The principle applies most often to the *less* predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.[209]

[B][1] Unexpected Results Require a Showing of Actual Differences

Evidence of unexpected properties cannot be based merely on evidence that the prior art did not describe the property possessed by the new compound. It requires proof that actual differences exist in the properties of the prior art and claimed compounds.[210] Moreover, a property or feature inherently in the prior art, although unknown to the prior art, "is not a basis for rebutting a prima facie finding of obviousness."[211]

[B][2] Compared to Closest Prior Art

Comparative tests to show unexpected results of a claimed compound must be with the closest prior art compounds.[212] "Direct comparison," however, "with the closest prior art is not required in all

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209. *Soni*, 54 F.3d at 750.

210. *In re* Albrecht, 514 F.2d 1389, 1396 (C.C.P.A. 1975) ("That a claimed novel compound possesses a certain advantageous activity which is not in fact possessed by a prior art compound is itself evidence of the non-obviousness of the subject matter as a whole."); *In re* Hoch, 428 F.2d 1341, 1344 (C.C.P.A. 1970) ("[A]ctual differences in properties are required to overcome a prima facie case of obviousness because the prima facie case, at least to a major extent, is based on the expectation that compounds that are very similar in structure will have similar properties. Therefore, to overcome the prima facie case, it must be shown that the expectation on which it is based was in fact unsound—as by showing that there are substantial, actual differences in properties."); *In re* Mod, 408 F.2d 1055, 1056 (C.C.P.A. 1969) ("In view of this showing by appellants that actually the prior art compounds do possess antimicrobial activity, we are not persuaded that the particular compounds claimed possess an unobvious property and are, therefore, patentable."). It should be noted that other references may bear on the issue of whether results of a comparison with the closest prior art are in fact "unexpected." *See In re* Merchant, 575 F.2d 865, 869 (C.C.P.A. 1978) ("Though particular results appear unexpected in a comparison with the closest single prior art reference, the teaching of another reference may establish that those results would have been expected by those skilled in the art.").

211. *In re* Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("Since the prior art bags plasticized with DEHP were inherently suppressing hemolysis, albeit unknown at the time of the Becker document, this hemolysis-suppressing function is not a basis for rebutting a prima facie finding of obviousness.").

212. *Payne*, 606 F.2d at 316; *Baxter*, 952 F.2d at 392 ("[W]hen unexpected results are used as evidence of non-obviousness, the results must be

cases."[213] Whether direct or indirect, unexpected properties must be assessed against the entire teaching of the closest prior art reference, not simply an unrepresentative example.[214] Hindsight cannot be used to choose the closest prior art.[214.1]

[B][3] Differences Must Match Scope of Claim

A showing of unexpected results "must be commensurate in scope with the claims to which it pertains."[215] Thus, a broader claim requires proof that the showing of unexpected results is applicable across the breadth of the claim, and not just to a limited number of species.[216] Narrower claims require fewer examples of unexpected properties.[217]

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shown to be unexpected compared with the closest prior art."); *In re* De Blauwe, 736 F.2d 699, 705 (Fed. Cir. 1984) ("[A]n applicant relying on comparative tests to rebut a prima facie case of obviousness must compare his claimed invention to the closest prior art."); *Merchant*, 575 F.2d at 869 ("An applicant relying upon a comparative showing to rebut a prima facie case must compare his claimed invention with the closest prior art.").

213. *Merchant*, 575 F.2d at 869 n.8 (citing *In re* Blondel, 499 F.2d 1311, 1317 (C.C.P.A. 1974)); *see also In re* Fouche, 439 F.2d 1237, 1241 (C.C.P.A. 1971) (comparison with unsaturated compound permissible even though closest prior art was a saturated compound, because literature "indicate[s] that the unsaturated derivatives are more active than the saturated ones, and [applicant's] evidence showed that the claimed compound was more active than the best of the unsaturated derivatives").

214. *See Payne*, 606 F.2d at 316–18 ("Payne may not, however, rely on his mere assertion that the *Addor I* compound is 'representative and superior in pesticidal properties to the compounds described in *Addor II, Addor III, Ghosh and Nikles.*' None of the latter, allegedly inferior compounds was tested."); *In re* Chapman, 357 F.2d 418, 423–24 (C.C.P.A. 1966) (rejecting evidence of difference from prior art because, inter alia, applicant only compared one example involving polyethylene of 60,000 molecular weight in prior art that was not representative of other examples at a molecular weight of 500,000 to 3,000,000).

214.1. Millennium Pharm. v. Sandoz Inc., 852 F.3d 1356, 1368 (Fed. Cir. 2017) (rejecting challenger's attempt to select a specific species encompassed within a prior art genus because it "was not specifically disclosed, prepared, or tested").

215. *In re* Dill, 604 F.2d 1356, 1361 (C.C.P.A. 1979).

216. *See Soni*, 54 F.3d at 751 (noting that where evidence of unexpected superiority is limited to a single species within a claimed range, an issue is raised as to whether proof is commensurate with the scope of the claims).

217. *In re* Greenfield, 571 F.2d 1185, 1188 (C.C.P.A. 1978) ("If appellants had established that several of the species within claims 7 and 9," which claim a small number of species, "were subject to decomposition . . . they would have a basis for arguing that the burden has been shifted back to the PTO.").

Several cases illustrate failure to comply with this requirement.[218] "If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that the embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims."[218.1]

[B][4] Magnitude of Difference in Properties

For results to be "unexpected," the differences between the claimed compound and the prior art should be a matter of kind rather than merely a matter of degree.[219] Thus, a "[m]ere improvement in properties does not always suffice to show unexpected results."[220] "Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time."[220.1] However, "substantially improved properties are *ipso facto* unexpected."[221] In *Soni*, the court found substantially improved properties when a species of a high molecular weight polymer within the scope of the claim was stated in the specification to have "at least a fifty-fold increase in tensile strength" and a "five-fold increase in peel strength as well as improved resistivity and recovery behavior properties" compared to a lower molecular weight polymer outside the scope of the claim.[222]

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218. *Dill*, 604 F.2d at 1361 (rebuttal evidence insufficient because it is limited to inserts that had been "tumbled two hours in a milling jar," while the claims do not require this); *Greenfield*, 571 F.2d at 1189 ("Establishing that one (or a *small* number of) species" in a claim covering thousands of compounds "gives unexpected results is inadequate proof . . . .").

218.1. *In re* Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

219. *In re* Merck & Co., 800 F.2d 1091, 1099 (Fed. Cir. 1986) (finding prima facie obviousness was not overcome where "the alleged difference in properties between amitriptyline [the claimed compound] and imipramine [the prior art compound] is a matter of degree rather than kind"); *In re* Lohr, 317 F.2d 388, 392 (C.C.P.A. 1963) ("substantially greater effectiveness is needed").

220. *Soni*, 54 F.3d at 751.

220.1. Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 739 (Fed. Cir. 2014); *accord In re* Harris, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (no unexpected results from increased efficacy, on a percentage basis); *In re* Budde, 319 F.2d 242, 246 (C.C.P.A. 1963) (no unexpected results because improved ranges of reaction time and temperature were a difference in degree not in kind); *In re* Aller, 220 F.2d 454, 456–57 (C.C.P.A. 1955) (no unexpected results from improved yields over prior art on a percentage basis).

221. *Id*.

222. *Id*. at 747–48. In *Soni*, the court also stated that "when an applicant demonstrates *substantially* improved results, as Soni did [to the Patent Office] here, and *states* that the results were *unexpected*, this should

[B][5] Multiple Properties

A claimed compound usually possesses a number of properties that can be compared with the prior art. This raises the question as to whether a showing of unexpected results with regard to fewer than all the properties of a claimed invention can be used to rebut a finding of prima facie obviousness. In other words, is a claimed invention non-obvious when it is unexpectedly superior to the closest prior art in one property, but is essentially the same with respect to all other properties?

This issue was addressed by the Federal Circuit in *In re Chupp*,[223] which involved a claimed herbicidal compound that was found prima facie obvious over a prior art homolog, also known to be a herbicide, which differed from the claimed compound by a single methylene ($-CH_2-$) group. In an effort to overcome the Patent Office's prima facie obviousness rejection, the applicant submitted experimental evidence that the claimed compound possessed at least five times the herbicidal activity and specificity of the prior art compound in two crops, corn and soybeans. The Patent Office was not persuaded by this evidence because it was limited to two crops and, as it turned out, the claimed compound was "at best run-of-the-mill" when used on other crops. The Federal Circuit reversed, concluding that the unexpected superiority with respect to two crops was sufficient to render the compound nonobvious over the prior art: "To be patentable, a compound need not excel over prior art compounds in all common properties. Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* obviousness."[224]

Similarly instructive is *In re May*,[225] which involved, among other issues, the patentability of novel analgesic compounds that were structurally obvious over prior art analgesic compounds such that "it would have been prima facie obvious to use the compounds recited in these

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suffice to establish unexpected results *in the absence of* evidence to the contrary." *Id*. at 751.

223. *In re* Chupp, 816 F.2d 643, 644 (Fed. Cir. 1987).

224. *Id*. at 646 (citation omitted). In reaching its conclusion, the *Chupp* court distinguished *In re* Payne, 606 F.2d 303, 316 (C.C.P.A. 1979), which held that "[a] finding of obviousness is not precluded, however, when only some, but not all, of the properties of a claimed compound are predictable from the prior art." In particular, the *Chupp* court stated that the showing of unexpected results failed in *Payne* because "[t]he *Payne* court held that the evidence submitted in that case was insufficient to rebut a *prima facie* case of obviousness, because the claimed compound was compared with too few prior art compounds." 816 F.2d at 646.

225. *In re* May, 574 F.2d 1082 (C.C.P.A. 1978).

claims as analgesics."[225.1] In appealing the PTO's rejection of claims to the use of such compounds and to pharmaceutical compositions of such compounds, applicants relied on evidence that their analgesic compounds were unexpectedly nonaddictive. The court concluded that the prima facie showing of obviousness was overcome because "it was totally unexpected that [the claimed compounds] would have exhibited . . . *nonaddictive* analgesia."[225.2] Thus, the unexpected property of nonaddictiveness overcame the expectation from the prior art that the claimed compounds would be analgesic.[225.3]

However, it should be noted that whether a showing of unexpected superiority for less than all properties can overcome a prima facie case of obviousness may depend on whether the showing of unexpected superiority is with respect to a significant property of the claimed invention. For example, if one skilled in the art would have been motivated to make the claimed invention to achieve an expected result in its most significant property, obviousness may not be negated by a showing that the claimed invention possesses other properties of lesser significance that were unexpectedly superior.[225.4]

225.1. *Id*. at 1090.

225.2. *Id*. at 1092 (emphasis added).

225.3. As the court stated, "[w]e are of the opinion that a novel chemical compound can be non-obvious to one having ordinary skill in the art notwithstanding that it may possess a known property in common with a known structurally similar compound." *Id*. at 1093. *See also In re* Murch, 464 F.2d 1051, 1055–56 (C.C.P.A. 1972) (claimed thermoplastic composition found non-obvious where it exhibited an unexpectedly improved property when compared to the prior art (weld line toughness) notwithstanding that the claimed composition would have been expected from the prior art to possess an improvement in another property (blend toughness)).

225.4. Illustrative of this point is the nonpharmaceutical case, *In re* Nolan, 553 F.2d 1261, 1267 (C.C.P.A. 1977). *Nolan* involved a gaseous discharge display/memory device that used a mixture of neon and argon gases in a specified range, which the PTO concluded was obvious from a combination of prior art references. On appeal, the court found that one skilled in the art would have been motivated to use the recited gas mixture in the claimed invention to lower the operating voltage to increase the memory margin, which was a property "of particular significance since it appears to be the most significant improvement for a memory device." This "expected" improvement in a property of "particular significance" supported the conclusion of obviousness, notwithstanding that other properties of the claimed device (higher luminous efficiency and lower peak discharge current) that were of a lesser significance were unexpectedly superior when compared to the prior art. *See also In re* Crounse, 363 F.2d 881, 884 (C.C.P.A. 1966) (a prima facie showing that a claimed dye compound was structurally obvious in view of the prior art was not overcome by a showing that the color of the claimed dye compound was unpredictable where it shared a number of significant properties with prior art dye compounds of similar structure).

[B][6] Evidence of Unexpected Properties Not Limited to Specification

[B][6][a] Evidence Need Not Be in Specification

Proof of unexpected results or superiority is often presented in the form of comparative tests with the prior art. Such evidence can be presented at any time, including:

- disclosing it in the patent specification,[225.5]
- introducing it in a post-filing declaration submitted to the Patent Office,[225.6] or
- developing it during a patent infringement litigation.[225.7]

Accordingly, "[t]here is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack."[225.8]

[B][6][b] Unexpected Property Need Not Be in Specification

Evidence of unexpected properties may be used to rebut obviousness even if the patent does not disclose that the claimed compound possesses the unexpected property, and even if the inventor was

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225.5. *In re* Soni, 54 F.3d 746, 749 (Fed. Cir. 1995).

225.6. Evidence of unexpected properties may be submitted in the form of a declaration under 37 C.F.R. § 1.132. *See* Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1482–83 (Fed. Cir. 1997) (holding that it is appropriate to consider evidence of unexpected results not set forth in the patent specification that was subsequently developed). The Federal Circuit has expressly rejected "the position that a patent applicant's evidence and/or arguments traversing a section 103 rejection must be contained within the specification." *In re* Chu, 66 F.3d 292, 299 (Fed. Cir. 1995).

225.7. Knoll Pharm. Co. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application. It is not improper to obtain additional support consistent with the patented invention, to respond to litigation attacks on validity."); *Richardson-Vicks*, 122 F.3d at 1483 (rebuking trial court for "discounting the evidence of unexpected results" because it was not in the specification and because it was unknown at the date of invention).

225.8. *Knoll*, 367 F.3d at 1385 (It is not "improper to conduct additional experiments and provide later-obtained data in support of patent validity.").

unaware of this property.[225.9] Nevertheless, there is some authority for questioning the evidentiary weight of unexpected properties that do not "'inherently flow' from what was disclosed in the specification."[225.10] Many cases have found that the cited unexpected property did "inherently flow" from the disclosure in the specification.[225.11]

[B][7] Illustrative Cases

[B][7][a] Prima Facie Obviousness Rebutted

In re Chupp[225.12]

Claim: The compound N-(ethoxymethyl)-2′-trifluorormethyl-6′-methyl-2-chloroacetanilide, stated to have herbicidal activity.

225.9. *Id*. ("no requirement that an invention's properties were fully known before the patent application was filed"); *Chu*, 66 F.3d at 299 ("arguments traversing a § 103 rejection" need not be in specification); *In re* Davies, 475 F.2d 667, 671 (C.C.P.A. 1973) ("there is no specific statutory requirement that compels an applicant to disclose all properties of chemical compounds or compositions in his application").

225.10. *Davies*, 475 F.2d at 670–71 (declining to credit affidavits describing unexpectedly "improved gloss, transparency and processibility" because the disclosure only revealed "improved mechanical properties" for use in bearing loads; "we do not consider this to be a statement of utility sufficiently clear to insure that others would be led to observe the improved properties which appellants now urge in support of their claims."); *In re* Herr, 304 F.2d 906, 908 (C.C.P.A. 1962) (failure to disclose property in specification puts applicant in unfavorable position to assert an affidavit to rely upon to show unexpected properties where the "'specification discloses no utility for the claimed compounds other than as intermediates for the production of other compounds having oral anabolic and androgenic activity.'").

225.11. *See, e.g.*, *In re* Khelghatian, 364 F.2d 870, 876 (C.C.P.A. 1966) (greater efficiency relied upon in affidavit entitled to weight because it "inherently flows" from disclosure); *In re* Zenitz, 333 F.2d 924, 928 (C.C.P.A. 1964) (applicant "disclosed a tranquilizer [that] is a better one for it minimizes the side effects of hypotensive activity [t]herefore . . . the latter property must be considered in determining [patentability]"); *In re* Lorenz, 333 F.2d 908, 912 (C.C.P.A. 1964) ("there is no requirement that superiority over the prior art be disclosed . . . it is enough if the basic property or utility is disclosed"); *Ex parte* Böttcher, 2002 WL 99677 (B.P.A.I. 2002) (unexpected antidopaminergic inherently flows from disclosing compound's use as an anti-anxiety, anti-depression treatment); *Ex parte* Mueller, 2001 WL 87827 (B.P.A.I. 2001) (unpublished) (stability inherently flows from disclosing compound's use as a pharmaceutical).

225.12. *In re* Chupp, 816 F.2d 643 (Fed. Cir. 1987).

Prior Art: The compound N-(ethoxyethyl)-2′-trifluorormethyl-6′-methyl-2-chloroacetanilide, also identified as having herbicidal activity.

Rebuttal Evidence: In declarations submitted during prosecution, applicant showed that the claimed compound was five times superior in terms of crop safety and weed killing as the prior art compound when used on corn and soybeans. However, the claimed compound did not possess such superiority with respect to other crops.

Holding: Prima facie obviousness rebutted: "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness."[225.13]

In re Soni[225.14]

Claim: A melt-processed composition comprising, among other things, an organic polymer having a molecular weight greater than 150,000 and a particulate conductive filler. The composition was stated to have "significantly improved physical and electrical properties."

Prior Art: Disclosure of the same composition, but no disclosure of using a polymer having a molecular weight greater than 150,000.

Rebuttal Evidence: The specification contained data comparing a composition within the claim wherein the organic polymer had a molecular weight of 203,000 and another composition wherein the organic polymer had a molecular weight of 148,000. The data showed that the claimed composition had at least a fifty-fold increase in tensile strength, five-fold increase in peel strength, as well as improved resistivity and recovery behavior properties.

Holding: Prima facie obviousness rebutted: "When an applicant demonstrates *substantially* improved results . . . and states that the results were unexpected this should suffice to establish *unexpected* results in the *absence* of evidence to the contrary."[225.15]

225.13. *Id*. at 646.
225.14. *In re* Soni, 54 F.3d 746 (Fed. Cir. 1995).
225.15. *Id*. at 751.

[B][7][b] Prima Facie Obviousness Not Rebutted

In re Mayne[225.16]

Claim: A fusion protein comprising a polypeptide sequence linking an enterokinase cleavage site to either HGH or BGH.

Met-Phe-Pro-Leu-$(Asp)_4$-Lys (HGH or BGH)

The enzyme enterokinase recognizes the cleavage site to produce mature HGH or BGH; "Met necessarily results from translation of RNA into proteins."

Prior Art: (a) The prior art taught fusion proteins having the sequence X-$(Asp)_4$-Lys-Y, where X is an enterokinase cleavage site and Y is the desired protein.

(b) The sequences for HGH and BGH and a motivation to link an enterokinase cleavage site to create a fusion protein.

(c) Enterokinase cleavage sites, including Phe-Pro-Ile.

Rebuttal Evidence: In response to a finding of prima facie obviousness, applicants argued two unexpected results: (1) it was unexpected that the claimed engineered proteins would induce a low immune response when administered by injection to rats; and (2) it was unexpected that the claimed proteins would be biologically active even before cleavage of the initial peptide chain.

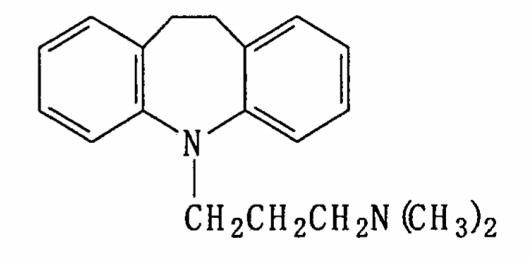
Holding: Prima facie obviousness not rebutted: (1) as to the low immune response of the claimed proteins, applicants failed to show comparative data that shows low immunogenicity of the claimed compound compared to similar fused proteins; and (2) with respect to the biological activity of the fused proteins prior to cleavage, applicants failed to show any evidence that HGH or BGH would be expected to be biologically inactive when fused to an enterokinase cleavage site.[225.17] In sum, applicants failed to make a proper showing that the properties of the claimed protein would have been unexpected from the state of the art.

225.16. *In re* Mayne, 104 F.3d 1339 (Fed. Cir. 1997).
225.17. *Id*. at 1344.

In re Merck & Co.[225.18]

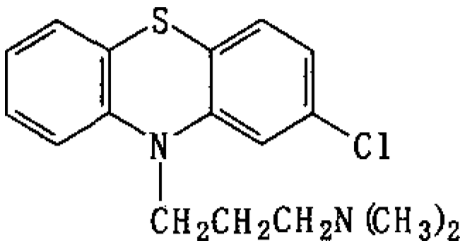
Claim: Method of treating depression in humans by the oral administration of amitriptyline.

Prior Art: (a) The compound imipramine



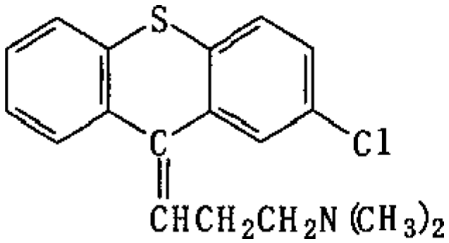
and its use as an antidepressant in humans.

(b) The theory of "biosterism," where the substitution of one atom or group of atoms for another atom or group of atoms having similar size, shape, and electron density provides molecules having the same type of biological activity, and a teaching that the interchange of the nitrogen atom in the central ring of chlorpromazine



for an unsaturated carbon atom as in the compound chlorprothiazine

225.18. *In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986).



does not change the strong tranquilizing activity of the compound.

(c) A suggestion that amitriptyline, based on its structural relationship to imipramine, should be tested for alleviation of depression.

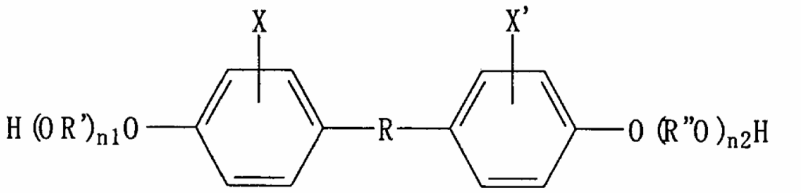
Holding: Prima facie obviousness not rebutted: The differences in activity between the claimed properties of amitriptyline and the prior art compound imipramine are insufficient to rebut the prima facie case of obviousness. In particular, the differences between the sedative properties of the two compounds was only "slight" and both compounds had anticholinergic effects that only differed in degree. The two compounds expectedly have the same type of biological activity. "In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected," the finding of prima facie obviousness was not rebutted.[225.19]

§ 7:2.3 Genus and Species Inventions

The discovery and development of chemical compounds often leads to patents that describe the invention both in terms of specific chemical compounds and in terms of a broader group or genus of compounds. For example, the inventor of a specific compound having a particular utility may conclude that the invention is broader than the single compound because other structurally related compounds should have the same or similar activities. The inventor may then synthesize a number of these related compounds and conclude that he has invented a genus of compounds. Such a genus is typically represented by a structure depicting variables that can be substituted with various chemical substituents to arrive at particular compounds within the genus.

225.19. *Id.* at 1099.

The following structure represents a genus of compounds:



wherein R is selected from substituted and unsubstituted alkylene radicals having from about two to about twelve carbon atoms, alkylidene radicals having from one to twelve carbon atoms, and cycloalkylidene radicals having from three to twelve carbon atoms; R′ and R″ are selected from substituted and unsubstituted alkylene radicals having from two to twelve carbon atoms, alkylene arylene radicals having from eight to twelve carbon atoms, and arylene radicals; X and X′ are selected from hydrogen or an alkyl radical having from one to four carbon atoms; and each n is a number from zero to four.

Such genus structures may include an extraordinary number of compounds, taking into consideration each of the possible substitutions that can be made.[225.20] In most cases, only a small fraction of these possible compounds are specifically described or exemplified in the patent specification.

The patentability of claims to both species inventions and genus inventions in view of the disclosures of the prior art has been the subject of many litigated cases. The Court of Appeals for the Federal Circuit has set forth the following general rule:

> On the one hand, this court has explained, "case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim." On the other hand, earlier disclosure of a genus does not necessarily prevent patenting a species member of the genus.[225.21]

The various issues relating to the patentability of both species and genus chemical compound inventions over the prior art are discussed below.

225.20. Indeed, the above genus, described in U.S. Patent 4,634,649, was found by the Federal Circuit in *In re* Baird, 16 F.3d 380, 382 (Fed. Cir. 1994), to encompass more than 100 million compounds.

225.21. Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003) (citation omitted).

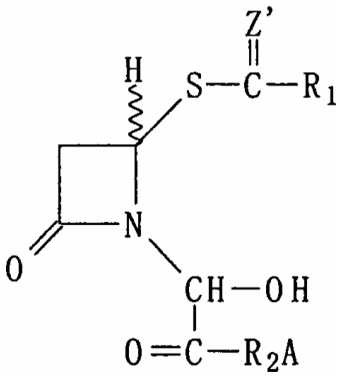
[A] Anticipation of a Chemical Genus by a Prior Art Species

[A][1] Prior Species Anticipates Genus

As a general rule, a claimed genus is anticipated by the description in the prior art of a single species within that genus.[225.22] With respect to a claim to a genus of chemical compounds, the prior art description of one or more compounds within the genus anticipates the genus claim. For example, in *In re Gosteli*, the patent applicant attempted to claim a genus of antibiotic compounds having the following general formula:[225.23]

225.22. Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art."); Brown v. 3M, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art."); *In re* Gosteli, 872 F.2d 1008, 1010 (Fed. Cir. 1989) ("generic claims are anticipated by prior art disclosing individual chemical species").

225.23. *Gosteli*, 872 F.2d at 1013. The variables in the genus formula are as follows: Z′ represents oxygen, sulphur or a methylidene group optionally mono- or di-substituted by lower aklyl, cycloalkyl, cycloalkyl-lower alkyl, phenyl, phenyl-lower aklyl or esterified carboxy; R_1 represents hydrogen; lower aklyl; lower aklyl monosubstituted by hydroxy, lower alkoxy, lower alkanoyloxy, halogen, mercapto, lower aklylthio, carboxyl, carbamoyl, cyano, nitro, amino, amino mono- or di-substituted by lower alkyl, lower alkyleneamino or amino acylated by acetyl, phenoxyacetyl, tert.butoxy-carbonyl, benzyloxy-carbonyl or p-nitrobenzeyl-oxycarbonyl; carboxyl; protected carboxyl; aminocarbonyl; aminocarbonyl mono- or di-substituted by lower alkyl; cycloalkyl; cyclo-alkyl-lower alkyl; phenyl; naphthyl; phenyl-lower alkyl; phenyl, naphthyl or phenyl-lower alkyl mono-substituted by lower alkyl, lower alkoxy, halogen, nitro, amino or di-lower alkylamino; pyridyl; thienyl; furyl; pyridyl-lower alkyl; thienyl-lower alkyl; furyl-lower alkyl; lower alkylthio; lower alkenylthio; cycloalkylthio; cycloalky-lower alkyl-thio; phenylthio or phenyl-lower alkylthio monosubstituted by hydroxy, lower alkoxy, lower alkanoyloxy, halogen, mercapto, lower alkylthio, carboxyl, carbamoyl, cyan, nitro, amino, amino mono- or di-substituted by lower alkyl, lower alkanoylamino or lower alkyleneamino; and R_2A, together with the carbonyl grouping -C (=O)- to which it is attached represents a protected carboxyl group, in racemic or optically active form.



The Federal Circuit held this genus claim anticipated by the prior art disclosure of two species within the scope of the claim.[225.24] This illustrates that a risk of pursuing broad generic claim coverage is the possibility of the claim being rendered invalid if it includes within its scope a prior art compound as a species.

[A][2] Conception of Species Before Prior Art Can Defeat Anticipation of Broader Genus

If the asserted prior art qualifies under section 102(b) of title 35, the inventor or patentee has no recourse to overcome the prior art reference.[225.25] However, if the asserted prior art describing the species became public less than one year before the filing of the patent application at issue, the disclosure can be overcome, and entitlement to the genus claim can be established, if the inventor can show prior invention of the same species described in the prior art reference or of different species within the claimed genus, coupled with evidence that the inventor considered the invention to be generic in nature.[225.26] The

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225.24. *Id*. at 1010. The two prior art species compounds that anticipated the genus were: 2[(4R,S)-4-Acetylthio-2-oxo-1-azetidinyl]-2-hydroxyacetic acid *p*-nitrobenzyl ester; and 2-[(4R,S)-4-Acetylthio-2-oxo-1-azetidinyl] -2-chloroacetic acid *p*-nitrobenzyl ester. *Id*. at 1009.

225.25. Prior art under section 102(b) is "statutory" prior art because it became public more than one year before the filing of the patent application at issue.

225.26. Under *In re* Stempel, 241 F.2d 755 (C.C.P.A. 1957), the prior art disclosure of the species was overcome by a showing that the inventor had in fact made the same species prior to the date of the reference. The court held that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show." *Id*. at 759. In subsequent cases, the holding of *Stempel* was extended to permit a patent applicant to antedate a prior art reference disclosing a genus by citing to prior work disclosing a species within that genus. *See In re* DaFano, 392 F.2d 280, 283, 284 (C.C.P.A. 1968) (holding that "reduction to practice of the copper naphthentate species, coupled with evidence that the inventor considered his invention to be a

need to establish a prior date of invention to antedate a reference may arise either in the PTO or in patent infringement litigation. In practice before the PTO, proof of prior invention is generally submitted in the form of inventor declarations.[225.27] In litigation, such proof would be provided by evidence in the form of documents or oral testimony.

[B] Validity of a Claimed Species Over a Prior Art Genus

More complex issues arise when determining the patentability of a claim to a particular chemical compound in view of a prior art description of a genus.

[B][1] Anticipation of Chemical Species by a Prior Art Genus

[B][1][a] General Rule

In general, a prior art disclosure of a genus does not anticipate a species falling within the genus.[225.28] This is because, with certain exceptions, the description of a genus does not usually *describe* to one skilled in the art each of the individual members of the genus, a requirement for anticipation.[225.29]

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generic one, is adequate to remove a reference disclosing the genus"); *In re* Walsh, 424 F.2d 1105, 1108 (C.C.P.A. 1970) (prior reduction of species was adequate to antedate reference disclosing a different species within the same genus). It should be noted, however, that where one seeks to antedate a genus reference by citing to a species, "[i]t is necessary that the species which were reduced to practice provide an adequate basis for inferring that the invention has generic applicability." *Id*. at 1108.

225.27. 37 C.F.R. § 1.131.

225.28. Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003); *see also* Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367 (Fed. Cir. 2004) ("A prior art reference that discloses a genus still does not inherently disclose all species within that broad category."); Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989) (rejecting argument that "a claim to a genus would inherently disclose all species"); *In re* Benno, 768 F.2d 1340, 1346 (Fed. Cir. 1985) ("The scope of a patent's claims determines what infringes the patent; it is no measure of what it discloses. A patent discloses only that which it describes, whether specifically or in general terms, so as to convey intelligence to one capable of understanding."); *In re* Luvisi, 342 F.2d 102, 107 n.2 (C.C.P.A. 1965).

225.29. *See, e.g.*, Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989) (rejecting argument that "a claim to a genus would inherently disclose all species").

[B][1][b] Exception for Small Prior Art Genus: *In re Petering*

Under special circumstances, "the disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited."[225.30] The classic example of such an anticipation is illustrated in *In re Petering*.[225.31] In *Petering*, a prior art patent disclosed a class of compounds, which, taking into consideration the "specific preferences in connection with [the] generic formula," had only twenty members. Given this disclosure, the court found that "one skilled in this art would, on reading [the prior art patent], at once envisage each member of this limited class."[225.32] Thus, the court held that the prior art patent "has described to those with ordinary skill in this art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name."[225.33] In effect, based on the particularity of the disclosure, the prior art described each specific individual compound. "For these reasons, we hold that each compound within the limited class in [the prior art patent] has been described in a printed publication within the meaning of 35 U.S.C. § 102(b), and that it is of no moment that each compound is not specifically named or shown in that publication."[225.34] Therefore, the prior art genus was held to anticipate a claim to a specifically claimed compound falling within the prior art genus.[225.35]

225.30. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001); *In re* Schaumann, 572 F.2d 312, 316–17 (C.C.P.A. 1978) ("When we consider also that claim 1 of [the prior art] patent, read in conjunction with the signification given the expression 'alkyl radical' in the specification, embraces a very limited number of compounds closely related to one another in structure, we are led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name."); Schering Corp. v. Precision-Cosmet Co., 614 F. Supp. 1368, 1373 (D. Del. 1985) ("The general rule is that a prior genus does not anticipate a later species. If, however, it is possible to derive a class of compounds of lesser scope than the genus disclosed in a prior art reference on the basis of preferences ascertainable from the remainder of the reference, anticipation may be found.") (citations omitted).

225.31. *In re* Petering, 301 F.2d 676 (C.C.P.A. 1962).

225.32. *Id*. at 681.

225.33. *Id*. at 682.

225.34. *Id*.

225.35. *See also Schaumann*, 572 F.2d at 316–17 (following *In re* Petering, finding anticipation: Where prior art "embraces a very limited number of compounds closely related to one another in structure, we are led inevitably to the conclusion that the reference provides a description of those

Recent Federal Circuit cases have rejected attempts to apply *Petering* in cases in which the asserted prior art reference did not establish preferences which would lead to the claimed compound. For example, in *Eli Lilly & Company v. Zenith Goldline Pharmaceuticals Inc.*,[225.36] the court concluded that claims to the antischizophrenia drug olazapine (sold under the trademark Zyprexa®) were not anticipated by a prior art reference which, among other things, expressed a preference for compounds having either fluorine or chlorine at a position, whereas olazapine had a hydrogen atom at the corresponding position.[225.37] Accordingly, unlike in *Petering*, "(n)o possible combination of those preferred substituents would lead to the components that make up olanzapine, because each would contain a fluorine or a chlorine."[225.38] The Federal Circuit concluded that *Petering* did not apply because to make olanzapine based on the asserted prior art reference, "one would have to depart from the teaching of the [prior art] article."[225.39] In *Sanofi-Synthelabo v. Apotex, Inc.*,[225.40] the Federal Circuit also rejected a *Petering* anticipation challenge to a claim to the platelet aggregation inhibiting drug clopidogrel bisulfate (sold under the trademark Plavix®) because the asserted prior art patent "does not point to bisulfates as preferred salts for clopidogrel."[225.41]

[B][2] Obviousness of a Chemical Species Over a Prior Art Genus

[B][2][a] General Rule

Absent the special *Petering*-type circumstances described above, the patentability of a specific compound or subgenus of compounds over a broader prior art genus is based on obviousness. As the Federal Circuit has stated, the "earlier disclosure of a genus does not necessarily prevent patenting a species member of the genus."[225.42] The test

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compounds just as surely as if they were identified in the reference by name").

225.36. Eli Lilly & Co. v. Zenith Goldline Pharm. Inc., 471 F.3d 1369, 1376–77 (Fed. Cir. 2006).

225.37. *Id*.

225.38. *Id*.

225.39. *Id*.

225.40. Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1377–78 (Fed. Cir. 2007).

225.41. *Id*.

225.42. Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003); *see also* Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006); Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1321 (Fed. Cir. 2004) ("[S]imply because an invention

is whether the prior art genus renders obvious the claimed species or subgenus.

[B][2][b] Prima Facie Case Based on Prior Art Genus Can Be Rebutted

In some cases, a prior art description of a genus will render the claimed compound or subgenus prima facie obvious in view of the description of the genus. As discussed above, in such circumstances, the burden shifts to the applicant or patentee to come forward with evidence that the claimed compound has unexpected properties compared with other members of the genus or other evidence of secondary consideration.[225.43] Thus, a claim to a specific compound or a subgenus of compounds may be patentable over the prior art disclosure of a genus within which the claimed subject matter falls.

Some species inventions are called "selection inventions" because they are based on the identification or "selection" of a narrower aspect of a prior art genus. As the Federal Circuit has stated, "improvement and selection inventions are ubiquitous in patent law."[225.44] Thus, "[i]nventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements of patentability."[225.45] As discussed above, a conclusion that the selected species is prima facie obvious over a prior art genus of which the species is a member can be overcome by a showing that the selected species possesses unexpected properties over the genus.

[B][2][c] Size of Prior Art Genus and Nature of Examples May Negate Prima Facie Case

In cases where the claimed compound is not prima facie obvious over the prior art genus, the compound should in general be found patentable over the prior art.

When the prior art genus is so large that it does not suggest the claimed species, it has been held that a case of prima facie obviousness is not made out even though the species is a member of the

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falls within a range disclosed by the prior art does not necessarily make it *per se* obvious. The genus and species may be patentable.").

225.43. *See, e.g.*, Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 806–09 (Fed. Cir. 1989) (claimed species held obvious where patentee failed to rebut prima facie case based on description of genus).

225.44. CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1340 (Fed. Cir. 2003).

225.45. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 364 F. Supp. 2d 820, 897 (S.D. Ind. 2005), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).

described prior art genus.[225.46] Two cases illustrate this point: *In re Jones* and *In re Baird*.

[B][2][c][i] In re Jones

In *In re Jones*,[225.47] the claim at issue was to a specific salt of a known herbicide, dicamba. The PTO had found the claimed salt prima facie obvious over a prior art reference that, although it did not disclose the specifically claimed salt, disclosed salts of dicamba, including "a genus which admittedly encompasses the claimed salt."[225.48] The Federal Circuit reversed, holding that the claimed salt was not sufficiently similar in structure to any of the specifically disclosed salts of the prior art reference to create a prima facie case of obviousness and that "[t]he lack of close similarity of structure is not negated by the fact that the claimed salt is a member of [the prior art reference's] broadly disclosed genus of substituted ammonium salts of dicamba."[225.49] The Federal Circuit rejected the proposition that "regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."[225.50] Indeed, in *Jones*, the prior art genus disclosed a "potentially infinite genus of 'substituted ammonium salts' of dicamba," without describing or suggesting the specifically claimed salt.

Therefore, without more, the fact that a claimed compound falls within the scope of a large prior art genus may not render the claimed compound prima facie obvious. And, as discussed above, absent a finding of prima facie obviousness, the burden does not shift to the patent applicant to come forward with evidence of nonobviousness.

[B][2][c][ii] In re Baird

In re Baird[225.51] involved a claim to toner composition comprising a bisphenol A. The PTO rejected the claimed composition over a prior art reference that disclosed a broad genus of compounds that included the claimed bisphenol A compound. The Federal Circuit reversed. The prior art genus encompassed more than "100 million different

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225.46. It should be noted that in a concurring opinion in Takeda Chem. Indus., Ltd. v. Alapharm Pty., Ltd., 492 F.3d 1350, 1364 (Fed. Cir. 2007), Judge Dyk of the Federal Circuit stated his view that "a species should be patentable over a genus claimed in the prior art only if unexpected results have been established." Judge Dyk's concurring opinion does not cite *In re Jones* or *In re Baird*.

225.47. *In re* Jones, 958 F.2d 347 (Fed. Cir. 1992).

225.48. *Id*. at 349.

225.49. *Id*. at 350.

225.50. *Id*.

225.51. *In re* Baird, 16 F.3d 380 (Fed. Cir. 1994).

diphenols."[225.52] "While the [prior art] formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of [the prior art reference] suggesting that one should select such variables."[225.53] Indeed, the Federal Circuit found that the prior art reference actually "appears to teach away" from the claimed compound because the prior art reference focused on structurally different and more complex subclasses of compounds within the genus.[225.54] The Federal Circuit summed up by stating that "[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds."[225.55]

[C] Written Description Support for Genus and Species Composition Claims

[C][1] Species or Subgenus Claims

A patent that discloses a genus and claims without specifically describing a particular species within that genus, may not satisfy the written description requirement without some disclosure directing one towards that species.[225.56]

[C][2] Genus Claims

The disclosure of a limited number of species that are not sufficiently representative of a genus may not satisfy the written

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225.52. *Id*. at 382.

225.53. *Id*.

225.54. *Id*.

225.55. *Id*. at 383.

225.56. *In re* Ruschig, 379 F.2d 990, 994 (C.C.P.A. 1967) ("Specific claims to single compounds require reasonably specific supporting disclosure and while . . . naming is not essential, something more than the disclosure of a class of 1,000 or 100, or even 48, compounds is required."); *see also* Fujikawa v. Wattanasin, 93 F.3d 1559, 1570–71 (Fed. Cir. 1996) (in the absence of disclosure that provides "blazemarks" leading to the claimed "tree" in the forest, "simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses"); Fields v. Conover, 443 F.2d 1386, 1391–92 (C.C.P.A. 1971) (broad genus and examples did not support sub-genus); *but see In re* Edwards, 568 F.2d 1349 (C.C.P.A. 1978); *In re* Driscoll, 562 F.2d 1245, 1250 (C.C.P.A. 1977) ("Any seeming similarity between *Ruschig* and the present case is illusory, however, because the structural formula there relied on could have described, at best, only a subgenus including the specific compound claimed, and not the compound itself. In this respect, *Ruschig* is readily distinguishable from the present case where the exact subgenus claimed is clearly discernible in the generalized formula of the thiadiazole urea set forth in the earlier filed application.").

description requirement for a claim to the genus.[225.57] Accordingly, in some cases courts have found the species disclosure to be insufficient to support the genus claim.[225.58] Other cases, on different facts, reached the opposite conclusion.[225.59] New species invented or discovered after a patent's priority date can serve as evidence of whether the patent has disclosed a representative number of species of the claimed genus.[225.60]

225.57. Amgen Inc. v. Sanofi, 872 F.3d 1367, 1375–76 (Fed. Cir. 2017) ("[I]n order to satisfy the written description requirement, a patentee may disclose either a representative number of species falling within the scope of the genus or disclose structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.").

225.58. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997) (a genus of compounds or DNA sequences was not described where a representative number of the compounds or DNA sequences were not recited); *In re* Wilder, 736 F.2d 1516 (Fed. Cir. 1984) ("synchronous scanning equipment" species did not support claim to "genus of indicating mechanisms that visually identify positions on a recording medium when" scanned); *see also In re* Gosteli, 872 F.2d 1008, 1012 (Fed. Cir. 1989); *In re* Smith, 458 F.2d 1389, 1395–96 (C.C.P.A. 1972) (rejecting argument that "disclosure of a genus and a species of a subgenus is a sufficient description of the subgenus"; and "claimed subgenus of coating compounds with at least 8 carbon atoms was not adequately described in the earlier application which disclosed compounds with at least 12 carbons"); *In re* Sus, 306 F.2d 494 (C.C.P.A. 1962); *In re* Cavallito, 306 F.2d 505 (C.C.P.A. 1962); *In re* Shokal, 242 F.2d 771, 775–76 (C.C.P.A. 1957) ("neither the broad language relied on by appellants nor the specific examples given by them are sufficient to identify or point out the particular genus recited").

225.59. *In re* Wallach, 378 F.3d 1330, 1333 (Fed. Cir. 2004) ("the complete amino acid sequence of a protein may put one in possession of the genus of the DNA sequences encoding it"); Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 967 (Fed. Cir. 2002) ("If those sequences are representative of the scope of the genus claims, *i.e.*, if they indicate that the patentee has invented species sufficient to constitute the genera, they may be representative of the scope of those claims."); *In re* Herschler, 591 F.2d 693, 700 (C.C.P.A. 1979) (using DMSO to enhance penetration across the skin of any steroid supported by example of using DMSO with one specified steroid); *In re* Surrey, 370 F.2d 349, 353 (C.C.P.A. 1966) ("specific examples . . . along with" statement in "specification that those aromatic radicals can be substituted with the same substituents exemplified for the phenyl radical" adequately supports chemical genus claim); *In re* Cavallito, 282 F.2d 357, 361 (C.C.P.A. 1960); *In re* Grimme, 274 F.2d 949, 952 (C.C.P.A. 1960).

225.60. *Amgen*, 872 F.3d at 1375 ("[T]he use of post-priority-date evidence to show that a patent does not disclose a representative number of species of a claimed genus is proper.").

Furthermore, one cannot claim a genus that is only supported by choosing an unmentioned characteristic of particular examples.[225.61]

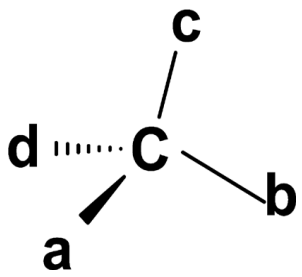
§ 7:2.4 Stereoisomers, Enantiomers, and Diastereomers

[A] Introduction

Stereochemistry is the study of how molecules are arranged in three-dimensional space.[226] Stereoisomers are molecules that are made up of the same atoms, connected by the same sequence of bonds, but have different three-dimensional structures.[227] Stereoisomers have one or more "chiral centers," which are "carbon atoms with four non-identical substituent atoms or groups of atoms."[228]

Fig. 7-1

Chiral Center—Carbon Atom (C) Attached to Four Different Groups of Atoms (a, b, c, and d)



Stereoisomers can be classified as either "enantiomers" or "diastereomers." Stereoisomers that are non-superimposable mirror images of each other are called enantiomers.[229]

225.61. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1327 (Fed. Cir. 2000) ("[P]ick[ing] a characteristic possessed by two of their [disclosed] formulations, a characteristic that is not discussed even in passing in the disclosure, and then make it the basis of claims that cover not just those two formulations, but any formulation that has that characteristic . . . is exactly the type of overreaching the written description requirement was designed to guard against.").

226. Pfizer Inc. v. Ranbaxy Labs. Ltd., 457 F.3d 1284, 1286 (Fed. Cir.), *reh'g denied*, 2006 U.S. App. LEXIS 28925 (Fed. Cir. Oct. 23, 2006); Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1372 (Fed. Cir. 2006).

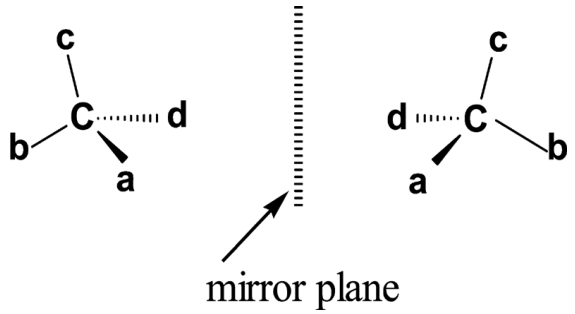
227. ANDREW STREITWIESER, INTRODUCTION TO ORGANIC CHEMISTRY 124 (Paul F. Corey ed., 4th ed. 1992) [hereinafter STREITWIESER].

228. *Pfizer*, 457 F.3d at 1286.

229. *Id.*; Aventis Pharma Deutschland GmbH v. Lupin Ltd., 2006 U.S. Dist. LEXIS 48246, at *11 (E.D. Va. July 17, 2006).

Fig. 7-2

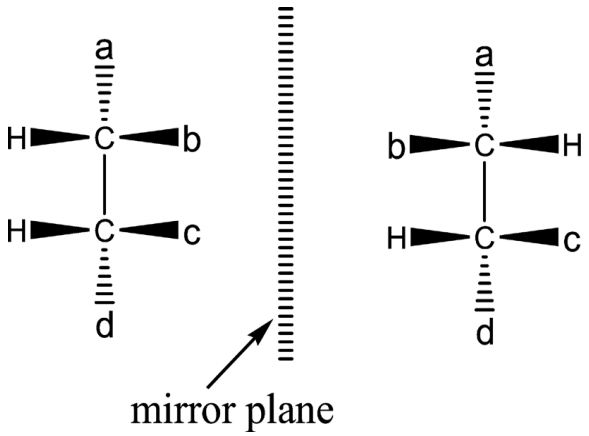
Enantiomers



Enantiomers are often compared to a right and a left hand.[230] Stereoisomers that are non-superimposable and not mirror images of each other are known as "diastereomers."[231]

Fig. 7-3

Diastereomers



Enantiomers are inherently "optically active."[232] Each member of a given pair of enantiomers will always rotate a plane of polarized light in "equal and opposite directions."[233] One enantiomer rotates polarized light in a clockwise direction and is called the dextrorotatory ((+)) enantiomer and the other enantiomer rotates polarized light in a

230. *Aventis Pharma*, 2006 U.S. Dist. LEXIS 48246, at *11; Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 720 (N.D. W. Va. 2004), *aff'd without opinion*, 161 F. App'x 944 (Fed. Cir. 2005).

231. *Aventis Pharma*, 2006 U.S. Dist. LEXIS 48246, at *11 ("Diastereomers are stereoisomers that are not enantiomers.").

232. *Ortho-McNeil*, 348 F. Supp. 2d at 720.

233. *Id. See also Pfizer*, 457 F.3d at 1286.

counterclockwise direction and is called the levorotatory ((–)) enantiomer.[234] An equal mixture of the two enantiomers is called a "racemic mixture" or a "racemate."[235] A racemic mixture is optically inactive because the light rotating properties of the two enantiomers cancel each other out.[236] The process for separating a racemic mixture into its constituent enantiomers is called "resolution."[237] It may also be possible to perform an "enantioselective" reaction, which will produce either one enantiomer or a mixture that is enriched in a target enantiomer, as opposed to the racemic mixture that most reactions produce.[238]

Stereoisomers may also be designated "R" or "S" depending on whether the peripheral groups around the chiral center are arranged in a clockwise (R) or counterclockwise (S) orientation.[239] The substituent groups attached to separate carbon atoms may be further characterized as having *cis* or *trans* configuration. When substituent groups lie on the same side of a plane of a molecule, the stereoisomer is called *cis*.[240] When substituent groups lie on opposite sides of a plane of a molecule, the stereoisomer is called *trans*.[241]

Fig. 7-4

Trans and Cis Configuration

Of significance to drug discovery is that although enantiomers generally have the same physical and chemical properties, they may

234. *Pfizer*, 457 F.3d at 1286; *Ortho-McNeil*, 348 F. Supp. 2d at 720.
235. *Pfizer*, 457 F.3d at 1286.
236. *Id.*, *Ortho-McNeil*, 348 F. Supp. 2d at 721.
237. *See, e.g.*, *Pfizer*, 457 F.3d 1284; *see also* STREITWIESER, *supra* note 227, at 737.
238. *See* discussion in *In re* Doyle, 293 F.3d 1355, 1356 (Fed. Cir. 2002).
239. *Pfizer*, 457 F.3d at 1286–87 & n.2; *see also* STREITWIESER, *supra* note 227, at 133.
240. *Pfizer*, 457 F.3d at 1287; Aventis Pharma Deutschland GmbH v. Lupin Ltd., 2006 U.S. Dist. LEXIS 48246, at *13 (E.D. Va. July 17, 2006).
241. *Pfizer*, 457 F.3d at 1287; *Aventis Pharma*, 2006 U.S. Dist. LEXIS 48246, at *13.

have different biological and physiological properties.[242] For example, the proton pump inhibitor Prilosec®, used to control stomach acid, contains as its active ingredient omeprazole, which is a racemic mixture of two enantiomers. The discovery that the S enantiomer is responsible for the activity of omeprazole led to a new product called Nexium® which contains only the S enantiomer.[243] Another well-known example is thalidomide—"one enantiomer is effective against morning sickness while the other causes birth defects."[244] Yet another example is the platelet aggregation inhibiting drug Plavix®, which was based on the discovery that the dextrorotatory enantiomer of an enantiomer pair was active and non-toxic while the levorotatory enantiomer was inactive and toxic.[245]

Diastereomers may have different physical and chemical properties[246] and may also have different biological properties.[247]

[B] Patentability of Stereoisomers

[B][1] Anticipation

In general, a claim to a separated enantiomer has not been held to be anticipated by a prior art disclosure of its racemate. Thus, it has been held that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate."[248] It has also been held

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242. ROBERT THORNTON MORRISON & ROBERT NEILSON BOYD, ORGANIC CHEMISTRY 134–35 (5th ed. 1987) [hereinafter MORRISON & BOYD].
243. Information relating to the development of Nexium can be found at www.nexium-us.com.
244. *Pfizer*, 457 F.3d at 1286 n.1. Information relating to thalidomide can be found at http://cerhr.niehs.nih.gov/common/thalidomide.html.
245. Sanofi-Synthelabo v. Apotex Inc., 2006 WL 2516486, at *12 (S.D.N.Y. Aug. 31, 2006), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006).
246. MORRISON & BOYD, *supra* note 242, at 143.
247. *See, e.g.*, Leslie H. Kondejewski et al., *Dissociation of Antimicrobial and Hemolytic Activities in Cyclic Peptide Diastereomers by Systematic Alterations in Amphipathicity, in* 274 J. BIOLOGICAL CHEMISTRY 13181 (1999).
248. *In re* May, 574 F.2d 1082, 1090 (C.C.P.A. 1978). *See also In re* Williams, 171 F.2d 319, 320 (C.C.P.A. 1948) ("[T]he holding by the tribunals of the Patent Office that the appealed claim, drawn to a laevo rotary compound substantially free from the dextro rotary form of the compound is fully anticipated by a mixture of the laevo and dextro rotary forms of the compound, must be reversed."); Pfizer Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 519 (D. Del. 2005), *aff'd in part, rev'd in part*, 457 F.3d 1284 (Fed. Cir.), *reh'g denied*, No. 06-1179, 2006 U.S. App. LEXIS 28925 (Fed. Cir. Oct. 23, 2006) ("[C]ourts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate or render the individual isomers of the racemate obvious."); Ortho-McNeil

that the disclosure of the dextro enantiomer of a compound in a prior art reference does not anticipate a claim to the levo enantiomer.[249] In another case, a claim to a "substantially pure" enantiomer was found not anticipated by the prior art disclosure of the racemate and a disclosure of the individual enantiomers with a prediction of their activity.[250]

These holdings are apparently premised on a finding that a separated or isolated enantiomer is novel in view of a prior art disclosure of the racemic mixture. This is consistent with the law that a prior art genus does not necessarily anticipate a claimed species.[251]

Pharm., Inc. v. Mylan Labs., Inc., 267 F. Supp. 2d 533, 545 (N.D. W. Va. 2003), *modified*, 348 F. Supp. 2d 713 (N.D. W. Va. 2004), *aff'd*, 161 F. App'x 944 (Fed. Cir. 2005) (claim to a separated levo enantiomer was not anticipated when the prior art disclosed only the racemic mixture).

249. *May*, 574 F.2d at 1087–90.

250. Forest Labs., Inc. v. Ivax Pharm., Inc., 438 F. Supp. 2d 479 (D. Del. 2006), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007). The district court found a claim to "substantially pure" (+)-citalopram, which corresponded to the (S)-enantiomer of citalopram, was not anticipated by a prior art reference that disclosed citalopram as a "racemic drug" and incorrectly predicted that the activity of the individual (R)-enantiomer would be "far more potent" as a serotonin uptake inhibitor than the claimed (S)-enantiomer. The court stated that the prior art reference only disclosed the chemical structure of the (R)-enantiomer and did not "disclose anything with regard to the purity of the [claimed] (S)-enantiomer . . . the Court cannot presume that the disclosure of (R)-citalopram, individually and not in any mixture, necessarily discloses substantially pure (S)- or (+)-citalopram." In addition, the court found that even if the prior art reference described (+)-citalopram, the prior art did not enable one skilled in the art to resolve the racemate to obtain the claimed (+)-citalopram enantiomer. 438 F. Supp. at 486–88. In affirming the district court's finding of no anticipation, the Federal Circuit agreed that the prior art reference did not enable obtaining the claimed (+)-citalopram enantiomer. In addition, the Federal Circuit noted that the reference incorrectly predicted that the (-)-enantiomer would be more potent. 501 F.3d at 1268.

251. *Pfizer*, 405 F. Supp. 2d at 519 (citing Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003)). It should be noted that a patent challenger may argue that the genus of stereoisomers disclosed in the prior art is sufficiently small so as to anticipate under the doctrine of *In re* Petering, 301 F.2d 676 (C.C.P.A. 1962). *See supra* chapter 5. Such an argument based on *In re Petering* was rejected in Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1377 (Fed. Cir. 2006), which held that a prior art patent did not disclose preferences that would limit a generic formula of a racemic compound to the claimed enantiomer in a specific salt form. The Federal Circuit did not decide whether one skilled in the art would interpret the prior art patent as disclosing both the racemate and the dextro and levo enantiomers of the compound at issue. *Id*. at 1375–76. Instead, the Federal Circuit based its decision of no anticipation on the failure of the prior art patent to describe the

Accordingly, the construction of a claim directed to an enantiomer may be very important to validity determinations. For example, a claim to levofloxacin, the levo enantiomer of the antibiotic ofloxacin, was construed to cover "an optically active and substantially pure quantity of levofloxacin" that was not anticipated by the prior art disclosure of the ofloxacin racemate.[252] In addition, courts have based conclusions of no anticipation on a finding that the prior art did not enable resolving a racemate into its component enantiomers.[253]

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compound in the bisulfate salt form. *Id*. at 1376 n.6. Subsequently, after a bench trial on the merits, the district court concluded that there was no anticipation because the prior art patent did not describe the claimed dextro enantiomer and because it was not described in the claimed bisulfate salt form. In addition, the district court concluded that the prior art patent did not enable making the dextro enantiomer in the bisulfate salt form, which also precluded a finding of anticipation. Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353, 383–86 (S.D.N.Y. 2007). In affirming the district court's decision on the merits, the Federal Circuit stated that "[t]he knowledge that enantiomers may be separated is not 'anticipation' of a specific enantiomer that has not been separated, identified, and characterized." Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1084 (Fed. Cir. 2008). Moreover, the Federal Circuit agreed with the district court's finding "that the reference patents would not have enabled a person of ordinary skill to obtain clopidogrel [the dextrorotatory enantiomer] substantially separated from the levorotatory enantiomer." 550 F.3d at 1085. The Federal Circuit did not identify the claimed bisulfate salt form as a basis for negating anticipation.

252. *Ortho-McNeil*, 348 F. Supp. 2d at 730. While the court acknowledged that the term "compound" could refer to only a single molecule, it concluded that by specifying the levo enantiomer, one skilled in the art would interpret the claim as requiring a measurable optical activity, which required a certain minimum number of molecules to rotate light. In addition, the court concluded that one skilled in the art would understand that 100% purity of the levo enantiomer could not be achieved, supporting an interpretation of "substantial" purity. Moreover, the claim to levofloxacin was held not to be inherently anticipated by the prior art administration of ofloxacin because of a failure to prove that the claimed levofloxacin compound exists as a monomer *in vivo*. *Id*. at 761–64.

253. *E.g.*, Forest Labs., Inc. v. Ivax Pharm., Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007) ("[W]e see no error in the finding that the Smith reference does not enable one of ordinary skill to make (+)-citalopram, and hence that the Smith reference does not anticipate claims to (+)-citalopram."); *Sanofi-Synthelabo*, 492 F. Supp. 2d at 386–87 (finding lack of enablement in part because "sanofi—whose chemists were highly sophisticated and well-trained in the relevant art—spent a considerable amount of time trying to obtain the enantiomers of PCR 4099 [the racemate]"). For a discussion of the requirement that an anticipating reference must be enabling, see *supra* section 5:2.2[C].

[B][2] Obviousness

The question of whether a claim to a separated stereoisomer is non-obvious over the prior art disclosure of a mixture of stereoisomers that includes the claimed isolated stereoisomer has also been addressed.

The Federal Circuit has, in dicta, included stereoisomers as among the types of chemical compounds that give rise to prima facie obviousness based on structural similarity.[254] However, in practice, courts have not applied a per se rule of prima facie obviousness to a claim reciting an isolated stereoisomer when the prior art discloses a mixture of stereoisomers, and have performed the test for obviousness set forth in *Graham v. John Deere Co.*[255]

In the Federal Circuit's first decision addressing *KSR* in the context of the validity of a claimed stereoisomer, the court, in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*,[256] reversed a district court judgment of nonobviousness and held obvious a patent claiming the pharmaceutical compound ramipril "substantially free of other isomers." Ramipril is the active ingredient in the blood pressure medication Altace®, an ACE inhibitor. The structure of ramipril contains five "stereocenters," or carbon atoms that may take either of two orientations, "R" or "S." All five stereocenters in ramipril are in the "S" orientation so that ramipril is known as the "SSSSS" or "5(S)" stereoisomer. While ramipril is one of thirty-two possible stereoisomers, the prior art included a composition that included only the 5(S) form of ramipril and the SSSSR stereoisomer. The court also considered that the prior art ACE inhibitors captopril and enalapril, like ramipril, have stereocenters that are all in the "S" configuration and that the SSS configuration of enalapril is 700 times as potent as the SSR form. The court concluded that "if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person with reason to believe that this is so, the purified compound is prima facie obvious

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254. *In re* Jones, 958 F.2d 347, 349–50 (Fed. Cir. 1992) (citing *In re* May, 574 F.2d 1082). For a discussion on prima facie obviousness in chemical compounds based on structural similarities, see *supra* section 7:2.2.

255. Graham v. John Deere Co., 383 U.S. 1, 17 (1966). *See Ortho-McNeil*, 348 F. Supp. 2d at 749 n.19 ("Mylan asserts that enantiomers are prima facie obvious vis-à-vis the racemic compound. . . . Although *Jones* and *May* support Mylan's contention, they are inconsistent with the Federal Circuit's directive to make *Graham* findings in *every* case to establish a prima facie case of obviousness.") (citing *In re* Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997)).

256. Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293 (Fed. Cir. 2007).

over the mixture even without an explicit teaching that the ingredient should be concentrated or purified."[257] Moreover, the court concluded that the prior art taught that the stereoisomers of ramipril can be separated by conventional methods.[258] Accordingly, the Federal Circuit concluded that claims to ramipril, "substantially free of other isomers," were prima facie obvious, a finding that was not rebutted by a showing of unexpected results.[259] The Federal Circuit cited *KSR* in concluding that obviousness did not require an "explicit teaching to purify the 5(S) isomer" and "[i]f it is known how to perform such an isolation, doing so 'is likely the product not of innovation but ordinary skill and common sense.'"[260]

In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*,[261] the district court rejected the argument that levofloxacin was obvious over the prior art disclosure of the racemate ofloxacin. The court stated that the party asserting obviousness had the burden of proving "by clear and convincing evidence that the prior art motivated a person of ordinary skill in the art to produce levofloxacin with a reasonable expectation of success."[262] The court's conclusion of non-obviousness was based in part on its finding that levofloxacin was unexpectedly superior to the prior art racemate ofloxacin in its combination of greater antibacterial activity and lower toxicity.[263] The court found this evidence sufficient to negate a finding of a "reasonable expectation of success" necessary to support a conclusion that the enantiomer was prima facie obvious over the racemate.[264] Alternatively, the court concluded that the findings of unexpected results and secondary considerations of nonobviousness, including commercial success, rebutted any prima facie case of obviousness.[265]

The Court of Customs and Patent Appeals came to a different conclusion in the 1960 case of *In re Adamson*.[266] In *Adamson*, the court found that a claim to the laevo enantiomer of a compound "substantially separated" from the dextro enantiomer was obvious over the prior art disclosure of the racemate combined with an organic

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257. *Id*. at 1301.
258. *Id*. at 1302.
259. In particular, the court rejected a showing of superiority of the 5(S) isomer over the RRSSS isomer because it was not a showing over the prior art mixture that contained the 5(S) and the SSSSR stereoisomer. *Id*. at 1302–03.
260. *Id*. at 1302 (quoting *KSR*, 127 S. Ct. 1727, 1742 (2007)).
261. *Ortho-McNeil*, 348 F. Supp. 2d 713 (N.D. W. Va. 2004), *aff'd without opinion*, 161 F. App'x 944 (Fed. Cir. 2005).
262. *Ortho-McNeil*, 348 F. Supp. at 752.
263. *Id*. at 755–56.
264. *Id*. at 754–55.
265. *Id*. at 760–61.
266. *In re* Adamson, 275 F.2d 952 (C.C.P.A. 1960).

chemistry text that described the principles of stereoisomerism and taught that racemates can be separated into enantiomers that may have different physiological properties.[267] The court found that non-obviousness was not established by evidence that the claimed laevo enantiomer had substantially greater activity with only a small increase in toxicity when compared with either the racemate or the dextro enantiomer.[268] The *Adamson* court distinguished its prior decision in *In re Williams*,[269] which held that a claimed enantiomer was patentable over the racemate. The *Adamson* court stated that the motivation to separate enantiomers, which was presented in the organic chemistry text, was not of record in *Williams*.[270]

The Federal Circuit distinguished *Adamson* in *Sanofi-Synthelabo v. Apotex, Inc.*[271] in affirming the grant of a preliminary injunction to the manufacturers and marketers of the drug Plavix®, which contains the dextro enantiomer of a racemic compound as a bisulfate salt called clopidogrel bisulfate. The Federal Circuit concluded that the generic drug manufacturing defendant had not raised a substantial question that the selection of the active dextro enantiomer in the claimed bisulfate salt form would have been obvious from the prior art disclosure of the "racemate free base" and "the dextrorotatory and

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267. *Id*. at 954. The claim in *Adamson* was directed to a *Markush* group of two compounds. *Id*. at 952.

268. *Id*. In *Ortho-McNeil*, 348 F. Supp. 2d at 754, the *Adamson* decision was distinguished because, "when compared to the typical antibiotic, levofloxacin represents the unusual case in which each of the desired properties is superior to (if not considerably superior to) those of its predecessor." Thus, the *Ortho-McNeil* court found it significant that the claimed enantiomer was both more active and less toxic than the racemate, whereas in *Adamson*, while the claimed laevo enantiomer was more active, it was also more toxic than either the dextro enantiomer or the racemate. *Id*. (citing *Adamson*, 275 F.2d at 953).

269. *In re* Williams, 171 F.2d 319 (C.C.P.A. 1948).

270. *Adamson*, 275 F.2d at 954. Subsequent to *Adamson*, the court in Brenner v. Ladd, 247 F. Supp. 51, 56 (D.D.C. 1965), cited *Adamson* in holding that, "in the absence of unexpected or unobvious beneficial properties, an optically active isomer is unpatentable over either the isomer of opposite rotation or . . . the racemic compound itself." *See also In re* Anthony, 414 F.2d 1383, 1386 (C.C.P.A. 1969). However, in reviewing this case law, the Patent Office Board of Appeals in *Ex parte* Bonfils, 64 U.S.P.Q.2d (BNA) 1456, 1462 (B.P.A.I. 2002), stated "[n]othing in these cases supports the . . . position that the disclosure of one enantiomer is sufficient by itself to establish a *prima facie* case of obviousness. . . ." The Board in *Bonfils* stated that a prima facie case of obviousness requires a showing that "one of ordinary skill in the art would have had a reasonable expectation that the claimed compounds would have similar biological properties as the reference compounds. . . ." *Id*. at 1463.

271. Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368 (Fed. Cir. 2006).

levorotatory enantiomers, as well as pharmaceutically acceptable salts, including the bisulfate."[272] Moreover, the Federal Circuit found no error in the district court's conclusion that it was unexpected that the dextro enantiomer would have "high pharmacological activity and low toxicity—two properties that are not necessarily generally associated with one enantiomer."[273]

The Federal Circuit concluded that "nothing directed a chemist to the particular enantiomer and salt, clopidogrel bisulfate."[274] In distinguishing *Adamson*, the court found that "[r]esolution of a racemic free base does not lead to a particular unnamed salt" and also credited the district court's finding that "resolving the racemate was not mere routine experimentation and that it was unexpected that the desirable activity of clopidogrel would be found only in the d-enantiomer."[275]

Subsequently, after a trial on the merits, the district court in *Sanofi-Synthelabo* concluded that the claimed clopidogrel bisulfate compound was nonobvious. While the district court assumed for the purposes of its analysis that the prior art rendered the claimed clopidogrel bisulfate compound prima facie obvious, it held that evidence of the unexpected superiority of the dextro enantiomer supported nonobviousness: "the prior art did not enable a person of ordinary skill in the art to predict with a reasonable expectation of success whether one enantiomer of PCR 4099 [the racemate] would have better pharmaceutical properties than the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity."[276] The Federal Circuit affirmed, concluding that "a person of ordinary skill in this field would not have reasonably predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity."[276.1] The Federal Circuit also found no clear error in the district court's conclusion of nonobviousness based on the absence of proof that the prior art enabled the separation of the racemate into its component enantiomers.[276.2]

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272. *Id*. at 1375–76.
273. *Id*. at 1378–79.
274. *Id*. at 1379.
275. *Id*. at 1380.
276. Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353, 390 (S.D.N.Y. 2007).
276.1. Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1087 (Fed. Cir. 2008).
276.2. *Id*. at 1087–88. As discussed *infra* at section 7:2.6[C][2], the Federal Circuit also found no clear error that the selection of the bisulfate salt form also supported nonobviousness. *Id*. at 1088.

In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*,[277] the district court found that defendants had not demonstrated by clear and convincing evidence that a claim to a "substantially pure" specific enantiomer ((S)-citalopram, or (+)-citalopram) was rendered obvious by prior art disclosing the racemic mixture and its use as an antidepressant. The enantiomer (S)-citalopram, or (+)-citalopram, in the oxalate salt form, is the active ingredient in the antidepressant drug product, Lexapro®, a selective serotonin reuptake inhibitor (or SSRI).[278] The court credited the testimony of plaintiff's expert that "a person of ordinary skill in the art of medicinal chemistry seeking to discover a new SSRI would have been motivated to design a new compound, rather than engage in the time consuming and unpredictable effort of resolving citalopram into its enantiomer."[279] The court discussed the difficulties in resolving racemic compounds into their enantiomers and the difficulty in predicting the activities of the individual enantiomers.[280] The court concluded that "[g]iven the significant difficulties identified by [plaintiffs' expert] in resolving citalopram and the unpredictable nature of the separation techniques and separation results of racemates in general, as well as the minimal gains that were typically predicted by the resolution of racemates into their constituent enantiomers," one skilled in the art would not have been motivated to resolve citalopram at the time of the invention.[281] The court further found that "a person skilled in the art seeking such a resolution would not have a reasonable expectation of success without undue experimentation."[282] In affirming the district court's conclusion of nonobviousness, the Federal Circuit agreed with the district court's analysis, focusing on the difficulty in separating the enantiomers, including "the failure of the inventors and others to resolve citalopram without undue experimentation."[283]

In *Pfizer Inc. v. Ranbaxy Laboratories, Ltd.*,[284] the court rejected a challenge that a claim to a specific calcium salt of a specific stereoisomer was obvious over a prior art disclosure of the racemate and a disclosure of calcium among at least fifty salts, without a stated

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277. Forest Labs., Inc. v. Ivax Pharm., Inc., 438 F. Supp. 2d 479 (D. Del. 2006), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007).
278. 438 F. Supp. 2d at 484.
279. *Id*. at 492.
280. *Id*. at 488–91.
281. *Id*. at 493.
282. *Id*.
283. 501 F.3d at 1269.
284. Pfizer Inc. v. Ranbaxy Labs., Ltd., 405 F. Supp. 2d 495 (D. Del. 2005), *aff'd in part, rev'd in part*, 457 F.3d 1284 (Fed. Cir.), *reh'g denied*, 2006 U.S. App. LEXIS 28925 (Fed. Cir. Oct. 23, 2006).

preference.[285] The court found a lack of motivation to resolve the racemate of the specific compound, atorvastatin lactone, into individual enantiomers or to use the claimed calcium salt form.[286]

The Federal Circuit, in *Spectrum Pharma, Inc. v. Sandoz Inc.*,[286.1] held that the district court did not err in finding claims to a mixture of two diastereoisomers containing at least 92% (and in some claims at least 95%) of the (6S) diastereoisomer obvious over "the prior art 50/50 mixture" and the knowledge "that the desired activity all lies in" the (6S) diastereoisomer. The court noted that the claimed substantially pure mixtures were "not shown to possess[ ] unexpected advantages over the prior art pure material."[286.2]

In *UCB, Inc. v. Accord Healthcare, Inc.*, the Federal Circuit affirmed the district court's finding that a claim to a lacosamide "compound . . . which contains at least 90% (w/w) R stereoisomer" was not obvious over prior art that disclosed the racemate of the lacosamide compound using a lead compound analysis.[286.3] Although the court acknowledged that a lead compound analysis was not required, the court nevertheless "[held] that the district court did not clearly err in finding that a person of ordinary skill in the art would not have selected [the racemate] as a lead compound."[286.4]

In *Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.*, the Federal Circuit held that the PTAB did not err in finding a claim to the (S)-enantiomer of sitagliptin dihydrogenphosphate not obvious over a combination of references disclosing, *inter alia*, sitagliptin in a list of thirty-three compounds—but nothing relating to (S)-sitagliptin or a racemic mixture of any sitagliptin salt—and a general disclosure on diastereomers encompassing millions of potential compounds and salts.[286.5] The court noted that no expected or theoretical benefit to making the (S)-enantiomer had been advanced by Mylan in the IPR.[286.6]

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285. 405 F. Supp. at 517.

286. *Id.* at 517–18. The court found that "the prior art indicates that the motivation at the time was to develop racemates and make structural changes to the compounds to increase their activity, not to resolve those racemates into individual isomers." *Id.* at 517.

286.1. Spectrum Pharma, Inc. v. Sandoz Inc., 802 F.3d 1326 (Fed. Cir. 2015).

286.2. *Id.* at 1334–35.

286.3. UCB, Inc. v. Accord Healthcare, Inc., 890 F.3d 1313, 1319, 1322, 1328–29 (Fed. Cir. 2018).

286.4. *Id.* at 1329.

286.5. Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp., 50 F.4th 147, 155–56 (Fed. Cir. 2022).

286.6. *Id.* at 156.

In *Amgen v. Sandoz*,[286.7] the Federal Circuit considered Sandoz's challenges to the district court's determinations regarding claims 3 and 6 of U.S. Patent No. 7,427,638 covering Amgen's drug product Otzela® (apremilast), indicated for the treatment of psoriasis. The '638 patent was directed to stereomerically pure apremilast, which Sandoz had asserted was invalid as obvious over a prior art patent disclosing a racemic mixture from which apremilast was separated. The district court held that claims 3 and 6 of the '638 patent were not invalid as obvious and Sandoz appealed.[286.8]

Sandoz contended that the district court had erred in finding claims 3 and 6 of the '638 patent nonobvious over the prior art '358 patent and the '606 application. Specifically, Sandoz argued that the prior art provided motivation to isolate apremilast from a known racemic mixture and that a skilled artisan would have had a reasonable expectation of success in doing so.

The Federal Circuit agreed with Amgen, affirming the district court's ruling that Sandoz had failed to establish obviousness. The court found that Sandoz did not meet its burden of proving a motivation to resolve the racemate mixture into its enantiomers or a reasonable expectation of success in doing so.[286.9] Additionally, the court determined that the district court had credited appropriately expert testimony in reaching its decision.[286.10]

[C] Claim Construction and Infringement

A claim to a compound that exists as stereoisomers can raise the issue as to whether the claim should be construed to cover a particular stereoisomer or enantiomer, or is limited to the racemic mixture. This claim construction issue was raised in *Pfizer Inc. v. Ranbaxy Laboratories Ltd.*,[287] involving a generic drug company's challenge to patents protecting the cholesterol-reducing drug Lipitor®.

The active ingredient of Lipitor® is atorvastatin calcium, which is the R-trans enantiomer of a compound that exists in four enantiomeric forms. Pfizer's '893 patent in suit claims a genus of compounds that exist as four stereoisomers: R-trans, S-trans, R-cis, and S-cis, but the cis isomers were disclaimed in the specification. The Federal Circuit rejected Ranbaxy's argument that the claim should be construed as covering only a racemic mixture of the R and S trans enantiomers and as not covering the specific R-trans enantiomer: "[T]he district court correctly found that no intrinsic evidence limits claim 1 of the

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286.7. Amgen Inc. v. Sandoz Inc., 66 F.4th 952 (Fed. Cir. 2023).
286.8. *Id*. at 960.
286.9. *Id*. at 962–63.
286.10. *Id*.
287. *Pfizer*, 457 F.3d 1284.

'893 patent to trans-racemates, as opposed to an R-trans enantiomer, an S-trans enantiomer or any (equal or unequal) mixtures thereof."[288]

Furthermore, the Federal Circuit rejected each of Ranbaxy's specific grounds for arguing that the claim did not cover the specific R-trans enantiomer. First, the court rejected the argument that the depiction in the '893 patent of the R-trans enantiomer was meant to represent the racemate:

> [E]ven accepting Ranbaxy's contention that a racemate is commonly represented by depicting one of its constituent enantiomers, it does not follow that the depiction of an R-enantiomer always represents only a racemate. Here, only an R-trans enantiomer is depicted in the '893 patent, yet the specification expressly indicates that there are four possible isomers of the compounds of structural formula I and limits the invention to the trans-form. If one skilled in the art would have understood the drawing of structural formula I to limit the scope of claim 1 to trans-racemates, then an express disclaimer of the cis-form would not have been necessary.[289]

Second, the court rejected the argument that the claim should be restricted to racemates because the reactions shown in the examples of the specification produced racemates. To so restrict the claims, the court held, "would improperly import limitations from the specification into the claims."[290] Finally, the court held that statements made during prosecution of foreign counterpart applications and during prosecution of a later U.S. application could not be used to interpret the claims of the '893 patent.[291]

This claim construction issue was also raised in *Sumitomo Dainippon Pharma Co. v. Emcure Pharmaceuticals Ltd*.[291.1] The court found that the claim at issue was not limited to a racemic mixture and that lurasidone, the (-)-enantiomer of the racemate, was also covered by the claim.

Lurasidone is the active ingredient in LATUDA®, plaintiffs' schizophrenia and bipolar depression drug. When defendants sought approval to market generic versions of LATUDA®, plaintiffs sued for infringement of claim 14 of their '372 patent. Claim 14 depicted a three-dimensional compound structure, which both parties agreed represented lurasidone. However, defendants argued that claim 14

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288. *Id*. at 1289.
289. *Id*. at 1290.
290. *Id*.
291. *Id*.
291.1. Sumitomo Dainippon Pharma Co. v. Emcure Pharm. Ltd., 887 F.3d 1153 (Fed. Cir. 2018).

should be construed as limited to the racemic mixture of two enantiomers and as excluding the (-)-enantiomer on its own. Focusing on the structural similarities between the compound depicted in the claim and Compound No. 101, a compound depicted in a separate section of the specification, defendants argued that because Compound No. 101 depicted only a racemic mixture, claim 14 did so as well. Additionally, they contended that ordinarily skilled artisans frequently draw a single enantiomer as a shorthand representation for a racemic mixture.

The Federal Circuit rejected each of defendants' arguments. First, it found that "the plain claim language and specification demonstrate that, at a minimum, claim 14 covers what it depicts: the (-)-enantiomer."[291.2] It noted that there was nothing "in the claim language limiting its scope to a 'racemate.'"[291.3]

The court also rejected the argument that claim 14's scope should be construed as being coextensive with Compound No. 101 on the grounds that it "relies on a series of inferences."[291.4] It determined that the specification was inconclusive as to whether Compound 101 was a racemic mixture and noted that, even if it were a racemate, there was nothing in the specification linking claim 14 to Compound 101, such that the claim's scope should be limited to the scope of Compound 101. The court explained that "Compound No. 101 just happens to be the only other place in the patent where claim 14's structure appears. This, of course, is not enough to restrict a claim's scope."[291.5] Finally, in light of the intrinsic record, the court rejected as irrelevant defendants' extrinsic evidence, such as organic chemistry textbooks and expert testimony, which they attempted to use to establish that it is conventional in the art to use a single enantiomer as shorthand for a racemic mixture.

§ 7:2.5 *Polymorphs*[*]

[A] What Is a Polymorph?

A chemical compound may exist in different crystalline forms called polymorphs. Although each polymorphic form has the same chemical formula, the polymorphs differ in their three-dimensional structure.[292] The conditions under which a compound is crystallized,

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291.2. *Id*. at 1157.
291.3. *Id*.
291.4. *Id*.
291.5. *Id*. at 1159.
[*] Written by Steven D. Roth.
292. David J.W. Grant, *Theory and Origin of Polymorphism*, *in* 1 POLYMORPHISM IN PHARMACEUTICAL SOLIDS 1–2, *in* 95 DRUGS AND THE PHARMACEUTICAL SCIENCES (Harry G. Brittain ed., 1999).

such as temperature, pressure, and presence of other ingredients or solvents, determine the resulting polymorphic form.[293] Some polymorphs may be more physically stable than others and over time, depending on storage conditions, such as temperature, pressure, and relative humidity, a less stable polymorph may convert to a more stable polymorph.[294]

Different polymorphic forms of a chemical compound have different properties, including density, solubility, dissolution, and physical and chemical stability.[295] Thermodynamic stability, which characterizes the stability of the crystal under various conditions, such as temperature, is important for the active ingredient in a drug product.[296] If the crystals of an active ingredient are not stable, they may degrade or convert to another crystalline form that may have different pharmacological properties.[297]

Measurement techniques to identify polymorphic forms are described below,[298] as are infringement issues that have been raised in connection with litigation involving polymorph patents.[299] Four such infringement issues are:

(1) the types of evidence offered to prove infringement,

(2) the minimum amount of the claimed polymorph in the accused drug product necessary for infringement,

(3) whether the patent claims cover a compound that initially does not infringe but converts to the infringing form over time, either in storage or in a patient's body, known as *in vivo* conversion, and

(4) claim construction.

Validity issues that have been raised in the course of litigation involving polymorph patents are addressed below.[300] These issues include indefiniteness and anticipation by inherency.

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293. Deodatt A. Wadke, Abu T.M. Serajuddin & Harold Jacobson, *Preformulation Testing, in* 1 PHARMACEUTICAL DOSAGE FORMS: TABLETS 1, 34 (Herbert A. Lieberman, Leon Lachman & Joseph B. Schwartz eds., 2d ed. 1989) [hereinafter Wadke, Serajuddin & Jacobson].
294. *Id*. at 38–39.
295. Grant, *supra* note 292, at 7.
296. *See* Wadke, Serajuddin & Jacobson, *supra* note 293, at 38.
297. *See id*. at 37–39.
298. *See infra* section 7:2.5[B].
299. *See infra* section 7:2.5[C].
300. *See infra* section 7:2.5[D].

[B] Techniques for Identifying Polymorphs

Patents describe at least three analytical methods for identifying the polymorphic form of a compound:

(1) X-ray powder diffraction,

(2) single crystal X-ray crystallographic analysis, and

(3) infrared absorption analysis.

Each of these methods involves the irradiation of a sample with a particular form of electromagnetic radiation (either X-ray or infrared).

[B][1] X-Ray Powder Diffraction

To perform X-ray diffraction on a powder (a group of crystals), an X-ray beam is directed onto a sample of the powder. The X-ray beam is diffracted by the crystals in the sample into a detector. The intensities of the diffracted X-ray beams may be used to generate an X-ray diffraction pattern, which is a series of peaks and troughs. Each peak in the diffraction pattern indicates a specific intensity of a diffracted X-ray beam at a specific angle of diffraction.[301] X-ray powder diffraction can be used to differentiate polymorphic forms because powders of different polymorphic forms have different crystalline structures, and each form will exhibit different peaks.

[B][2] Single Crystal X-Ray Crystallographic Analysis

This analytical procedure is conducted in a similar way as X-ray powder diffraction.[302] One notable difference is that the sample consists of a single crystal (rather than a group of crystals), which diffracts the X-ray beam onto film. The exposed film shows spots of different intensities. Using mathematical equations, the data on the film can be used to characterize the crystal in terms of its three-dimensional structure and the positions of the atoms within the crystal. These characteristics of the crystal measured by single crystal X-ray crystallographic analysis identify the polymorphic form of the crystal.

[B][3] Infrared Absorption Analysis

This analytical procedure is conducted on a sample consisting of crystals of the chemical compound being investigated and another

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301. *See* DOUGLAS A. SKOOG & JAMES J. LEARY, PRINCIPLES OF INSTRUMENTAL ANALYSIS 357–82 (4th ed. 1992) [hereinafter SKOOG & LEARY].

302. *See* Ron Jenkins & Robert L. Snyder, *Introduction to X-Ray Powder Diffractometry, in* 138 CHEMICAL ANALYSIS: A SERIES OF MONOGRAPHS ON ANALYTICAL CHEMISTRY AND ITS APPLICATIONS 57 (J.D. Wineforder ed., 1996).

chemical compound such as potassium bromide combined into a pellet. Infrared light is passed through the pellet and into a detector that measures the intensity of the light that passed through the pellet. The test is conducted over the entire spectrum of infrared light. When the infrared spectrum is scanned, a pattern, called an infrared absorption spectrum, is produced by the detector. It indicates the percentage of infrared light that is absorbed by the sample and the percentage of infrared light that passes through the sample at various wave numbers (or wavelengths) within the infrared light spectrum.[303] Because powders of different polymorphic forms have different crystalline structures, they will exhibit different infrared spectrum when exposed to infrared light. Thus, infrared spectroscopy may be used to identify different polymorphic forms.

[C] Infringement

Courts have dealt with four basic issues involving the infringement of polymorph patents:

(1) the nature of the evidence required to prove infringement,

(2) the minimum amount of the infringing polymorphic form in the accused drug product necessary for infringement,

(3) the conversion of a non-infringing polymorphic form to an infringing polymorphic form in storage or in the patient's body,[304] and

(4) claim construction.

[C][1] Evidentiary Issues

As discussed above, patent claims often specify the method by which the identity of the polymorphic form may be determined, usually by listing peaks of an X-ray powder diffraction pattern or infrared spectrum. These peaks uniquely identify the polymorphic form. The Federal Circuit has held that the patentee (depending on the claim language) must show that all or substantially all of the claimed peaks recited in a claim are present in the accused product. Thus, a patentee's showing of infringement that focused on only one out of twenty-nine claimed infrared peaks was held insufficient because "[i]t is elementary patent law that all limitations are material" and therefore all twenty-nine claimed peaks must be identified.[305]

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303. SKOOG & LEARY, *supra* note 301, at 252–88.
304. For a discussion of whether patents claiming polymorphs may be submitted for listing in the FDA's Orange Book, see *infra* section 8:1.2[A][3].
305. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1566 (Fed. Cir. 1997).

Similarly, the Federal Circuit held that the presence of twenty-two peaks out of thirty-seven claimed peaks, or about 60% of the claimed peaks, was insufficient for infringement, because "[a]lthough the term 'essentially' recited in the claim permits some leeway in the exactness of the comparison with the specified 37 lines [peaks] of the claim, it does not permit ignoring a substantial number of lines altogether."[306]

Although the patentee must show that all, or substantially all, of the claimed peaks of an IR spectrum or X-ray diffractogram are present, the peaks do not have to be visible; any methodology otherwise admissible showing that the claimed peaks are present may be sufficient to prove infringement, even if some of those peaks cannot be identified with the naked eye.[307] The Federal Circuit held, for example, that a statistical computer method, known as partial least squares (PLS), may be used to prove that all the claimed peaks of the infrared spectrum were present in the accused product, even though several of these peaks were not visible.[308]

Patent infringement cases involving polymorph patents generally arise when a drug company obtains and lists in the FDA's Orange Book a patent on a new polymorphic form of an existing compound and a generic drug company files an ANDA with a certification that the polymorphic form of its compound is not covered by the patent on the new polymorph. The patentee's allegation of infringement is usually based on an assertion that the generic drug has some amount of the infringing polymorphic form or will convert to the infringing polymorphic form over time.

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306. Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1424 (Fed. Cir. 1994); *see also In re* Sebela Patent Litig., No. CV 14-6414 (CCC) (MF), 2017 WL 3449054, at *13–15 (D.N.J. Aug. 11, 2017) ("Accordingly, the Court concludes that all of the listed peaks must be present in order to show infringement. As each Defendants' ANDA product is missing one of the claimed peaks at Plaintiff's preferred error range, Plaintiff cannot meet its burden of showing infringement.").

307. *See* Glaxo Grp. v. Torpharm, Inc., 153 F.3d 1366, 1373–74 (Fed. Cir. 1998).

308. *See id*. at 1373. Glaxo's expert generated an IR (infrared) spectrum for each of thirteen different known mixtures of the two forms at issue (the infringing form and the prior art form). These IR spectra were then input into a spectral analysis software program, which generated a calibration model using a partial least squares (PLS) algorithm. The IR spectrum of the accused product was then input into the model, which indicated the percentage of the infringing form present in the accused product. Glaxo's expert opined that this analysis demonstrated that all the claimed peaks were present in the accused product.

The Federal Circuit has held that the focus of the infringement inquiry in a Hatch-Waxman case is the product "likely to be sold following FDA approval."[309] When determining the product likely to be sold following FDA approval, the court may consider "the ANDA itself, the materials submitted by [the generic drug company] to the FDA, and other pertinent evidence provided by the parties."[310]

Furthermore, it is the patentee's burden to prove that the product likely to be sold by the defendant will infringe its patents; it is not the defendant's burden to prove that it will not infringe. Specifically, the Federal Circuit in *Glaxo, Inc. v. Novopharm, Ltd.*[311] held that the patentee had not met its burden of proof solely by pointing to the accused infringer's ANDA specification that merely allowed for the possibility of a small amount of the infringing polymorph:

> Glaxo seems to be arguing that the act of infringement consisting of the filing of the ANDA presumptively settles the issue of infringement of the patent when the product is marketed and that anything possibly within the scope of the ANDA must be shown by the applicant not to infringe. . . .
>
> We conclude that, especially in a case such as this, involving a compound capable of existing in various forms, the statute requires an infringement inquiry focused on what is likely to be sold following FDA approval. This inquiry must be based on all of the relevant evidence, including the ANDA. As is well-established for infringement actions brought under § 271 . . . , a patentee seeking relief under § 271(e)(2) must prove by a preponderance of the evidence that what is to be sold will infringe. That burden is not shifted under § 271(e)(2).[312]

Thus, a patentee cannot prove infringement of a polymorph patent solely by relying on a defendant's ANDA specification that permits

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309. *Novopharm Ltd.*, 110 F.3d at 1568.

310. *Id*. at 1570. *See also* Merck Sharp & Dohme Corp. v. Amneal Pharm. LLC, 881 F.3d 1376, 1385 (Fed. Cir. 2018).

311. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562 (Fed. Cir. 1997); Kowa Co., Ltd. v. Amneal Pharm., LLC, No. 14-CV-2758 (PAC), 2017 WL 10667089, at *44–45 (S.D.N.Y. Sept. 19, 2017), *aff'd*, 745 F. App'x 168 (Fed. Cir. 2018) ("As explained *supra*, a POSA would understand the limitations of claims 1 and 24 not to require an exact match of every peak position and relative intensity; but would rather understand the limitations to be met if the claimed Form A can be identified in the experimental XRPD data by reference to the characteristic reference pattern set forth in claims 1 and 24. As explained in detail herein, every characteristic peak need not be present, nor be a precise match (in terms both of 29 position and relative intensity), in the sample for a POSA to do so.").

312. *Id*. at 1567–68.

impurities that may include the infringing polymorphic form. Of course, it is a different situation if the ANDA specification *requires* that the infringing polymorphic form be present, in which case the specification itself demonstrates literal infringement, or where a specification necessarily excludes the presence of an infringing polymorphic form, in which case the specification will demonstrate no literal infringement.[313]

[C][2] Quantity Required

A claim to a polymorphic form of a molecule is infringed by a product that contains only trace amounts—even undetectable amounts—of the claimed compound.[314]

In 1988, SmithKline obtained a patent on the hemihydrate form of paroxetine HCl, the active ingredient in the drug product Paxil®. In 1998, Apotex filed an ANDA proposing to manufacture a generic version of Paxil® with the prior art anhydrous form of paroxetine HCl. SmithKline sued Apotex alleging that Apotex's manufacturing facility is likely to produce at least trace amounts of the infringing hemihydrate form. Evidence at trial showed that the amount of hemihydrate produced by Apotex's manufacturing process would be less than 5% and probably less than 2% to 4%.

SmithKline argued that even if Apotex's generic paroxetine HCl product contains a single crystal of the hemihydrate (an undetectable quantity) the patent would be infringed. The district court disagreed, holding that if the claim "were to be interpreted as broadly as SmithKline now contends, it would fail for indefiniteness" because a single crystal is undetectable.[315] Instead, the court interpreted the patent claim "as excluding hemihydrate produced by involuntary conversion of a proportion of an anhydrous mixture so small as to lack any commercial significance."[316]

The Federal Circuit reversed the district court's claim interpretation, holding that a claim to a specific molecule covers any product containing any amount of the molecule.[317] The Federal Circuit

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313. *See* Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1249–50 (Fed. Cir. 2000) (holding that the specification in Elan's ANDA "mandates a finding of no literal infringement").

314. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir.), *reh'g denied*, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005); *Kowa Co.*, 2017 WL 10667089, at *8.

315. SmithKline Beecham Corp. v. Apotex Corp., 247 F. Supp. 2d 1011, 1028 (N.D. Ill. 2003), *rev'd*, 403 F.3d 1331 (Fed. Cir.), *reh'g denied*, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005).

316. 247 F. Supp. 2d at 1029–30.

317. *SmithKline*, 403 F.3d at 1339 ("the conclusion is inescapable that the claim encompasses, without limitation, PHC hemihydrate—a crystal

rejected the district court's analysis that the manufacturing advantages touted in the specification imparted a requirement that only a commercially significant amount can infringe. The Federal Circuit reasoned that "[a] description of characteristics does not redefine a compound with an established and unambiguous structural definition."[318] The Federal Circuit also disagreed with the district court's opinion that the "commercial significance" limitation is necessary to preserve the claim's validity in the face of an indefiniteness challenge. The district court found that potential infringers could not detect trace amounts rendering the claims indefinite. But the Federal Circuit held that the test for indefiniteness is not whether competitors can determine if they infringe, but whether one skilled in the art would understand the bounds of the invention:

> The test for indefiniteness does not depend on a potential infringer's ability to ascertain the nature of its own accused product to determine infringement, but instead on whether the claim delineates to a skilled artisan the bounds of the invention. In this case, the problem for Apotex is that it cannot accurately ascertain the nature of its own product. The scope of this claim is clear; the infringement of the Apotex product is not. Even if a claim is broad enough to embrace undetectable trace amounts of the claimed invention, "breadth is not indefiniteness." *In re* Gardner, 57 C.C.P.A. 1207, 427 F.2d 786, 788 (CCPA 1970). Stated more precisely, this claim is neither broad nor narrow, but definitive of this particular chemical structure. For inventing and disclosing this structure, the inventor enjoys the exclusive right to practice that invention of the patent's limited term. Accordingly, claim 1, as construed above, is not indefinite under 35 U.S.C. § 112, second paragraph.[319]

Thus, a drug product may infringe a patent even if it contains only trace amounts of the polymorph covered by the patent.[320]

[C][3] Conversion

Polymorphs are known to convert from one polymorphic form to another over time when exposed to certain environmental conditions.

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form of paroxetine hydrochloride that contains one molecule of bound water for every two molecules of paroxetine hydrochloride in the crystal structure").

318. *Id*.

319. *Id*. at 1340–41.

320. As discussed in *infra* section 7:2.5[D][1], in SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir.), *reh'g denied*, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005), the Federal Circuit held the claimed polymorph form invalid by inherent anticipation.

This conversion can take place during storage in a warehouse, during the tablet manufacturing process, in a patient's home or in a patient's body.[321]

The Federal Circuit was confronted with the conversion issue in *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*[322] The case concerned the drug cefadroxil, an antibiotic. The patent on the basic compound had expired. But Bristol had discovered a new crystalline form, a monohydrate form, which had certain manufacturing advantages over the previously existing hemihydrate form of cefadroxil. Bristol obtained a patent on the new monohydrate form. Zenith sought FDA approval for the prior art hemihydrate form. Bristol conceded that Zenith's drug product did not infringe the monohydrate patent in its pre-ingested form, but nevertheless argued that Zenith's product infringed because it converted into the patented form in the stomach of a patient. The district court agreed and found that Zenith infringed the patent.

The Federal Circuit reversed, finding, as discussed above, that Bristol's evidence of *in vivo* conversion improperly focused on substantially less than all the claimed peaks.[323] But, significantly, the court found that *in vivo* conversion was a viable theory of infringement. The court found that, despite the fact that Bristol emphasized the manufacturing advantages of the monohydrate form during the prosecution of the patent, the claim as written was not limited to the pre-ingested form. The claim as written simply described a compound, which may infringe the patent even if it exists for a brief period of time in the body as the claimed form.[324]

Note that although the manufacturing advantages discussed in the patent specification could not be read into the claim for purposes of avoiding literal infringement, the Federal Circuit relied on the asserted manufacturing advantages in its further holding that the hemihydrate form is not equivalent to the claimed monohydrate form.[325]

Judge Posner also dealt with the issue of conversion in *SmithKline Beecham Corp. v. Apotex Corp.*[326] The court rejected SmithKline's

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321. See *infra* section 7:2.7 for a general discussion of infringement by conversion to a patented form.
322. Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418 (Fed. Cir. 1994).
323. See *supra* section 7:2.5[C][1] for a discussion of claims covering specified polymorph peaks.
324. *See Zenith Labs.*, 19 F.3d at 1421–22.
325. *See id*. at 1425.
326. SmithKline Beecham Corp. v. Apotex Corp., 247 F. Supp. 2d 1011 (N.D. Ill. 2003), *rev'd*, 403 F.3d 1331 (Fed. Cir.), *reh'g denied*, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005).

argument that conversion to the claimed polymorph in the patient's home or body infringes the patent because SmithKline would have to prove infringement by inducement, which requires evidence of intent.[327] The Court held that the only evidence of Apotex's intent demonstrated that Apotex did not want conversion to occur. Judge Posner explained, "[e]ven if a patient's gastrointestinal juices convert the nonpatented product that Apotex plans to manufacture to the product patented by SmithKline and Apotex knows this will happen, there is no evidence that Apotex intends, in the sense of desires or is working to achieve, this result. For the gastrointestinal 'infringement' does nothing for Apotex commercially; it merely increases Apotex's exposure to liability."[328] Thus, although conversion remains a viable infringement theory, if a patentee alleges infringement by inducement, the elements of induced infringement must be proven in addition to direct infringement.[329]

[C][4] Claim Construction

In *Abbott Laboratories v. Sandoz, Inc.*,[329.1] the Federal Circuit affirmed the construction of a claim to crystalline cefdinir, reciting seven specific X-ray diffraction peaks as limited to one specific crystalline form (Crystal A) and excluding another form (Crystal B) which was used by the defendants. The court noted that the specification of the patent had identified Crystal A by the same seven peaks recited in the claim.[329.2] In addition, the court concluded that the prosecution history showed a "clear and intentional disavowal of claim scope beyond Crystal A,"[329.3] noting that disclosure regarding Crystal B had been removed from the Japanese priority application before filing in the United States and that a co-inventor's declaration submitted during prosecution focused on the stability of Crystal A.[329.4]

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327. 247 F. Supp. 2d at 1014–15 (citing to 35 U.S.C. § 271(b)).
328. 247 F. Supp. 2d at 1015.
329. *See infra* chapter 10.
329.1. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282 (Fed. Cir. 2009). See *infra* section 7:5.2 for a discussion of the en banc holding in *Abbott Labs.* regarding the construction of product-by-process claims.
329.2. *Id*. at 1289.
329.3. *Id*. at 1290.
329.4. *Id*.; *see also* Astellas Pharma Inc. v. Actavis Elizabeth LLC, No. CV 16-905-JFB-CJB, 2018 WL 4776372, at *5–11 (D. Del. June 18, 2018) (construing the terms "α-form crystal" to mean "α-form crystal which is a term of reference for a polymorphic crystal form of (R)-2-(2-aminothiazol-4-yl)-4′-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide that can be distinguished from other forms by its characteristic peak(s) and DSC analysis as identified in the specification" and the term "β-form crystal"

Based on this claim construction, the Federal Circuit affirmed a grant of summary judgment of non-infringement, including under the doctrine of equivalents.[329.5]

[D] Validity

In several cases an accused infringer argued under section 102(b) of title 35 that a prior art process, public use, or sale anticipated a polymorph patent. But courts have held that the accused infringer must prove, by clear and convincing evidence, that the patented polymorph necessarily existed in the prior art, sale, or public use. If so, the patent may be held invalid even if the prior art or those involved in the prior sale or public use were unaware of the identity of the polymorph.

[D][1] Inherent Anticipation

In *Glaxo, Inc. v. Novopharm, Ltd.*,[330] the issue was whether a prior art patent example inherently disclosed and thus invalidated Glaxo's patent on a new polymorph of ranitidine HCl. Novopharm's experts performed the process disclosed in the prior art example thirteen times and each time found the patented polymorph. But Glaxo and its experts were able to practice that example without making the patented polymorph. The Federal Circuit held that because the prior art example "could yield crystals of either polymorph," there was no inherent anticipation of Glaxo's patent.[331]

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to mean "β-form crystal which is a term of reference for a polymorphic crystal form of (R)-2-(2-aminothiazol-4-yl)-4′-[2-[(2-hydroxy-2phenylethyl) amino]ethyl]acetanilide that can be distinguished from other forms by its characteristic peak(s) and DSC analysis as identified in the specification"); *cf.* ViiV Healthcare Co. v. Lupin Ltd., No. CV 17-1576, 2019 WL 4722701, at *5–9 (D. Del. Sept. 26, 2019) (construing the terms "a crystal form of a sodium salt of a compound of formula AA" and "a crystal form of a hydrate of a sodium salt of a compound of formula AA" to encompass crystal forms defined by reference to the measurement data recited in the claims rather than the particular hydration state exemplified by the two crystal forms described in the specification).

329.5. The Federal Circuit also concluded that Crystal B was effectively disclaimed and could not be recaptured under the doctrine of equivalents. *Abbott Labs.*, 566 F.3d at 1297–98.

330. Glaxo, Inc. v. Novopharm, Ltd., 52 F.3d 1043 (Fed. Cir. 1995).

331. *Id.* at 1047–48; *see also* Kowa Co., Ltd. v. Amneal Pharm., LLC, No. 14-CV-2758 (PAC), 2017 WL 10667089, at *13–23 (S.D.N.Y. Sept. 19, 2017) (holding the asserted patent was not inherently anticipated by the prior art because "[d]efendants have failed to meet their heavy burden of proving by clear and convincing evidence that practice of [the prior art] 'necessarily and inevitably' results in [the claimed polymorph]").

The Federal Circuit in *SmithKline Beecham Corp. v. Apotex Corp.*[332] again addressed the issue of the inherent anticipation of a polymorph patent. The district court held that the prior art patent that disclosed a method of making the anhydrous form did not anticipate the later patent on the hemihydrate form because Apotex did not introduce clear and convincing evidence that it was impossible to make the pure anhydrous form when practicing the prior art patent. The Federal Circuit reversed, holding that whether it was actually possible to make the pure anhydrate form is irrelevant.[333] Rather, the Federal Circuit held that anticipation by inherency may be found if the evidence shows that "the natural result flowing from the operation as taught [in the prior art] would result in the claimed product."[334] The Federal Circuit further found that the hemihydrate form naturally results from the process discussed in the prior art patent disclosing the anhydrous form from the fact that scientists made the hemihydrate form simply by practicing the prior art process for making the anhydrous form.[335]

[D][2] On-Sale Bar

The Federal Circuit held in *Abbott Laboratories v. Geneva Pharmaceuticals, Inc.* that the sale of a compound having a patented polymorphic form more than one year before the patent application is filed invalidates the patent pursuant to section 102(b), even though the parties to the sale were not aware of the polymorphic form of the material sold.[336] The court cited to the U.S. Supreme Court's decision in *Pfaff v. Wells Electronics, Inc.*[337] for the two elements of the on-sale bar; namely, that before the "critical date" (one year before the patent application) the invention must (1) be the subject of a commercial sale or offer for sale, and (2) be ready for patenting (that is, reduced to practice). The Federal Circuit found that both prongs were satisfied based on actual sales of the compound having the patented form.[338] In response to Abbott's argument that the parties to the sale did not know of the polymorphic form, the court held that "[i]t is well settled in the law that there is no requirement that a sales offer specifically identify all the characteristics of an invention offered for sale or that

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332. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir.), *reh'g denied*, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005).
333. 403 F.3d at 1344.
334. *Id*. at 1343.
335. *Id*. at 1344–45.
336. *See* Abbott Labs. v. Geneva Pharm., Inc., 182 F.3d 1315 (Fed. Cir. 1999).
337. Pfaff v. Wells Elecs., Inc., 525 U.S. 55 (1998).
338. *Abbott*, 182 F.3d at 1318.

the parties recognize the significance of all of these characteristics at the time of the offer."[339]

[D][3] Public Use

In *UCB, Inc. v. Watson Laboratories Inc.*, the Federal Circuit affirmed the district court's invalidation under section 102(a) of a patent claiming a specific polymorph (Form II) of rotigotine due to prior public use.[339.1] The Federal Circuit reasoned that the evidence of record showed that one lot of the patent owner's original rotigotine transdermal patches[339.2] contained the claimed polymorph and that the patches were used by one patient prior to the filing date of the patent, even though the patent owner did not know of the polymorph.[339.3] In response to the patent owner's argument that the patient's use of the patch "[did] not count as a 'use'" of the claimed invention because the claimed polymorph could not penetrate the skin, the court stated that section 102(a) "[did] not require that the invention be used for a particular purpose" if the patches administered to the patient contained the claimed polymorph.[339.4]

[D][4] Obviousness

In *Grunenthal GMBH v. Alkem Labs. Ltd.*,[339.5] the Federal Circuit held the district court had not clearly erred in finding that a patent directed to the Form A polymorph of tapentadol hydrochloride was not obvious over prior art that disclosed the Form B polymorph in view of FDA guidance that suggested performing polymorph screenings of pharmaceutical solids. The court rejected the defendant's arguments that a skilled artisan would have had a reasonable expectation

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339. *Id*. at 1319; *see also* Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1378 (Fed. Cir. 2003) ("In sum, this court's precedent does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention.").

339.1. UCB, Inc. v. Watson Labs. Inc., 927 F.3d 1272, 1291 (Fed. Cir. 2019).

339.2. Before the filing of the application, the patent owner manufactured and sold rotigotine transdermal patches until August 2007, when it discovered an unknown solid that precipitated during the dissolution step. *Id*. at 1276. Upon investigation, the patent owner concluded that the solid was a polymorph of rotigotine and subsequently filed the patent application resulting in the asserted patent. *Id*. However, prior to the discontinuation of the original rotigotine patch, the patent owner sold one lot of patches containing crystals of the claimed polymorph that were used by one patient who reported symptoms associated with the claimed polymorph's presence. *Id*. at 1277.

339.3. *Id*. at 1289–91.

339.4. *Id*. at 1291.

339.5. Grunenthal GMBH v. Alkem Labs. Ltd., 919 F.3d 1333, 1341 (Fed. Cir. 2019).

of success producing Form A by undertaking polymorph screening of Form B because Form A was more stable at room temperature.[339.6] The court noted that a skilled artisan "would not reasonably expect any polymorph screening of Form B to necessarily result in the 'most stable form' of tapentadol hydrochloride," that is, Form A.[339.7] The Federal Circuit also rejected the defendant's argument that it would have been obvious to try to produce Form A based on the same prior art for similar reasons.[339.8]

In *Amgen v. Sandoz*,[339.9] the Federal Circuit considered Sandoz's challenges to the district court's determination regarding claims 1 and 15 of U.S. Patent No. 7,893,101 covering Amgen's drug product Otzela® (apremilast), indicated for the treatment of psoriasis. The '101 patent was directed to a crystalline form of apremilast known as Form B. The district court held that claims 1 and 15 of the '101 patent were not invalid as obvious.[339.10]

Sandoz challenged the district court's finding that the claims were entitled to a March 2002 priority date of the '515 provisional application. Sandoz argued that the '515 provisional application did not inherently disclose crystalline Form B of apremilast and that Amgen had failed to meet the written description requirement.[339.11]

The appeals court agreed with Amgen and affirmed the district court's ruling. The court found that Amgen had provided sufficient experimental evidence replicating Example 2 of the '515 provisional application, demonstrating the disclosure of crystalline Form B. Moreover, the court concluded that a finding of inherency was unnecessary, as the evidence presented by Amgen had sufficiently established the disclosure.[339.12] The court also concluded that, because Sandoz had failed to argue obviousness based on prior art before the March 2022 priority date, it had failed to prove obviousness.[339.13]

[D][5] Utility

In *Grunenthal GMBH*, discussed above, the Federal Circuit also affirmed the district court's rejection of an invalidity challenge for alleged lack of utility of the claimed crystal form, as there was sufficient evidence "that Form A is shown to be stable at room temperature

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339.6. *Id*. at 1341–43.
339.7. *Id*. at 1343–45.
339.8. *Id*. at 1345.
339.9. Amgen Inc. v. Sandoz Inc., 66 F.4th 952 (Fed. Cir. 2023).
339.10. *Id*. at 960.
339.11. *Id*. at 966.
339.12. *Id*.
339.13. *Id*. at 96.

and useful for pain relief."[339.14] In particular, the patent specification taught that Form A "is used for the treatment of pain or the treatment of urinary incontinence," and the district court had found that "a POSA would have believed that, at the time of filing the '364 patent, Form A was more stable than Form B at room temperature."[339.15] In reaching its decision, the Federal Circuit stated that "[a] patent fails to satisfy the utility requirement under 35 U.S.C. § 101 only if the invention is 'totally incapable of achieving a useful result.' . . . For pharmaceutical patents, practical utility may be shown by evidence of 'any pharmacological activity.'"[339.16]

§ 7:2.6 *Pharmaceutical Salts of Active Ingredients**

[A] What Is a Salt?

Chemically, a salt is the result of a neutralization reaction that occurs when an acid and a base react.[340] According to the Bronsted-Lowry theory, an acid is a substance that can donate (or lose) a proton, and a base is a substance that can accept (or remove) a proton. A neutralization reaction occurs when an acid and base react, and the resulting compound is called a salt.

The general form for a neutralization reaction is as follows:

(acid) + (base) = (salt) + (water)[341]

When in solution, the base of the salt is a positively charged ion called a "cation," and the acid of the salt is a negatively charged ion called an "anion." The active compound in a pharmaceutical salt could be either an acid or a base.

[B] Development of Pharmaceutical Salts

The discovery of a compound with desired therapeutic properties is, of course, a major development for a drug discovery program. The therapeutic properties, however, are not the only properties that must

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339.14. Grunenthal GMBH v. Alkem Labs. Ltd., 919 F.3d 1333, 1346 (Fed. Cir. 2019) (citations omitted).

339.15. *Id*.

339.16. *Id*. at 1345.

* Written by Richard G. Greco, David K. Barr, and Joseph Saphia.

340. *See generally* Stephen M. Berge, Lyle D. Bighley & Donald C. Monkhouse, *Pharmaceutical Salt*, 66 J. PHARMACEUTICAL SCI. 1 (1977) [hereinafter Berge].

341. The reverse of a neutralization reaction, hydrolysis, may occur when a salt is placed in an aqueous medium. When hydrolyzed, a salt reacts with water in this general form:

(salt) + (water) = (acid) + (base)

be considered in actually formulating an active compound into a drug that can be manufactured and delivered to a patient. Physicochemical properties, such as aqueous solubility, stability, and processing properties must be considered in formulating the active compound into a commercially viable dosage form, such as a tablet, capsule, or injectable solution.

Occasionally, the active compound itself will have physicochemical properties, such as solubility and stability, which are sufficient without modification to allow the active compound to be formulated into a commercial dosage form together with inactive ingredients. Often, however, the active compound itself will not have ideal, or even adequate, physical and chemical properties to enable it to be used in a pharmaceutical formulation. For example, the active compound might be too insoluble to allow sufficient absorption by the body, or it may be too unstable to avoid excessive breakdown during commercial distribution.

One way in which pharmaceutical scientists attempt to improve the physiochemical properties of active compounds for formulation into drug products is to convert the active compound into a salt.[342] If the active compound is a base, a salt is formed by reacting the base with an acid. If the active compound is an acid, the salt is formed by reacting it with a base. The acid or base that is reacted with the active compound to form the salt can generally be referred to as the "counter-ion."

The physiochemical properties that a new salt will have are largely unpredictable.[343] Berge identifies many counter-ions that had been used to make a salt of active compounds, but cautions that "[u]nfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound."[344] As a consequence, the selection of a salt for an active compound is usually an empirical exercise.[345]

[C] Patentability of New Salts

Patent issues arise specifically concerning pharmaceutical salts when an active compound, known in the prior art in one salt form or referred to generally in the prior art as useful in the form of pharmaceutically acceptable salts, is formed into a specific new salt by creating a new acid-base combination.

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342. *See generally* Berge, *supra* note 340.
343. *Id.*
344. *Id.* at 1.
345. *Id.*

[C][1] Anticipation

In *Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.*, the Federal Circuit held that the PTAB did not err in finding the claimed 1:1 sitagliptin dihydrogenphosphate and hydrates thereof not expressly or inherently anticipated by a Merck-owned publication and the equivalent U.S. patent, which disclosed sitagliptin in a list of thirty-three compounds, phosphoric acid in a list of eight "particularly preferred" acids, and a sitagliptin hydrochloride salt with 1:1 stoichiometry.[345.1] The court distinguished *In re Petering*, which involved a "limited class" of twenty compounds that a skilled artisan may "at once envisage," from the broad class of 957 predicted salts disclosed in the Merck-owned publication.[345.2]

[C][2] Determinations of Obviousness/ Nonobviousness of New Salt Forms of Compounds

The determination of whether a new salt form of a known compound is obvious is likely to involve a fact-intensive inquiry into whether the prior art described the compound in other salt forms, whether the prior art provided any reason or motivation to select the claimed salt form from among the other possible salt forms, and whether there was a reasonable expectation of success for the claimed salt form. The cases discussed below provide insight into the obviousness inquiry for salt forms.

In *Pfizer, Inc. v. Apotex, Inc.*,[346] the Federal Circuit reversed a district court judgment and held a patent claiming the anti-hypertensive compound amlodipine in the besylate (also called benzene sulphonate) salt form obvious over the prior art. Pfizer first attempted to develop an amlodipine drug product as a maleate salt, which was the only amlodipine salt disclosed in the prior art, but determined that the maleate salt of amlodipine in tablet form presented problems with stability and stickiness.[347] These problems were solved by using the besylate salt form of amlodipine, which Pfizer then patented.[348]

The prior art asserted at trial included a patent (the '909 patent), which disclosed "that the pharmaceutically acceptable acid addition

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345.1. Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp., 50 F.4th 147, 153–54 (Fed. Cir. 2022).

345.2. *Id*. at 154. The specific number defining a "limited class" depends on the "class" at issue. *Id*.

346. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir.), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007).

347. 480 F.3d at 1353–54.

348. *Id*. at 1354–56.

salts of amlodipine 'are those formed from acids that form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts,' and that the preferred salt is maleate."[349] The prior art '909 patent did not disclose the besylate salt of amlodipine,[350] and disclosed only examples of the maleate salt of amlodipine.[351] However, other prior art references disclosed the use of the besylate salt with other compounds, and one 1977 reference ("Berge") included besylate as one of 53 acids that had been previously used to make salts approved by the FDA, although its frequency of use was 0.25%.[352] The Federal Circuit concluded that a person skilled in the art would have been motivated to combine the prior art '909 patent and the Berge reference to make the besylate salt of amlodipine. In particular, the court pointed to the structural aspects of the maleate salt (acyclic structure with a double bond between carbon atoms) that were responsible for the stability problems and that would have led one skilled in the art to select a salt for amlodipine, such as the besylate having a different structure (cyclic and lacking the double bond). The court concluded that prior art references described the use of the besylate salt form with other compounds resulting in improved properties, including stability, and that these references would "provide ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate [besylate]."[353] In doing so, the court rejected the plaintiffs' expert testimony that one could not draw a conclusion about the properties of a new salt based on the use of the same acid with a different drug. It drew its own conclusion of reasonable expectation of success based on its reading of a reference that mentioned benzene sulphonic acid as a possible salt forming acid for use with other drug compounds. The court stated that its conclusion on motivation was not undermined by the fact that the besylate salt form was only used in 0.25% of FDA-approved drugs because after the most common salt form, hydrochloride, most anions were used in less than 1% of all drug products.[354]

The Federal Circuit also concluded that "the skilled artisan would have had [a] reasonable expectation of success that an acid addition salt of besylate would form and would work for its intended

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349. *Id.* at 1353.
350. *Id.* at 1361.
351. *Id.*
352. *Id.* at 1355.
353. *Id.* at 1363.
354. *Id.*

purpose."[355] This conclusion was not undermined by the Federal Circuit's acceptance of the district court's finding that "it was generally unpredictable as to whether a particular salt would form and what its exact properties would be" because "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there is a reasonable probability of success."[356] Thus, the court rejected "a rule of law equating unpredictability to patentability."[357] The Federal Circuit also rejected the argument that it was at most "obvious to try" the besylate salt form, concluding that, "*on the particularized facts of this case*,"[358] based on the teachings of the prior art, one skilled in the art had a reasonable expectation of success "and merely had to verify that expectation."[359]

Finally, the Federal Circuit rejected the district court's finding that unexpected properties supported nonobviousness, concluding that "Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine."[360] The court found the superior properties of stability and ease of processing, and the overall combination of good properties, were not adequate to overcome prima facie obviousness because the improvements did not improve the therapeutic value of the drug compared to the maleate salt that it concluded was also useable.

In two cases predating *KSR*, a new salt of an active compound was found to be nonobvious based on the unpredictability of the properties of the new salt form of the compound.

In *Sanofi-Synthelabo v. Apotex, Inc.*,[361] the patent claimed the bisulfate salt of the d-enantiomer of a compound sold in the form of clopidogrel bisulfate under the trade name Plavix®.[362] A prior art patent had disclosed the racemate of the compound and included a disclosure that pharmaceutically acceptable salts could be made of compounds within a genus that included the particular racemate. The prior art patent also gave examples of compounds within the genus, including the particular racemate as a hydrochloride salt and additional compounds outside of the genus as other salts, including

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355. *Id*. at 1364.
356. *Id*.
357. *Id*.
358. *Id*. at 1367.
359. *Id*.
360. *Id*. at 1371.
361. Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368 (Fed. Cir. 2006).
362. *Id*. at 1372.

bisulfate but without showing a preference for bisulfates.[363] The district court granted a preliminary injunction, ruling that Apotex failed to make a substantial showing that the patent was likely invalid. The district court based its conclusion in part on the "unpredictability of salt formation," relying on the defendants' expert testimony that the "salt formation was an unpredictable exercise that would require a chemist 'to engage in experimentation to determine which salt would in fact be suitable.'"[364] On these findings of fact, the Federal Circuit affirmed the district court's holding that Apotex had not raised a substantial issue of invalidity of the patent because of obviousness.

Subsequently, after a full trial on the merits, the district court in *Sanofi-Synthelabo v. Apotex, Inc.*[365] rejected Apotex's challenge that the claimed clopidogrel bisulfate compound was invalid. As to anticipation, the district court found that the prior art patent, which disclosed the racemate of which clopidogrel is the d-enantiomer, did not expressly or inherently describe the d-enantiomer or the d-enantiomer in the bisulfate salt form.[366] As to obviousness, the district court separately addressed the selection of the d-enantiomer of the racemate and the selection of the bisulfate salt form. While the district court assumed that the d-enantiomer would have been prima facie obvious, it concluded that there was no reasonable expectation of success that the d-enantiomer would have had all of the pharmaceutical activity and none of the toxicity of the racemate.[367] In addition, the district court found that the selection of the bisulfate salt form was nonobvious because it was unexpected that the bisulfate would be the only salt form of clopidogrel obtained by Sanofi that demonstrated a highly favorable combination of properties.[368]

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363. *Id*. at 1377–78.

364. *Id*. at 1379.

365. Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353 (S.D.N.Y. 2007).

366. *Id*. at 383–86. The district court also found no anticipation because it concluded that the prior art did not enable making clopidogrel bisulfate without undue experimentation. *Id*. at 386–87. In particular, the district court concluded that the prior art did not disclose to a person skilled in the art how to separate the enantiomers of the racemate; that the prior art also did not provide any specific guidance leading to the bisulfate salt; and that making the determination to use the bisulfate salt would have taken undue experimentation. *Id*.

367. *Id*. at 390.

368. *Id*. at 391. These favorable properties included "a high melting point, long-term stability, non-hygroscopicity, and good stability." *Id*. at 375. The district court also noted that a "prior art reference—the Berge publication—did not even list the bisulfate salt in its list of FDA-approved commercially marketed salts; the bisulfate appears only on the list of non-FDA approved salts, making it all the more surprising that the

In reaching its decision that the bisulfate salt form of clopidogrel was nonobvious, the district court considered and distinguished the Federal Circuit's decision in *Pfizer, Inc. v. Apotex, Inc.*[369] First, the district court pointed to the conclusion in *Pfizer* that there was an identifiable structural feature that would have led one skilled in the art to select the claimed besylate salt to solve the problems experienced with the prior art maleate salt, whereas there were no structural features that would have led to the selection of any particular salt form for clopidogrel.[370] Second, the district court pointed out that in *Pfizer*, prior art references "specifically suggested to a person of ordinary skill in the art that the use of the besylate salt would offer improved stability in the particular compound at issue,"[371] whereas there was "no prior art teaching that that the bisulfate salt was particularly likely to be a successful salt form of clopidogrel."[372] On appeal, the Federal Circuit affirmed, on the basis that both the selection of the dextrorotatory enantiomer and the bisulfate salt form were nonobvious.[372.1] With regard to the bisulfate salt form, the Federal Circuit agreed with the district court that *Pfizer v. Apotex* was distinguishable because in that case, there was evidence that the prior art would have narrowed the choice of salt forms to only a few, including the claimed besylate salt, whereas in *Sanofi v. Apotex*, the evidence taught away from the use of sulfuric acid with an enantiomer because it could encourage re-racemization of the separated enantiomers.[372.2]

In *Pfizer Inc. v. Ranbaxy Labs., Ltd.*,[373] the prior art patent had identified the drug compound and its use in the form of

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bisulfate salt of clopidogrel, in fact, proved to be a highly suitable pharmaceutical formulation." *Id*.

369. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir.), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007). The district court in *Sanofi-Synthelabo*, however, did not cite the Supreme Court's decision in KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007).

370. *Sanofi-Synthelabo*, 492 F. Supp. 2d at 391.

371. *Id*.

372. *Id*. at 391–92. The district court in *Sanofi-Synthelabo* also pointed out that the "Federal Circuit emphasized" that *Pfizer v. Apotex* "rested on its 'particularized facts.'" *Id*. at 392.

372.1. Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008). A discussion of the selection of the dextrorotatory enantiomer is discussed *supra* at section 7:2.4[B][2].

372.2. *Id*. at 1088. The district court in its discussion of the development of the bisulfate salt form had noted that "the highly acidic nature of the bisulfate posed a significant risk of racemization, which made it unattractive for use with an enantiomeric compound." 492 F. Supp. 2d at 375.

373. Pfizer Inc. v. Ranbaxy Labs., Ltd., 405 F. Supp. 2d 495, 517 (D. Del. 2005), *rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006).

pharmaceutically acceptable salts, and had identified fifty counterions, including calcium, that could be used to make salts of the compound. The district court found that the claim of the patent in suit to the calcium salt of the therapeutic compound was at most obvious to try, but was not obvious, because the properties of new salts are unpredictable.[374] On appeal, the Federal Circuit held that the claim was invalid because it was improperly dependent, but did not discuss the nonobviousness determination.[375]

In *Pfizer Inc. v. Mylan Pharmaceuticals Inc.*,[375.1] in addition to finding the claimed compound fesoterodine (the active ingredient in Pfizer's Toviaz® product) nonobvious, the district court found that the hydrogen fumarate salt form of fesoterodine was nonobvious because only the hydrogen fumarate salt form of the more than seventy salt forms prepared by the inventor formed the desired crystalline solid rather than an oil. The court noted that "[p]reparation of salt forms of a compound, like prodrugs, is a highly unpredictable exercise."[375.2]

In *Bristol-Myers Squibb Co. v. Sigmapharm Laboratories, LLC*, the Federal Circuit affirmed the District Court of Delaware decision in *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, which found that the patent claim covering a "pharmaceutically acceptable salt form" of apixaban (the active ingredient in Eliquis®) was nonobvious.[375.3] Bristol-Myers Squibb asserted that Sigmapharm's ANDA product infringed one of its patents because it contained crystalline apixaban particles. One of Sigmapharm's arguments in response was claiming that the patent covering salt formulations of apixaban was obvious, despite the claim language requiring that the "crystalline apixaban particles have a D_{90} equal to or less than about 89 μm." Sigmapharm asserted that a POSA would have been motivated to

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374. Patent claims are not obvious if the prior art suggests that their subject matter is merely "obvious to try." *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988); *see also In re* Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987). Claims are merely "obvious to try" where there is a teaching to "try each of numerous possible choices until [reaching] a successful result," but no teaching "as to which of many possible choices is likely to be successful." *O'Farrell*, 853 F.2d at 903.

375. *Pfizer*, 457 F.3d at 1291–92.

375.1. Pfizer Inc. v. Mylan Pharm. Inc., No. 1:15-cv-000079-GMS, 2017 WL 3412301, at *14 (D. Del. Aug. 9, 2017), *appeal dismissed*, No. 2017-2531, 2018 WL 1305632 (Fed. Cir. Jan. 9, 2018).

375.2. *Id*.

375.3. Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc., 477 F. Supp. 3d 306 (D. Del. 2020), *aff'd sub nom.* Bristol-Myers Squibb Co. v. Sigmapharm Labs., LLC, 858 F. App'x 359 (Fed. Cir. 2021).

reduce the particle size of crystalline apixaban, that a POSA would have had a reasonable expectation of success that apixaban's bioavailability could be improved by increasing its dissolution rate to this size, and that this would be obvious to a POSA in view of a combination of the prior art. The district court disagreed with Sigmapharm's reasoning given the factual evidence presented and the failure of any combinations of the prior art to teach the claimed particle size or dissolution rate limitations.

[C][3] Most Common Salt Form Used for Known Active Found Obvious in Obviousness-Type Double Patenting Analysis

In *Eli Lilly & Co. v. Barr Labs., Inc.*,[376] the court held that nonstatutory type double patenting was not avoided where the first patent claimed the use of the compound fluoxetine or pharmaceutically acceptable salts thereof to treat anxiety, and the second patent claimed the use of fluoxetine hydrochloride salt to inhibit the uptake of serotonin.[377] The Federal Circuit held that the later claim was invalid for double patenting on anticipation grounds because the administration of fluoxetine to treat anxiety claimed in the first patent inherently inhibited the uptake of serotonin as claimed in the second patent. The second patent merely claimed the mechanism of action of fluoxetine that resulted in the treatment of anxiety. The Federal Circuit also found that the second claim's limitation to the particular hydrochloride salt of fluoxetine did not provide a patentable distinction over the first claim, stating "[a] person of ordinary skill in the art would have recognized that fluoxetine hydrochloride is a pharmaceutically acceptable salt of fluoxetine. In fact, hydrochloride salts are the most common pharmaceutically acceptable salts of basic drugs, and hence are obvious compounds. *See, e.g.*, The Merck Index of Chemicals and Drugs (Paul G. Stecher et al. eds., 7th ed. 1960)."[378] The Federal Circuit did not refer to any argument concerning whether there was a reasonable expectation of success.

§ 7:2.7 Infringement by Conversion to a Patented Form

Although a product as manufactured may not fall within the scope of a patent claim, infringement may be alleged based on the

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376. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 969 (Fed. Cir. 2001).
377. *Id.* at 969.
378. *Id. See also* Berge, *supra* note 340 (which also reports that hydrochloride was the most commonly used acid to make salts of active base compounds, it having been used in over 42.9% of salts that were approved by the FDA, far more than any other acid).
379. [Reserved.]

subsequent conversion of that product to a form that does fall within the patent claim. With respect to pharmaceutical products, such conversion may be alleged to occur, for example, after a drug product is administered to a patient (by metabolism or some other *in vivo* mechanism) or under various storage conditions. Infringement of a pharmaceutical patent based on "conversion" to a patented from has been addressed by several courts.[380]

[A] *In Vivo* Conversion

In vivo conversion from one form of a drug to another in the body can result from conversion to a new crystalline form, a metabolite or a polymorph.

[A][1] Claim Construction

The Court of Appeals for the Federal Circuit held in *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*[381] that a patent claim can be infringed by the conversion in the body of a non-patented compound into a patented compound.[382] In *Zenith*, the antibiotic

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380. In non-pharmaceutical cases, courts have addressed infringement by conversion of a product through normal use and wear to a patented form. *See, e.g.*, Elyria Nat'l Rubber Heel Co. v. I.T.S. Rubber Co., 263 F. 979, 982 (6th Cir. 1920) (patent to a rubber heel for a shoe held not infringed by ordinary use of defendants' shoe because only some shoes would be worn down to patented form, thus "[t]here are too many contingencies and uncertainties to justify bringing such a situation within the rule of contributory infringement"); Stash, Inc. v. Palmgard Int'l, Inc., 937 F. Supp. 531, 537 (D. Md. 1996) ("If a purchaser of the . . . glove would almost certainly use the glove in such a way as to cause the padding to become flexible, [the accused infringer] might be liable for infringement."); Omark Indus., Inc. v. Carlton Co., 458 F. Supp. 449, 453 (D. Or. 1978) ("[M]anufacture of an article which as a result of wear becomes identical with the patented article does not necessarily constitute infringement."), *aff'd*, 652 F.2d 783 (9th Cir. 1980); Cadwell v. Firestone Tire & Rubber Co., 13 F.2d 483, 488 (E.D.N.Y. 1926) (patent to tire with particular shape held not infringed by conversion due to wear: "It may well be true that, if used long enough, the recesses on the face of the tread of the defendant's tire would be so worn down as to no longer function, but that would not constitute infringement, because it would not be the normal intended use of the tire.").

381. Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418 (Fed. Cir. 1994).

382. In Ortho Pharm. Corp. v. Smith, 18 U.S.P.Q.2d (BNA) 1977 (E.D. Pa. 1990), *aff'd*, 959 F.2d 936 (Fed. Cir. 1992), the district court held that a patent that claimed the compounds norgestrel and norgestrel acetate was infringed under the doctrine of equivalents by Ortho's norgestimate which was shown to break down in the body to the claimed compounds. This holding was not appealed to the Federal Circuit.

cefadroxil had been described and claimed in an expired patent owned by Bristol-Myers Squibb (BMS). BMS developed and obtained a patent on a crystalline form of cefadroxil, called Bouzard monohydrate, which claimed the compound by its name and by its X-ray diffraction pattern. BMS brought suit against the filer of an ANDA for a form of cefadroxil known as cefadroxil DC, which is structurally distinct from Bouzard monohydrate, under the theory that the cefadroxil DC converts into the patented Bouzard monohydrate form after ingestion. After reviewing the claim language, the patent specification, and prosecution history, the Federal Circuit concluded that the claim covered Bouzard monohydrate formed in the body: "We conclude, therefore, that while the claim as issued is limited to the crystalline form of cefadroxil exhibiting the specified x-ray diffraction pattern, it is not limited to the compound in its preingested form. . . ."[383]

The Federal Circuit reaffirmed the principle of infringement by *in vivo* conversion of a drug product to a patented compound in *Hoechst-Roussel Pharmaceuticals Inc. v. Lehman*.[384] At issue was whether a patent claiming a metabolite of the active ingredient in an FDA-approved drug product was subject to the patent term extension provisions of section 156 of title 35. The Federal Circuit concluded that "the right to exclude may arise from the fact that when administered, tacrine hydrochloride metabolizes into another product, 1-hydroxy-tacrine."[385]

However, the claim at issue may be construed as excluding infringement by *in vivo* conversion. For example, in *Novartis Pharmaceuticals Corp. v. Eon Labs Manufacturing, Inc.*,[386] the Federal

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383. *Zenith Labs.*, 19 F.3d at 1422. The court found that infringement was not established because BMS did not prove that the compound formed in the body satisfied the thirty-seven-line X-ray diffraction pattern recited in the claim. *Id*. at 1423–24. For a discussion of issues relating to infringement of claims which define compounds by X-ray diffraction patterns, see *supra* section 7:2.5[B] and [C].

384. Hoechst-Roussel Pharm. Inc. v. Lehman, 109 F.3d 756 (Fed. Cir. 1997).

385. *Id*. at 759. However, the court held that the metabolite patent was not entitled to a patent term extension because the statute is limited to patents that "claim" the approved drug product and does not extend to patents that claim a metabolite formed in the body after administration of the approved drug product. The court determined that "claim" as used in the statute is narrower in scope than the concept of infringement and is limited to patents that actually "claim the FDA-approved product or its use." *Id*. at 760. Patent term extensions under 35 U.S.C. § 156 are discussed *infra* section 8:4.

386. Novartis Pharm. Corp. v. Eon Labs. Mfg., Inc., 363 F.3d 1306 (Fed. Cir. 2004).

Circuit distinguished its *Zenith* decision and construed a claim as limited to a "medicinal preparation prepared outside the body" that did not cover the conversion of an ingested drug product into the claimed form.[387] In *Novartis*, the claim recited a "hydrosol which comprises solid particles of cyclosporin." Novartis contended that although Eon's capsule formulation of cyclosporin was not a hydrosol, an infringing hydrosol is formed after the capsule is ingested. In reviewing the claim language, specification, and prosecution history, the court concluded that the term "hydrosol" is "limited to a medicinal preparation consisting of a dispersion of solid particles in a liquid colloidal solution prepared outside the body."[388] The court's claim construction was informed by the absence of description or examples in the specification of making a hydrosol in a patient's body, the repeated description of the invention as a "pharmaceutical composition," and the argument made in distinguishing prior art during prosecution that the invention can be administered by "intravenous injection."[389] Based on this claim construction, the court held that Eon's capsule did not literally infringe. Moreover, the court held that there could be no infringement under the doctrine of equivalents by conversion in the body because such a finding would "vitiate the claimed requirement that the dispersion be prepared outside the body."[390]

Although *Zenith* supports the principle of infringement by conversion to a patented form, under *Eon* the decision of whether a claim covers a converted product may be an issue of claim construction. The difference between the decisions may be explained by the fact that in *Zenith* "[t]he claim as written and allowed simply describes a compound having specified chemical properties,"[391] whereas in *Eon*, the claim was construed to cover a "medicinal preparation."[392] As shown below, claim construction is often determinative of the validity and infringement of patent claims asserted in cases involving an assertion of conversion to a patented form.

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387. *Id*. at 1312.
388. *Id*. at 1311.
389. *Id*. at 1310–11.
390. *Id*. at 1312. In Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 761–64 (N.D. W. Va. 2004), the defendant argued that a claim to levofloxacin, the levo enantiomer of the prior art drug ofloxacin, was anticipated because ofloxacin converts *in vivo* to the claimed levofloxacin enantiomer. The court rejected the argument because of a failure of proof that the claimed levofloxacin compound exists as a monomer *in vivo*. Patent issues relating to enantiomers are discussed in *supra* section 7:2.4.
391. Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1421 (Fed. Cir. 1994).
392. *Eon*, 363 F.3d at 1309.

[B] Infringement and Anticipation

A number of pharmaceutical patent cases have addressed whether the manufacture of a pharmaceutical compound described in a prior art patent can be blocked by a later patent claiming an active metabolite of the prior art compound under the theory that the formation of the claimed metabolite in the body of a patient is an infringement of the metabolite patent.

[B][1] Schering v. Geneva

The Federal Circuit in *Schering Corp. v. Geneva Pharmaceuticals, Inc.*[393] held anticipated a claim to a metabolite compound based on the disclosure in a prior art patent of the parent compound and its administration even though "the prior art supplies no express description of any part of the claimed subject matter."[394]

A prior art expired patent described the compound loratadine, the active ingredient in Schering's antihistamine drug product Claritin®, and its administration to treat allergic conditions. Schering asserted that a second patent claiming the metabolite of loratadine, descarboethoxyloratadine (DCL), would be infringed by generic manufacturers of loratadine products because the claimed metabolite DCL compound would be formed in the patient's body. The parties agreed that the claim in suit, which simply recited the chemical structure of DCL, should be construed to "cover DCL in all its forms, including 'metabolized within the human body' and 'synthetically produced in a purified and isolated form.'"[395] The Federal Circuit found that the claim to DCL was inherently anticipated by the prior art description of loratadine and its administration.[396]

The court acknowledged that the prior art did not describe DCL, but rejected "the contention that inherent anticipation requires recognition in the prior art" or that "an inherent feature of a prior art reference must be perceived as such by a person of ordinary skill in the art before the critical date."[397] Moreover, the court held that "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure."[398] This requirement was satisfied by the prior art disclosure of loratadine and its administration, which necessarily resulted in the formation of DCL.

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393. Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373 (Fed. Cir. 2003).
394. *Id*. at 1378.
395. *Id*. at 1376.
396. For a discussion of the principles of inherent anticipation, see *supra* section 5:2.2[D].
397. *Schering*, 339 F.3d at 1377.
398. *Id*. at 1380.

While holding the compound claim in *Schering* invalid as anticipated, the Federal Circuit took care to note that its decision "does not preclude patent protection for metabolites of known drugs."[399] While "broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound," the court stated that "the metabolite may be claimed in its pure and isolated form . . . or as a pharmaceutical composition (for example, with a pharmaceutically acceptable carrier)."[400] According to the court, the prior art disclosure of the parent compound does not enable such claims because it does not disclose the metabolite in its isolated form.[401]

*[B][2] Pre-*Schering *District Court Decisions*

Prior to *Schering*, metabolite patents had been asserted in litigations relating to the pharmaceutical products Seldane®,[402] Prilosec®,[403] and Buspar®.[404] In each of these cases, the district court rejected the patent owner's argument that its patent on an active metabolite formed in the body of a person ingesting a prior art pharmaceutical compound could block the manufacture of that prior art compound. Although the judgments in each of these prior cases was based on a construction of the claims of the metabolite patents that precluded a determination of infringement, an underlying issue was the validity of the metabolite patent over the prior art parent compound notwithstanding that there was no description in the prior art of the chemically distinct metabolite compound.

[B][2][a] *Marion Merrell Dow*

In *Marion Merrell Dow v. Baker Norton Pharmaceuticals, Inc.*,[405] a generic drug company, Marion Merrell Dow (MMD), filed an ANDA for approval to make a generic version of the antihistamine Seldane®, which contained the active ingredient terfenadine. MMD listed in the Orange Book its patent claiming the active metabolite of terfenadine (TAM) and a method of treating allergic reactions by administering an effective amount of TAM. MMD asserted that Baker would

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399. *Id*. at 1381.
400. *Id*.
401. *Id*.
402. Marion Merrell Dow Inc. v. Baker Norton Pharm., Inc., 948 F. Supp. 1050 (S.D. Fla. 1996).
403. *In re* Omeprazole Patent Litig., 2001 WL 585534 (S.D.N.Y. May 31, 2001).
404. *In re* Buspirone Patent Litig., 185 F. Supp. 2d 340 (S.D.N.Y. 2002).
405. Marion Merrell Dow Inc. v. Baker Norton Pharm., Inc., 948 F. Supp. 1050 (S.D. Fla. 1996).

induce infringement of the metabolite patent because terfenadine would convert *in vivo* to the claimed metabolite. MMD's patent on terfenadine (the parent compound) had expired and was prior art to the metabolite patent.

On summary judgment, the district court construed the claims of the asserted metabolite patent as limited to the synthetically made compound and as excluding the metabolite as made *in vivo* after ingestion of the parent compound.[406] Accordingly, the court granted Baker summary judgment of non-infringement, and did not decide whether the claims to the metabolite compound or its administration were valid over the prior art.

The court based its claim construction of the MMD metabolite patent on the language of the other claims of the patent, the specification, and the prosecution history:

1. The court considered that other claims of the metabolite patent directed to a "pharmaceutical composition" containing the metabolite and to "pharmaceutically acceptable salts" of the metabolite depended from the independent claim reciting the compound itself. The court found that these dependent claims supported a construction of the word "compound" to mean a synthetically made compound because pharmaceutical compositions of the metabolite compound would be made from synthesized TAM, and not from "impure TAM created in the body by metabolism."[407]
2. The court took note that the specification "exhaustively discusses and gives examples of the chemical formulations of TAM, the usefulness of TAM as an antihistamine, and the modes for administering TAM in effective amounts. . . . By contrast, the specification contains no reference whatsoever to TAM created *inter vivo* by metabolism."[408] The specification therefore supported limiting the claims to synthetically made metabolite.
3. The court also stated that "[f]ar more compelling," the prosecution history of the metabolite patent supported a construction limiting the claims to synthetically made compound. MMD had filed a dependent claim which recited the compound as "an essentially pure" compound. The patent examiner had rejected both claims because she did not believe that there was a proper distinction in scope between the claims. To obviate the rejection, MMD canceled the dependent claim to the "essentially pure" compound and the Patent Office

406. *Id*.
407. *Id*. at 1054.
408. *Id*. at 1055.

> allowed the independent claim without the "essentially pure" limitation. The court concluded that "MMD necessarily adopted the examiner's interpretation of 'compound' as limited to that formed by synthetic means."[409] The court found that the patent examiner believed that both claims were limited to "essentially pure" compound, including the issued claim that did not have this language.[410]

Thus, in *Marion Merrell Dow*, the court interpreted a claim that simply recited a chemical compound to be limited to the compound made synthetically and as not covering the compound that was made through metabolism.

[B][2][b] *Omeprazole*

In *In re Omeprazole Patent Litigation*,[411] the patent asserted against the ANDA filer claimed a metabolite (a sulphenamide) of the active ingredient (omeprazole) contained in the approved drug product, Prilosec®. The prior art patent on the omeprazole compound was due to expire in several months while the patent on the metabolite would not expire for another three and a half years. The court construed the claims of the metabolite patent as limited to synthetically made compound based on the following reasoning:

1. The court concluded that the language of both the asserted and unasserted claims supported limiting the asserted claims to the synthetically made compound. Because claim 1 recited "a pharmaceutically acceptable anion," the court found that "[b]y describing the invention in terms of an anion chosen pursuant to pharmaceutical standards, the inventors . . . suggested a degree of control over the formulation of the [compound]; such control is available only in the synthetic context and is nonsensical in the in vivo context."[412] The court also found that claims depending from claim 1 recited "chemical components not found in vivo, and thus must also refer only to synthetic [compounds]."[413]
2. The court found that limiting the claims to the synthetically made compound was supported by the disclosure in the specification of a synthetic method for making the metabolite, notwithstanding that the specification also taught the metabolic route:

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409. *Id*. at 1055–56.
410. *Id*.
411. *In re* Omeprazole Patent Litig., 2001 WL 585534 (S.D.N.Y. May 31, 2001).
412. *Id*. at *4.
413. *Id*. at *5.

> "[T]he specification . . . reveal[s] that sulphenamides are formed in the body when omeprazole is ingested. This reference to omeprazole's in vivo conversion to sulphenamides, however, merely provides a description of the prior art which gives the context for the discovery of the claimed invention. If anything, it is an implied admission that the sulphenamides formed in vivo are inherent in the prior omeprazole art."
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> . . . .
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> "The detail of the description of the processes for the synthesis of the claimed sulphenamides contained in the patent also demonstrate an intention to teach and claim those synthetic processes that is absent from the description of the in vivo formation of sulphenamides."[414]

3. The court found that the prosecution history did not clearly support either claim construction.

Based on the above analysis, the *Omeprazole* court limited the claims to the synthetically made compound and granted summary judgment to the defendant that its proposed ANDA product would not infringe the metabolite patent. Moreover, after finding non-infringement, the court determined that if it had construed the claims to cover the *in vivo* formation of the metabolite, the claims would be invalid for anticipation by the prior art. Accordingly, the court stated that it would still have had to construe the claim to cover "only pre-ingestion sulphenamides in order to preserve the patent's validity."[415]

The *Omeprazole* court determined that a claim attempting to cover the formation of the metabolite *in vivo* after administration of the prior art parent compound would be invalid because it would, in effect, be explaining how the prior art worked.[416]

[B][2][c] *Buspirone*

In re Buspirone Patent Litigation[417] also addressed whether a claim could be construed to cover the *in vivo* conversion of a parent

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414. *Id*. at *6.
415. *Id*. at *12.
416. The court stated that "[b]y claiming patent protection for sulphenamides formed *in vivo* after the oral administration of omeprazole, Astra has merely attempted to patent the unpatentable—'a scientific explanation for the prior arts functioning.'" *Id*. at *12 (quoting Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999)).
417. *In re* Buspirone Patent Litig., 185 F. Supp. 2d 340 (S.D.N.Y. 2002).

compound to the claimed compound. The district court granted the defendants' summary judgment of non-infringement by construing a claim that recited the administration of a metabolite of buspirone to exclude the administration of the metabolite through the *in vivo* conversion of buspirone to the metabolite.

The only claim of the Bristol-Myers patent at issue recited "[a] process for ameliorating an undesirable anxiety state in a mammal comprising systemic administration to the mammal of an effective but non-toxic anxiolytic dose of [the metabolite of buspirone] or a pharmaceutically acceptable acid addition salt or hydrate thereof."[418]

The court found that the word "dose" as used in the claim did not support administration of the recited metabolite through *in vivo* conversion after administering buspirone because dose "has a clear meaning in reference to an externally measured amount of a substance that is to be ingested or administered into the body all at once."[419]

The court also found that the specification did not support Bristol-Myers' position that "systemic administration" of the metabolite included the administration of buspirone as a pro-drug because the specification stated that the method disclosed "improves upon and differs from the known standard method of oral administration of buspirone."[420] Thus, the court found that "systemic administration" of the metabolite must mean something other than the prior art method of administering buspirone which the FDA had previously approved.

Finally, and most persuasive to the court, the prosecution history supported a finding that Bristol-Myers had relinquished claim coverage for *in vivo* metabolism of buspirone to the metabolite when it deleted the pro-drug route from its claims during prosecution: "In sum, every time Bristol-Myers explicitly claimed a use of 'buspirone' or a 'prodrug' of the 6-hydroxy-metabolite, the application was rejected. Bristol-Myers only obtained the '365 patent after omitting all references in the claim to 'buspirone' and any 'prodrug,' and after making express declarations that the amendments acted to exclude uses of buspirone."[421]

Similar to *Omeprazole*, in *Buspirone*, the court concluded by stating that under Bristol-Myers' proposed claim construction, the claim would read on the prior art administration of buspirone and therefore

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418. *Id*. at 352.
419. *Id*. at 353.
420. *Id*. at 354.
421. *Id*. at 359.

would be invalid under section 102(b). The district court stated that if the claim at issue was construed to cover the administration of buspirone (the parent compound), the claim would be anticipated by the prior art administration of buspirone. In particular, the court held that if the claims covered the *in vivo* formation of the metabolite, they would be invalid under the "on-sale" bar of section 102(b) because the parent compound "buspirone [had] been on the commercial market in this country as a drug for the treatment of anxiety since 1986, when Bristol-Myers first obtained and published its FDA-approved labeling instructions for Buspar®."[422]

[C] Conversion Outside the Body: Polymorphic Form Conversion

In *SmithKline Beecham Corp. v. Apotex Corp.*,[423] the maker of the drug product Paxil® asserted that Apotex, the filer of an ANDA directed to the prior art anyhydrate form of paroxetine hydrochloride (PHC), would infringe a patent directed to the hemihydrate form of PHC because the anhydrate form would convert (albeit in very small, and perhaps undetectable amounts) to the patented hemihydrate form. The Federal Circuit rejected the district court's claim construction which limited the claim at issue to "commercially significant quantities" of the hemihydrate.[424] The Federal Circuit also rejected the district court's attempt to fashion an "equitable" defense to infringement by trace amounts of the hemihydrate where the presence of the hemihydrate could be attributed to the patentee's creation of a "seeded environment" by its production of the hemihydrate.[425]

While the Federal Circuit held that the claim was infringed by the ANDA product because of the necessary conversion from the prior art anhydrate form to the patented hemihydrate form, the Federal Circuit held that the patent was invalid because it was inherently anticipated by the prior art patent disclosing the anhydrate form. The court concluded, based in part on admissions by SmithKline, that SmithKline's prior art patent on the anhydrate form "inevitably results in the production of at least trace amounts of anticipating PHC hemihydrate."[426] The Federal Circuit stated that Apotex "did

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422. *Id*.

423. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir. 2005). The Federal Circuit vacated its prior opinion in the case which had been reported at 365 F.3d 1306 (Fed. Cir. 2004).

424. 403 F.3d at 1339–40.

425. The presence of small amounts, or "seeds" of the hemihydrate was argued to cause the conversion of the anhydrate to the hemihydrate. *Id*. at 1342.

426. *Id*. at 1344.

not need to prove that it was impossible to make PHC anhydrate in the United States that contained no PHC hemihydrate, but merely that 'the disclosure [of the prior art] is sufficient to show that the natural result flowing from the operation as taught [in the prior art] would result in' the claimed product."[427] The court concluded that the practice of the prior art anhydrate patent "naturally results in the production of PHC hemihydrate."[428]

Accordingly, while the Federal Circuit found infringement based on a post-manufacture conversion from a prior art polymorphic form to a patented form, the court found that evidence that the same conversion occurred in the prior art led to anticipation.[429]

§ 7:2.8 *Particle Size of Active Ingredient**

[A] What Is Particle Size?

The particle size of an Active Pharmaceutical Ingredient (API) is generally defined in terms of its mean diameter (in microns) or specific surface area (SSA). The SSA is the exposed surface area of the particles, and is measured in meters squared per gram (m^2/g). The smaller the particle size, keeping the mass constant, the larger the specific surface area. Thus, for example, particles less than about 10 microns in diameter may be roughly correlated to an SSA greater than about 1 m^2/g.[430] This correlation may depend on the nature of the API and its process of manufacture. For example, particles having an uneven or irregular surface may have a higher SSA than smooth particles of the same size, because the uneven particles have more exposed surface area.

Micronization refers to the reduction of particle size to a very small diameter typically measured in microns (1 micron is 10^{-6} meters). Micronization of APIs can result in an increased dissolution rate and a faster onset of drug in the blood plasma because smaller particles

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427. *Id*. at 1343 (quoting *In re* Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981)).
428. *SmithKline*, 403 F.3d at 1344. It is worth noting that there was no proof that practicing the prior art patent at the time it was filed in 1975 would produce the PHC hemihydrate (as Judge Newman noted in her dissent from the denial of rehearing en banc). *Id*. at 1329–30 (Newman, J., dissenting). There was evidence, however, that the PHC hemihydrate was formed in 1984, prior to the filing in 1985 of the patent directed to PHC hemihydrate.
429. See *supra* section 7:2.5 for a more extensive discussion on polymorph patents.
* Written by Steven D. Roth.
430. *See* Wadke, Serajuddin & Jacobson, *supra* note 293, at 12.

have more surface area exposed to the media that allows them to dissolve faster. But micronization does not always result in faster dissolution and bioavailability. For example, micronized particles tend to agglomerate, which may reduce effective surface area and slow dissolution.[431] Micronization can also lead to manufacturing, content uniformity and stability problems.[432]

[B] Infringement of Particle Size Patents

Four infringement issues that have been raised in connection with particle size patents are:

(1) whether particle size is measured on the API raw material or on the API in the formulation,

(2) the effect of a particle size specification in an application to the FDA,

(3) the method of measurement, and

(4) infringement under the doctrine of equivalents.

[B][1] Measured on the API Raw Material or in the Formulation

An important issue, which has been raised but not yet decided in any published opinion, is whether the particle size must be measured on the API raw material before it is mixed with other ingredients, or on the API in the mixture. Putting aside the question of whether it is even technically feasible to measure particle size of an API in a mixture or to extract an API from a mixture without altering its particle size,[433] the preliminary question that must be resolved is one of claim construction. This issue was raised but not resolved in *Bayer AG v. Elan Pharmaceutical Research Corp.*[434]

Nevertheless, in other contexts, it has been held that, depending on the claim construction, if a patent claim is directed to a composition or mixture comprising various ingredients having certain characteristics, the claim may be interpreted as requiring the ingredient(s)

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431. *See id*. at 5–6.
432. *See id*.
433. The Federal Circuit has held that a patent claim is definite if one skilled in the art could understand the bounds of the invention, not whether the person skilled in the art has the ability to ascertain its presence in a specific product. *See SmithKline*, 403 F.3d at 1340–41.
434. *See* Bayer AG v. Elan Pharm. Research Corp., 2001 U.S. Dist. LEXIS 23882 (N.D. Ga. Mar. 21, 2001), *vacated sub nom.* Bayer AG v. Biovail Corp., 279 F.3d 1340 (Fed. Cir. 2002).

to possess those characteristics as the ingredients exist in the composition or mixture. Thus, for example, in *Exxon Chemical Patents, Inc. v. Lubrizol Corp.*,[435] the Federal Circuit held that a claim to a composition having certain ingredients is limited to the claimed features of the ingredients as they exist in the composition:

> Exxon claims a product, not merely a recipe for making whatever product results from the use of the recipe ingredients. This conclusion respects that which is claimed, namely a chemical composition. The chemical composition exists at the moment the ingredients are mixed together. Before creation of the mixture, the ingredients exist independently. The particular proportions specified in the claims simply define the characteristics of the claimed compositions.[436]

Similarly, the Federal Circuit in *Mars, Inc. v. H.J. Heinz Co.*,[437] relying in part on the definition of the terms "ingredients" and "mixture" in *Webster's Third New International Dictionary* (2002), held that the claim term "a mixture of solid and lipid ingredients" does not refer to the characteristics of the starting material, but to ingredients "at any time after they have been mixed together."[438] The Federal Circuit also indicated that the patent specification may provide a basis for deviating from this interpretation, but noted that "[t]he mere fact that the patent examples appear to use the term 'ingredients' to refer to starting materials is not a sufficient reason, in and of itself, to deviate from the ordinary meaning of claim language."[439]

Although no court in a published decision has yet decided the issue of whether a claim on the particle size of an API is limited to the API raw material or the API in a composition, it is ultimately a question of claim construction that will be decided on a case-by-case basis.

[B][2] Infringement of Particle Size Patents in Hatch-Waxman Cases

Infringement of particle size patents has generally been raised in the context of Hatch-Waxman litigation. A drug company has a patent claiming a range of particle diameter or SSA for an API, and a generic drug company files an ANDA that specifies a mean diameter or SSA

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435. Exxon Chem. Patents, Inc. v. Lubrizol Corp., 64 F.3d 1553 (Fed. Cir. 1995).
436. 64 F.3d at 1557–58.
437. Mars, Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1374–75 (Fed. Cir. 2004).
438. *Id*.
439. *Id*. at 1375.

of its API outside the claimed range. The Federal Circuit in *Bayer AG* held that such an ANDA specification avoids literal infringement.[440]

The patent in the *Bayer AG* case claimed nifedipine having an SSA in the range of 1 to 4 m^2/g. Elan's ANDA included a specification limiting the nifedipine raw material SSA, as measured within five days of tableting, to "5 m^2/g or greater."[441] (The five-day limitation was inserted to avoid the possibility that the particles will grow and SSA decline between SSA measurement and tableting.) The Federal Circuit affirmed summary judgment of no literal infringement, reasoning that Elan legally can only use non-infringing nifedipine in its ANDA product:

> [T]he specification in Elan's ANDA defines its product in a way that directly addresses the question of infringement—the SSA of the nifedipine crystals. Elan is bound by this specification . . . Elan is required, under 21 C.F.R. § 314.94(a)(9), to comply with 21 C.F.R. § 314.50(d)(1)(i) and state the ANDA drug's specification, including its particle size and the process controls used in manufacturing to assure the specification is met.
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> * * *
>
> If any of the statements in Elan's specification are false, Elan is subject to civil penalties, see 21 U.S.C. § 335b(a)(1), and the withdrawal of the approval of its drug, see 21 U.S.C. § 335c(a)(1). . . . . In short, the only drug Elan can produce upon approval of the ANDA at issue is a drug that does not literally infringe the '446 patent.[442]

Thus, the Federal Circuit held that an ANDA specification can resolve the issue of literal infringement in a Hatch-Waxman case. The Federal Circuit also held that Bayer's measurements of nifedipine SSA in Elan's "biobatch" (tablet batch which was utilized in the bioequivalence studies reported in the ANDA) was not relevant to the issue of literal infringement, because the ANDA specifications "directly addresse[d] the question of infringement."[443]

[B][3] Method of Measurement

Another infringement issue that may be raised is the method of measurement of particle size. Many patents specify, but generally do

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440. *See* Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241 (Fed. Cir. 2000).
441. *Id*. at 1246.
442. *Id*. at 1249–50.
443. *Id*. at 1250.

not claim, the so-called "BET" method for measuring SSA,[444] and further specify measurement methodology, such as multi-point or single-point analysis, or the gas used for adsorption.[445] But as a matter of law, claims are not limited to unclaimed methods of measurement described in the specification.[446] Generally, any method reasonably relied upon by those skilled in the art should be acceptable.[447]

Particle size measurements are generally conducted on a sample consisting of many particles, not on a single particle. The result of a BET measurement of SSA is a single number representing a collective SSA. But the result of a laser diffractometer (for example, a malvern instrument) measuring particle diameter is a mean particle size with a distribution. Patents claiming particle diameter can define the particle size limitation in terms of the mean particle size or percent distribution. An issue that has been raised, but not yet decided, is the interpretation of such a particle size claim limitation that is not defined in terms of a mean or distribution. For example, does a claim term requiring a particle size of "less than 10 microns" cover a product whose mean particle size is less than ten microns or only those particles less than ten microns? This could be an important infringement issue, if, for example, the mean diameter of an accused infringer's product is greater than ten microns, but some percentage of the particles have a diameter less than ten microns. The Federal Circuit has recently held that even trace amounts of a claimed product are sufficient for patent infringement.[448]

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444. *See* Stephen Brunauer, P.H. Emmett & Edward Teller, *Adsorption of Gases in Multimolecular Layers*, 60 J. AM. CHEMICAL SOC'Y 309 (1938).

445. The BET method is based on the measurement of a quantity of gas (usually nitrogen for SSA greater than 1 m^2/g) adsorbed into the active surface of the particles. A single-point technique relies on a single partial pressure for the gas and a multi-point technique relies on several different partial pressures. Multi-point may in some cases result in a more accurate result, but the difference is typically less than 5%. *See* S. Lowell et al., *Characterization of Porous Solids and Powders: Surface Area, Pore Size and Density* 58–69, *in* PARTICLE TECHNOLOGY SERIES (Brian Scarlett ed., 2004).

446. *See, e.g.*, PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1562–63 (Fed. Cir. 1996); Grain Processing Corp. v. Am. Maize-Prods. Co., 840 F.2d 902, 909–10 (Fed. Cir. 1988).

447. Nevertheless, a patent specification disclosing a particular method of measurement could serve to eliminate potential problems under 35 U.S.C. § 112.

448. *See* SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331 (Fed. Cir.), *reh'g denied*, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005).

[B][4] Infringement Under the Doctrine of Equivalents

With respect to infringement under the doctrine of equivalents, the infringement issues are subject to the same limitations, such as estoppel and dedication to the public that other patents are subject to. For example, the Federal Circuit in *Bayer AG v. Elan Pharmaceutical Research Corp.*,[449] held that Bayer was estopped from demonstrating that nifedipine SSA greater than 4 m^2/g is equivalent to the claimed range of 1 to 4 m^2/g based on amendments and arguments made by Bayer to the Patent Office during prosecution. Bayer originally claimed 0.5 to 6 m^2/g, but narrowed the range to 1 to 4 m^2/g, which the court found was in response to a patentability rejection.[450] The examiner rejected the claim based on his assertion that micronization to improve dissolution or bioavailability was obvious. The court found that in response, Bayer submitted declarations to demonstrate that over the 1 to 4 m^2/g range, dissolution and bioavailability remained substantially constant (the so-called "plateau effect"), and decreased at a SSA above 4 m^2/g.[451] Thus, the court found that Bayer disclaimed SSA outside the 1 to 4 m^2/g range.

[C] Validity

[C][1] Obviousness

Micronization of drug particles can result in increased dissolution because more drug surface area is exposed to the dissolution media.[452] There are many examples of a correlation between an increase in SSA and increase in dissolution and bioavailability, particularly for poorly water soluble drugs.[453] Thus, in many cases involving patents covering micronized drug particles, the accused infringer asserts an invalidity defense based on obviousness. But, there have been very few published decisions addressing the question of whether micronization to improve bioavailability is obvious. The Federal Circuit touched on the issue in *Upjohn Co. v. MOVA Pharmaceutical Corp.*,[454] when it reversed a judgment based on a jury verdict that a patent claiming a pharmaceutical composition containing micronized glyburide

449. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1250–54 (Fed. Cir. 2000).
450. *Id*. at 1251–52.
451. *Id*. at 1252–53.
452. *See* Wadke, Serajuddin & Jacobson, *supra* note 293, at 5–6.
453. *See id*.
454. Upjohn Co. v. MOVA Pharm. Corp., 225 F.3d 1306 (Fed. Cir. 2000).

and at least 70% spray-dried lactose was obvious. The Federal Circuit recognized that there was evidence teaching away from the use of micronized particles as they might agglomerate into larger particles and interfere with powder flow and content uniformity.[455]

Although micronization often increases dissolution of poorly soluble drugs, it can cause problems, and indeed, even lead to decreased dissolution. For example, micronization can:

(1) cause mixing problems leading to a nonuniform tablet dose,

(2) cause electrostatic and other surface effects creating undue stickiness of the powder resulting in poor bioavailability, powder flow and nonuniformity, and

(3) cause the micronized particles to react with other ingredients or the environment, resulting in stability problems.[456]

An example of the unpredictability of micronization is micronized nifedipine, discussed above, which was the subject of the *Bayer AG* litigation. The inventors of the Bayer patent at issue found that, above an SSA of 1 m^2/g, there was no further increase in dissolution or bioavailability (the "plateau effect"), and indeed, above an SSA of 4 m^2/g, dissolution/bioavailability decreased.[457] Thus, micronization of an API can lower dissolution and bioavailability.

[C][2] Written Description

The Federal Circuit, in *Eli Lilly & Co. v. Teva Pharmaceuticals USA, Inc.*, affirmed a district court's finding that a particle size claim construed to apply to raloxifene particles before and after formulation lacked written description because the specification only disclosed the size prior to formulation and did not disclose whether formulation changed the particle size.[457.1] On the other hand, in *Takeda Pharmaceuticals Co. v. Zydus Pharmaceuticals USA, Inc.*, the Federal Circuit distinguished *Eli Lilly* and upheld the validity of a particle size claim because "the evidence established only a hypothetical possibility that tableting *could* affect particle size in a relevant way."[457.2]

In *Bristol-Myers Squibb Co. v. Sigmapharm Laboratories, LLC*, the Federal Circuit affirmed the District Court of Delaware decision in

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455. *Id*. at 1311–12.
456. *See* Wadke, Serajuddin & Jacobson, *supra* note 293, at 5–6.
457. *Bayer AG*, 212 F.3d at 1241, 1253.
457.1. Eli Lilly & Co. v. Teva Pharm. USA, Inc., 619 F.3d 1329, 1344–45 (Fed. Cir. 2010).
457.2. Takeda Pharm. Co. v. Zydus Pharm. USA, Inc., 743 F.3d 1359, 1368 (Fed. Cir. 2014).

Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc., which found that Sigmapharm's ANDA product, which contained crystalline apixaban particles, infringed two of Bristol-Myers Squibb's patents covering apixaban (the active ingredient in Eliquis®).[457.3] Sigmapharm argued that both patents were invalid for lack of written description. Regarding the first patent, which covers apixaban or a "pharmaceutically acceptable salt form" of apixaban, Sigmapharm argued that the written description was insufficient as it included only a general description of salt formation and a list of various compounds, some of which did not even have salts. Despite the fact that "the inventors did not themselves ever make pharmaceutically acceptable apixaban salts," the court held that "a POSA would understand from the four corners of the [first] patent that the inventors possessed pharmaceutically acceptable apixaban salts."[457.4]

As to the second patent, which covered formulations of apixaban, Sigmapharm argued that the claim language required that the "crystalline apixaban particles have a D_{90} equal to or less than about 89 μm," but the written description did not describe or contemplate determining the D_{90} of the apixaban particles once formulated. The court held that, because the term "apixaban particles have a D_{90}" was construed as having its plain and ordinary meaning, the particle size limitation was to be interpreted as describing "a feature of the claimed invention, not a measurement requirement."[457.5] Using this definition, the court held that the second patent was valid and the written description sufficient given that the patent provided "substantial direction to a POSA seeking to practice the asserted claims" and that the process of measuring the crystalline apixaban before formulation and ensuring it was within the desired size range or measuring after formulation would be known by a POSA to ensure that what was produced had the desired feature.

§ 7:3 Pharmaceutical Formulations*

§ 7:3.1 What Is a Pharmaceutical Formulation?

While the identification of an active ingredient is generally the foundation of a pharmaceutical product, typically active ingredients must be formulated into a dosage form suitable for delivery to a patient.

457.3. Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc., 477 F. Supp. 3d 306 (D. Del. 2020), *aff'd sub nom.* Bristol-Myers Squibb Co. v. Sigmapharm Labs., LLC, 858 F. App'x 359 (Fed. Cir. 2021).

457.4. *Id.* at 353.

457.5. *Id.* at 354.

* Written by David K. Barr.

Pharmaceutical products may be administered using a number of dosage forms including solid dosage forms such as tablets or capsules, liquid dosage forms, ointments, and aerosols. Pharmaceutical products can be administered through many routes of administration:[458]

- oral
- aerosolized
- subcutaneous
- rectal
- intradermal
- intravenous
- nasal
- transdermal
- aural
- intramuscular

Formulating a pharmaceutical product usually involves combining the active ingredient with one or more inactive ingredients to provide a dosage form that can be administered in a safe, effective and convenient manner. Inactive ingredients used in pharmaceutical formulations are often called "excipients."[459] The following diagram illustrates the basic concepts of drug formulation for an orally administered solid dosage form, such as a tablet:

458. Leslie Z. Benet & Lewis B. Sheiner, *Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination, in* THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 3–13 (Alfred Goodman Gilman et al. eds., 7th ed. 1985).

459. "[E]xcipients are inactive ingredients that are routinely and purposefully added to the active ingredient to enhance the performance of the active ingredient." Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1347 (Fed. Cir. 2004).

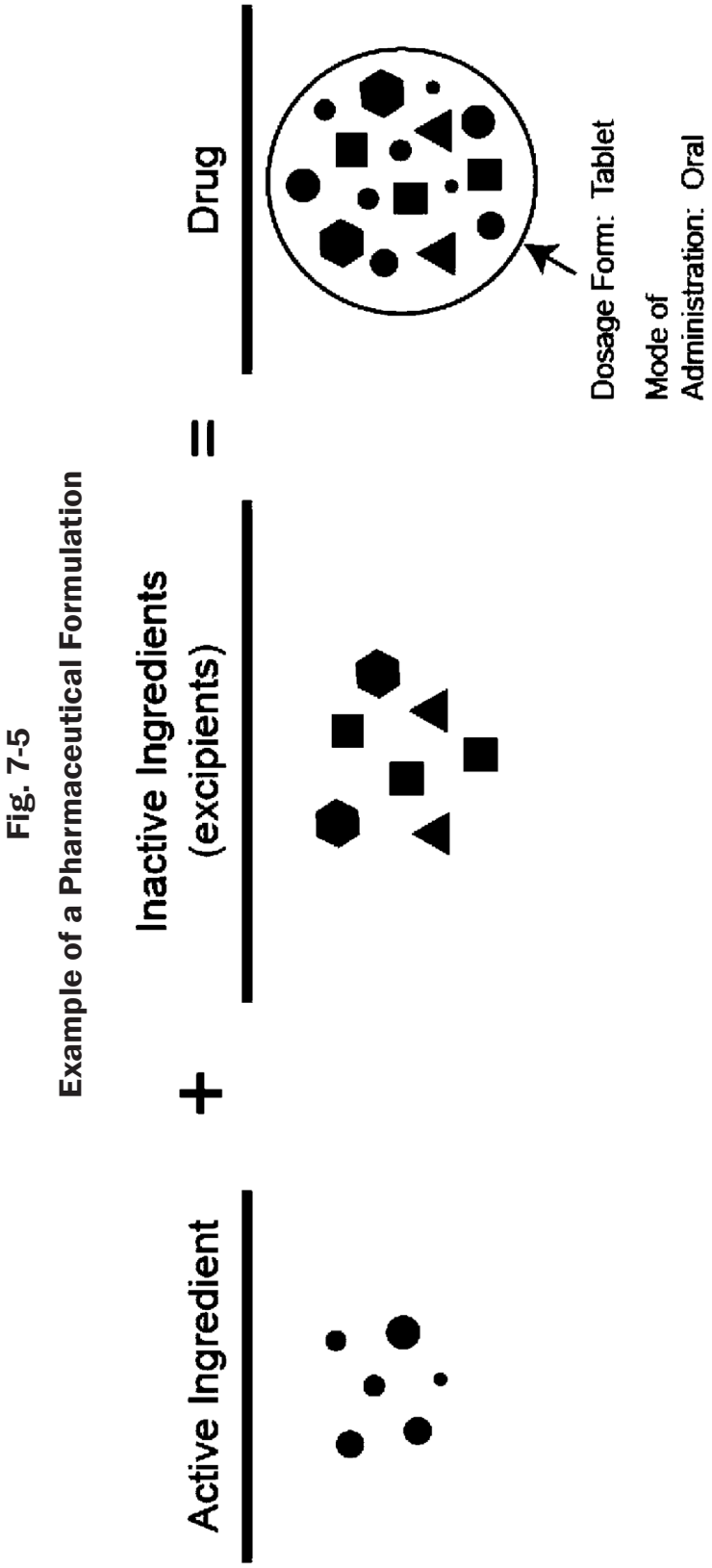


Fig. 7-5
Example of a Pharmaceutical Formulation

Excipients generally perform one or more functions in a dosage form for a pharmaceutical product. The following table provides examples of types of excipients and functions commonly associated with them. Particular formulations, however, may use any given excipient for a different purpose depending on the amount used and the other ingredients in the formulation.[460]

Table 7-1

Examples of Excipient Types Used in a Solid Dosage Form

EXCIPIENT TYPE	TYPICAL FUNCTION
diluents or fillers	provide bulk
disintegrants	facilitate the breakdown of a tablet or capsule after administration
binding agents	form aggregates of the active ingredient and excipients during manufacturing process to facilitate uniform distribution of active ingredient and provide other properties
glidants	improve flow of powder materials through the manufacturing equipment
lubricants	reduce adhesion of material to the tablet press

The choice of which excipients to use and what amounts often depends on the manufacturing process used to make the dosage form.

Most solid dosage forms are made by using either a direct compression process or some form of granulation. The following figure illustrates the tablet compression process by which powder containing the drug and other excipients is compressed on a tableting die into tablets.

460. For background on the use of excipients in pharmaceutical manufacturing, see Edward M. Rudnic & Joseph D. Schwartz, *Oral Dosage Forms, in* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 858, 860–63 (Alfonso R. Gennaro et al. eds., University of the Sciences in Philadelphia 20th ed. 2000) [hereinafter REMINGTON]. A bibliography of texts in pharmaceutical science is provided in *infra* section 7:3.5.

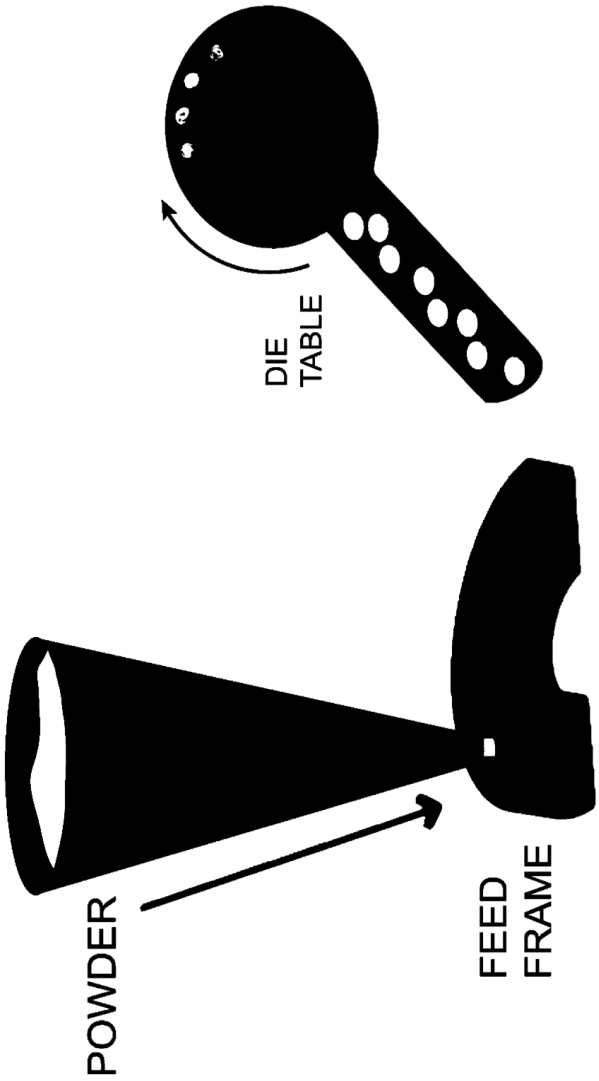
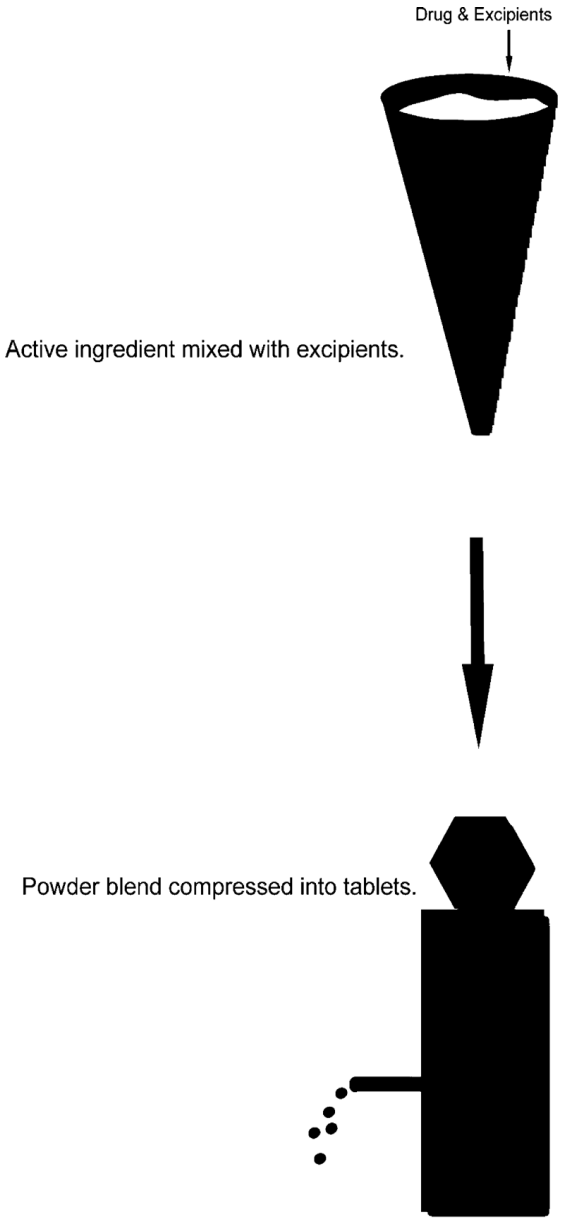


Fig. 7-6
Tablet Compression Process

Each process has certain advantages and disadvantages. The choice of which process to use depends on the ingredients and the requirements imposed on the final product. Direct compression involves simply blending the active ingredient with excipients and directly compressing the materials into tablets.

Fig. 7-7

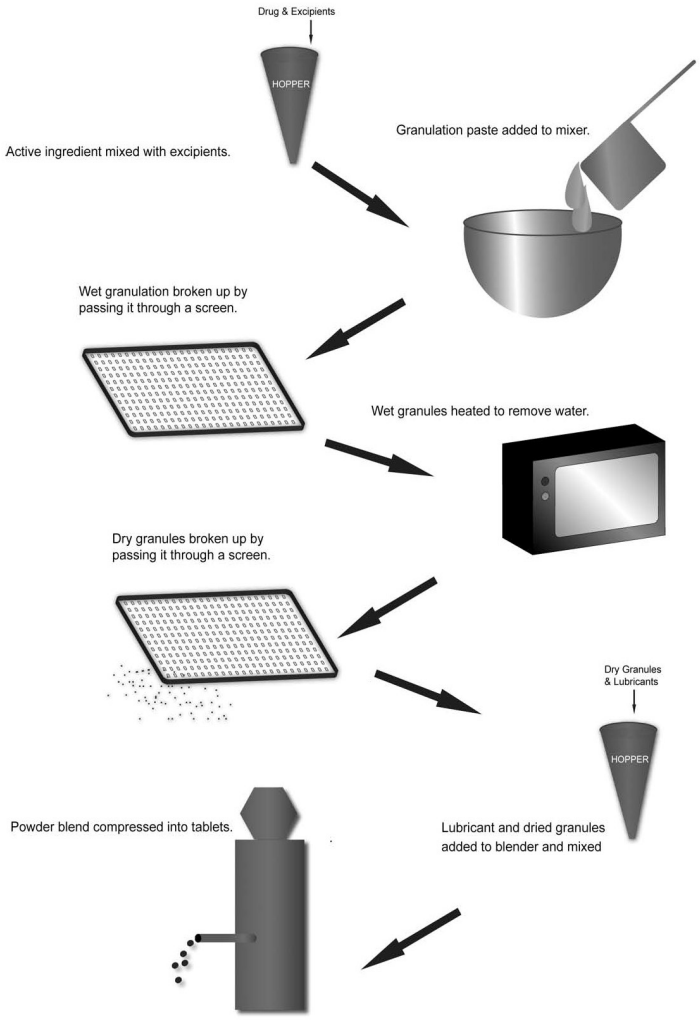
Direct Compression Process



Granulation involves granulating the active ingredient with the excipients to improve material flow and processing. In general, granulations can be either "wet" or "dry." Wet granulation generally uses a solvent and a binding agent to make aggregates of the individual ingredients, followed by drying and milling the aggregates into granules.

Fig. 7-8

Wet Granulation Process



Dry granulation generally involves a process called "roller compaction" or "slugging" in which the dry ingredients are compressed and then milled into granules.[461] Issues also arise in the development of

461. For background on tablet manufacture, see REMINGTON, *supra* note 460, at 865–71.

injectable and intravenous dosage forms, liquid formulations for oral administration, topical formulations, etc., in which the active ingredient is also generally combined with other inactive ingredients to make the product suitable for administration.

The choice of excipients is also influenced by whether the goal is to have an immediate release of the active ingredient, or a sustained or delayed release of the active ingredient. For example, certain excipients can be used to control the release of the active ingredient after administration to the patient. Many other factors come into play, including the chemical and physical compatibility of the active ingredient with the excipients under consideration. The choice of excipients may also influence the stability and shelf life of the dosage form, including, for example, preservatives to prevent breakdown of the active ingredient and additives to prevent contamination.

Given these many considerations, pharmaceutical formulations are often the subject of patents that may provide protection in addition to any protection afforded by patents directed to the active ingredient itself. Formulation patents may be listed in the FDA's "Orange Book" and are frequently the subject of litigation involving generic drug companies' efforts to make a generic version of a branded drug product.[462]

The following discussion provides some illustrations of the kinds of issues raised by patents directed to pharmaceutical formulations.

§ 7:3.2 *Claim Construction Issues*

Claim construction often determines the outcome of patent infringement litigation. Although the general principles of claim construction discussed in this book[463] apply to formulation claims, a review of some cases involving pharmaceutical formulations will be helpful.

[A] "Solubilizer" Limited to Surfactants

The Federal Circuit's decision in *AstraZeneca AB v. Mutual Pharmaceutical Co.*[464] involved a claim to an extended release formulation for compounds having low water solubility that recited a "solubilizer" as an ingredient. Although the parties had agreed that "artisans would understand the term 'solubilizer' to embrace" the "co-solvent" solubilizer used in the defendant's formulation,[465] the Federal Circuit concluded that "solubilizer" should be construed as limited to

462. *See infra* section 7:3.3.
463. *See infra* chapter 9 (Claim Construction).
464. AstraZeneca AB v. Mut. Pharm. Co., 384 F.3d 1333 (Fed. Cir. 2004).
465. *Id*. at 1336.

"surfactants," resulting in a finding of non-infringement. The Federal Circuit concluded that the patent's specification "disavow[ed] non-surfactant solubilizers" and that the prosecution history contained remarks showing that applicants considered the term "solubilizers" to embrace only surfactants.[466] The construction of the claim as limited to solubilizers that were surfactants resulted in a determination of non-infringement with respect to the defendant's formulation that used a non-surfactant solubilizer.

[B] "Lipophilic Component" Construed to Include More Than Surfactants

Novartis Pharmaceuticals Corp. v. Abbott Laboratories[467] involved a claim to a formulation of the drug cyclosporin, a highly hydrophobic compound that was difficult to administer to patients. At issue was whether the use in the accused product of the surfactant Span 80 satisfied the claim limitation of a "lipophilic component." The Federal Circuit concluded that while "surfactants may form a part of the lipophilic component, the intrinsic record shows that this component cannot be composed entirely of surfactants."[468] In particular, the specification taught that if a surfactant was part of the lipophilic phase, a "co-solvent" is used. Therefore, the court concluded, that the use of a surfactant alone, as in defendant's product, did not meet the claim limitation of a "lipophilic component." Based on this claim construction, the Federal Circuit affirmed a grant of a judgment as a matter of law of non-infringement.

[C] Claim Not Limited to Particular Grade of an Excipient

In another case, the Federal Circuit in *Glaxo Wellcome Inc. v. Andrx Pharmaceuticals, Inc.*[469] reversed a district court's grant of summary judgment of non-infringement of a patent directed to a sustained release formulation of the drug bupropion hydrochloride. The claims had been limited during prosecution to the use of hydroxypropyl methylcellulose (HPMC) as the sustained release material, but the court rejected the defendant's argument that the claims should be limited to the particular grade of HPMC used in the patent's examples. Thus, the fact that the accused product used a different grade of

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466. *Id*. at 1340–42.
467. Novartis Pharm. Corp. v. Abbott Labs., 375 F.3d 1328 (Fed. Cir. 2004).
468. *Id*. at 1336.
469. Glaxo Wellcome, Inc. v. Andrx Pharm., Inc., 344 F.3d 1226 (Fed. Cir. 2003).

HPMC than that used in the patent's examples did not alone avoid infringement.[470]

[D] Purity Limitations

Purity limitations in composition claims may also raise issues on claim construction. For example, in *Glaxo Group Ltd. v. Apotex, Inc.*,[471] the patents in suit claimed amorphous cefuroxime axetil having a "purity of at least 95%." The defendant argued that the term "purity" should be construed to take into consideration "any other compounds" added to the amorphous cefuroxime axetil, including excipients.[472] The court rejected this position, noting that the

> patent . . . uses the term impurities in a manner similar to its ordinary usage, where impurity is considered as an unwanted reaction product formed during synthesis. . . . In contrast, excipients are inactive ingredients that are routinely and purposefully added to the active ingredient to enhance the performance of the active ingredient. . . . To one of ordinary skill in the art, excipients are almost universally used with the active ingredient, and therefore do not act to affect the purity of the drug.[473]

Accordingly, the addition of excipients was not taken into consideration in determining the purity of defendant's amorphous cefuroxime axetil products, which were found to infringe because they contained less than 2% by weight impurities.[474]

[E] "Hydrosol" Limited to "Medicinal Preparation"

The Federal Circuit, in *Novartis Pharmaceuticals Corp. v. Eon Labs Manufacturing, Inc.*,[475] construed a claim covering a "hydrosol which comprises solid particles of cyclosporin" as limited to a "medicinal preparation prepared outside the body."[476] The claim therefore did not cover the conversion of an ingested drug product into the claimed form.[477] Novartis contended that, although Eon's capsule formulation of cyclosporin was not a hydrosol, an infringing hydrosol is formed

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470. *Id*. at 1233.
471. Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339 (Fed. Cir. 2004).
472. *Id*. at 1346–47.
473. *Id*. at 1347.
474. *Id*.
475. Novartis Pharm. Corp. v. Eon Labs. Mfg., Inc., 363 F.3d 1306, 1312 (Fed. Cir. 2004).
476. *Id*. at 1312.
477. *Id*. See *supra* section 7:2.7 for a discussion of *in vivo* conversion.

after the capsule is ingested. The court, however, concluded that the term "hydrosol" is "limited to a medicinal preparation consisting of a dispersion of solid particles in a liquid colloidal solution prepared outside the body."[478]

The court based its claim construction on the lack of disclosure in the specification of making a hydrosol in a patient's body, the repeated description of the invention as a "pharmaceutical composition," and the distinction of prior art during prosecution by the argument that the invention can be administered by "intravenous injection."[479] Based on this claim construction, the court held that Eon's capsule did not literally infringe. Moreover, the court held that there could be no infringement under the doctrine of equivalents by conversion in the body because such a finding would "vitiate the claimed requirement that the dispersion be prepared outside the body."[480]

[F] "Saccharides" Includes "Polysaccharides"

In *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*,[481] the patents-in-suit claimed a formulation of an ACE inhibitor (a compound used to treat hypertension) that would prevent degradation of the active ingredient due to cyclization, hydrolysis, and oxidation. The claim recited a formulation using an alkali or alkaline earth metal carbonate to inhibit cyclization and discoloration and a "saccharide" to inhibit hydrolysis.[482] In a prior litigation involving the same patents asserted against Teva's ANDA for a formulation of the ACE inhibitor quinapril, the parties had stipulated that "saccharide" should be construed to mean "a sugar, and specifically includes only lower molecular weight carbohydrates, specifically, mono- and disaccharides and their simple derivatives, including such substances as lactose, sucrose, mannitol and sorbitol."[483]

Subsequently, Ranbaxy filed an ANDA for its own quinapril formulation. Ranbaxy reached an agreement with Teva by which Teva relinquished to Ranbaxy its potential 180-day generic market

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478. *Id*. at 1311.
479. *Id*. at 1310–11.
480. *Id*. at 1312.
481. Pfizer, Inc. v. Teva Pharm. USA, Inc., 429 F.3d 1364 (Fed. Cir. 2005).
482. *Id*. at 1369.
483. *Id*. at 1370–71. This earlier case is reported at Warner-Lambert Co. v. Teva Pharm. USA, Inc., 418 F.3d 1326 (Fed. Cir. 2005). In this prior case, the Federal Circuit had reversed and remanded a grant of summary judgment in favor of the patentee on the issues of enablement and infringement.

exclusivity period, resulting in final FDA approval of Ranbaxy's product, which Teva began selling.[484] Warner Lambert and its corporate parent Pfizer then sued Teva and Ranbaxy and sought a preliminary injunction, which was granted by the district court.

On appeal of the grant of the preliminary injunction, Ranbaxy argued that the construction of "saccharide" agreed to by the parties in the previous case should apply and that under this construction, its formulation, which used microcrystalline cellulose, a polysaccharide, did not infringe. The Federal Circuit rejected this argument, holding that issue preclusion did not apply because the stipulation on claim construction in the prior case was "for the purposes of that litigation only."[485] Construing the term "saccharide" in light of the specification, the Federal Circuit agreed with the district court that the term included "polysaccharides" and that because microcrystalline cellulose is a polysaccharide, plaintiffs had made the requisite showing of likelihood of success on its claim that the Ranbaxy formulation infringed.[486] The grant of the preliminary injunction was affirmed.[487]

§ 7:3.3 Literal Infringement and Infringement Under the Doctrine of Equivalents

Patents claiming pharmaceutical formulations can present "design around" opportunities for competitors, particularly for patents that claim formulations by reciting specific ingredients and/or quantities of ingredients for the formulation. For example, a patent that claims a tablet formulation by reciting a specific disintegrant may invite a competitor to use a different disintegrant to avoid literal infringement. While the substitution of another disintegrant for the specific disintegrant recited in the claim may avoid literal infringement, it raises the issue of infringement under the doctrine of equivalents.[488]

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484. *Teva Pharm.*, 429 F.3d at 1371. Warner-Lambert, the NDA holder did not sue Ranbaxy within the statutory forty-five-day period that would have triggered a thirty-month stay of FDA approval. *Id.*
485. *Id.* at 1376.
486. *Id.* at 1373–76.
487. The Federal Circuit, noting that a claim construction on a preliminary injunction motion may be revisited, proceeded to analyze infringement under the doctrine of equivalents under an alternative claim construction. The court agreed with the district court that plaintiffs had also shown a likelihood of success under the doctrine of equivalents. *Id.* at 1377–80. *See also infra* section 7:3.3.
488. Literal infringement and infringement under the doctrine of equivalents are discussed in chapter 10.

If literal infringement of a formulation claim is avoided, a determination of infringement under the doctrine of equivalents will generally involve inquiry into the substantiality of the differences between the claimed element and the corresponding feature of the accused product[489] and whether recourse to the doctrine of equivalents is barred by prosecution history[490] or another doctrine.[491] When determining what function a claimed excipient performs in a formulation, a court will not only consider the intrinsic record but also "what the claim element's function in the claimed composition is to one of skill in the art" which can be based on extrinsic evidence.[491.1] A review of some cases will help show how the doctrine of equivalents has been addressed in pharmaceutical formulation patent cases.

[A] Using Different Excipients

[A][1] Non-Equivalence

Infringement litigation over ANDAs filed for Upjohn's patented formulation for the anti-diabetic drug glyburide illustrates both the inquiry into the substantiality of the differences between the excipients in a claimed and an accused formulation and the use of prosecution history to preclude infringement under the doctrine of equivalents. In *Upjohn Co. v. MOVA Pharmaceutical Corp.*,[492] the Federal Circuit affirmed a jury verdict of non-infringement of a patent claiming a formulation of micronized glyburide that recited the specific excipient "spray-dried lactose" in an amount "at about not less than seventy percent (70%) by weight of the final composition."[493] At issue was whether the accused generic formulation in the defendant's ANDA, which did not literally infringe because it included only 49% by weight of spray-dried lactose, infringed under the doctrine of equivalents because it also included 46.3% to 49.1% of another excipient,

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489. *See* Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 39–40 (1997).
490. *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 733–35 (2002).
491. For example, under the Federal Circuit's decision in Johnson & Johnston Assocs. v. R.E. Serv. Co., 285 F.3d 1046, 1054 (Fed. Cir. 2002) (citing Maxwell v. J. Baker, Inc., 86 F.3d 1098, 1107 (Fed. Cir. 1996)), equivalents that are disclosed in a patent's specification but not claimed may be deemed "dedicated" to the public, precluding infringement under the doctrine of equivalents. See *infra* chapter 10 for further discussion on this topic.
491.1. Intendis Gmbh v. Glenmark Pharm. Inc., 822 F.3d 1355 (Fed. Cir. 2016).
492. Pfizer, Inc. v. Teva Pharm. USA, Inc., 225 F.3d 1306 (Fed. Cir. 2000).
493. *Id*. at 1308.

Starch 1500 (pregelatinized corn starch).[494] The Federal Circuit observed that "Upjohn presented a valid criticism that MOVA's evidence related to 100% Starch 1500 and not to the actual formulation in the ANDA."[495] Nevertheless, it concluded substantial evidence supported the jury's verdict of non-infringement based on the testimony of defendant's expert that Starch 1500 released the active ingredient by disintegration whereas spray-dried lactose released the active ingredient by dissolution.[496] "[T]he jury could reasonably have found that the ANDA formulation delivered the drug differently from a 70% spray-dried lactose formulation."[497] Accordingly, technical inquiry into the differences between the two excipients was determinative of infringement under the doctrine of equivalents.

[A][2] Equivalence

In *Intendis Gmbh v. Glenmark Pharmaceuticals Inc.*, the Federal Circuit affirmed the district court's determination that the excipient in the accused formulation, isopropyl myristate, "performed substantially the same function as the claimed triglyceride and lecithin."[497.1] The court relied on expert testimony and the statements in the ANDA that isopropyl myristate and the claimed excipients both "function as penetration enhancers."[497.2] The Federal Circuit rejected the argument that the patent's "lack of disclosure of the claimed excipients as penetration enhancers" is fatal to the infringement case.[497.3]

[A][3] Prosecution History Estoppel

By comparison, a case involving the assertion of the same patent against another generic drug company's ANDA turned on prosecution history estoppel, which precluded infringement under the doctrine of equivalents, thereby obviating the need for any inquiry into the substantiality of differences between the claims and the accused product. In *Pharmacia & Upjohn Co. v. Mylan Pharmaceuticals, Inc.*,[498] the Federal Circuit affirmed summary judgment of non-infringement of a generic drug company's formulation of micronized glyburide that substituted the excipient anhydrous lactose for the recited spray-dried

494. *Id.*
495. *Id.* at 1309.
496. *Id.* at 1309–10.
497. *Id.* at 1309.
497.1. *Glenmark*, 822 F.3d at 1361.
497.2. *Id.*
497.3. *Id.* at 1362.
498. Pharmacia & Upjohn Co. v. Mylan Pharm., Inc., 170 F.3d 1373 (Fed. Cir. 1999).

lactose. The court concluded that statements made during prosecution barred assertion under the doctrine of equivalents, including statements that the use of spray-dried lactose was a "critical feature" of the claimed invention.[499]

[B] Controlled Release Formulations: Foreseeability of Substitution

[B][1] Prosecution History Estoppel Bars Equivalence

Another illustrative case is the Federal Circuit's decision in *Glaxo Wellcome, Inc. v. Impax Laboratories, Inc.*,[500] in which the court affirmed a grant of summary judgment of non-infringement of a patent claiming a sustained release formulation for the drug bupropion.[501] The application for patent was filed with original claims that recited tablets which resulted in particular plasma concentration levels of bupropion over twenty-four hours and specific bupropion release rates, but which did not recite a particular release mechanism.[502] The patent examiner rejected the claims for lack of enablement under 35 U.S.C. § 112 because the specification only disclosed the use of hydroxypropyl methylcellulose (HPMC) to achieve a sustained release of the drug and that disclosure "could not support a broad generic claim to other sustained release mechanisms."[503] The claims were allowed after they were amended to specifically recite HPMC as the sustained release mechanism. Relying on the Supreme Court's *Festo* decision,[504] the Federal Circuit held that this narrowing amendment created a presumption that the patentee had surrendered the range of equivalence between the original and the amended claims to preclude reliance on the doctrine of equivalents to cover defendant's formulation that used as a sustained release mechanism hydroxypropyl cellulose (HPC), which was known at the time of the amendment to be equivalent to HPMC.[505]

As originally filed, the claims "embraced all controlled sustained release tablets comprising bupropion hydrochloride. The application

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499. *Id*. at 1378.
500. Glaxo Wellcome, Inc. v. Impax Labs., Inc., 356 F.3d 1348 (Fed. Cir. 2004).
501. This case involved the same patent as Glaxo Wellcome, Inc. v. Andrx Pharm., Inc., 344 F.3d 1226 (Fed. Cir. 2003), discussed above.
502. *Impax Labs.*, 356 F.3d at 1352.
503. *Id*.
504. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002).
505. SmithKline Beecham Corp. v. Excel Pharm., Inc., 356 F.3d 1357, 1361–62 (Fed. Cir. 2004).

did not enable any sustained release agents other than HPMC, however, because it only disclosed HPMC's time release and plasma profiles."[506] Thus, the narrowing amendment of the claims to recite HPMC operated to "surrender[ ] other controlled sustained release agents known to act as equivalents of HPMC."[507] Moreover, the Federal Circuit concluded that the presumption under *Festo* that the claim amendment surrendered equivalents to cover HPC was not rebutted because the evidence showed that one skilled in the art at the time of the amendment would have found it foreseeable to use HPC as a suitable sustained release agent for bupropion.[508]

[B][2] No Prosecution History Estoppel

In contrast, in another case involving the same patent asserted against a different generic drug company's sustained release formulation of bupropion, *SmithKline Beecham Corp. v. Excel Pharmaceuticals, Inc.*,[509] the Federal Circuit reversed a grant of summary judgment of non-infringement where the excipient polyvinyl alcohol (PVA) was substituted for the claimed HPMC ingredient. Although the court concluded that the claim had been narrowed for reasons of patentability, it remanded for a determination as to whether the use of PVA in lieu of the claimed HPMC would have been foreseeable in the sustained release formulation, noting that unforeseeability of the substitution can be used to rebut the presumption precluding recourse to the doctrine of equivalents.[510] In particular, the court stated that if the use of PVA were determined to be a "later-developed technology" (that is, a "technology that was not known in the relevant art"), then "it would not have been foreseeable."[511] The court stated that "the quintessential example of an enforceable equivalent, after-arising technology, would always be unclaimable new matter. In that sense, the doctrine of equivalents compensates for the patentee's inability to claim unforeseeable new matter."[512]

Thus, the different outcomes in *Glaxo Wellcome, Inc. v. Impax Laboratories* and *SmithKline Beecham Corp. v. Excel Pharmaceuticals, Inc.* turned on whether the excipient used in the generic drug company's formulation in place of the claimed HPMC ingredient would

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506. *Id*. at 1362.
507. *Id*.
508. *Id*. at 1364–65.
509. SmithKline Beecham Corp. v. Excel Pharm., Inc., 356 F.3d 1357 (Fed. Cir. 2004).
510. *Id*. at 1363–65.
511. *Id*. at 1363 (citing Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. (*Festo IX*), 344 F.3d 1359, 1369 (Fed. Cir. 2003)).
512. *SmithKline*, 356 F.3d at 1364.

have been "foreseeable." While the Federal Circuit found sufficient evidence supported the foreseeability of HPC in *Glaxo Wellcome*, in *SmithKline Beecham* it remanded for a determination of the foreseeability of the use of PVA. These cases illustrate the importance the selection of excipients for a pharmaceutical formulation can have in the determination of infringement.

[C] Controlled Release Formulations: Prosecution History Estoppel

Another example of a prosecution history estoppel precluding the use of the doctrine of equivalents for a patent claiming a pharmaceutical formulation is *Merck & Co. v. Mylan Pharmaceuticals, Inc.*,[513] which involved a patent claiming a controlled release formulation of the drugs levodopa and carbidopa, used to treat Parkinson's disease. The claim recited a formulation of levodopa and carbidopa in a combination of the "water-soluble" polymer HPC and the "less water-soluble" polymer polyvinyl acetate-crotonic acid (PVACA). The Federal Circuit affirmed a grant of summary judgment that the defendant's formulation of the same two drugs using the polymer combination of HPC and HPMC did not infringe based on prosecution history estoppel.

As originally filed, the claims recited a general formulation of the two drugs with a combination of "a water soluble polymer" and "a less water soluble polymer."[514] The claims were rejected over prior art describing controlled release formulations of levodopa and carbidopa in a mixture of polymers, including HPC and HPMC, the combination used by the defendant in the case. Subsequently, a continuation-in-part (CIP) application was filed that claimed the polymer combination in Markush format, listing a number of polymers within the "water soluble" category, which included HPC and HPMC, among others, and a number of different polymers within the "less water soluble" category, which included PVACA. Subsequently, a second CIP application was filed with claims narrowed to the specific polymer combination of HPC and PVACA.[515] Finally, a divisional application was filed that retained the broader Markush claims. During prosecution of this divisional application, the examiner issued a restriction requirement that a single species be elected for prosecution and issued a rejection over the same prior art references asserted in the prior application that described the use of the combination of HPC and HPMC. The patent applicant elected to prosecute the combination of

513. Merck & Co. v. Mylan Pharm., Inc., 190 F.3d 1335 (Fed. Cir. 1999).
514. *Id*. at 1338.
515. *Id*. at 1338–40.

HPC and PVACA and distinguished the prior art because it did not describe this combination.[516]

Based on this prosecution history, the Federal Circuit concluded that the patentee was estopped from asserting infringement of the HPC/HPMC polymer combination under the doctrine of equivalents: "Since the examiner rejected the Markush claims in light of references that described a HPC/HPMC polymer vehicle, when Merck limited its claims to HPC/PVACA combination it became estopped as to that vehicle in the dropped claims."[517] In reaching this decision, the court found that the narrowing of the claims was for purposes of patentability, and rejected Merck's argument that estoppel should not apply because it amended the claims to comply with the examiner's restriction requirement.[518]

[D] Infringement by Equivalents: No Dedication of Equivalent Excipient

Recourse to the doctrine of equivalents may be foreclosed if it is determined that the equivalent in question was disclosed but not claimed in a patent and therefore was "dedicated" to the public.[519] This issue may arise in formulation patent cases where the specification includes a general discussion of excipients, including an excipient that is used in the accused formulation, but which is not claimed in the patent. Whether the use of the particular excipient was dedicated to the public may turn on whether it was identified by the patentee as an alternative to a claim limitation.

The "dedication" doctrine was raised by the defendant, but rejected by the Federal Circuit in *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*[520] In that case, the claim, directed to a formulation of an ACE inhibitor that is susceptible to cyclization, hydrolysis, and discoloration, recited as an ingredient "a suitable amount of a saccharide to inhibit hydrolysis."[521] At issue was whether defendant's use of the excipient microcrystalline cellulose in its ANDA formulation satisfied this limitation.

While the Federal Circuit affirmed the district court's grant of a preliminary injunction to Pfizer based on its conclusion that microcrystalline cellulose literally satisfied this limitation under the claim

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516. *Id*. at 1339–40.
517. *Id*. at 1341–42.
518. *Id*. at 1340–41.
519. Johnson & Johnston Assocs. v. R.E. Serv. Co., 285 F.3d 1046, 1054 (Fed. Cir. 2002).
520. Pfizer, Inc. v. Teva Pharm. USA, Inc., 429 F.3d 1364, 1379 (Fed. Cir. 2005).
521. *Id*. at 1369.

construction it had performed at the preliminary injunction stage of the case, it also analyzed whether there was a likelihood of success as to infringement under the doctrine of equivalents if an alternative claim construction was applied that excluded microcrystalline cellulose from the literal scope of the claim.[522] The defendants asserted that reference to microcrystalline cellulose in the specification along with the failure of the patent to claim that ingredient triggered the dedication doctrine precluding infringement by equivalence. The Federal Circuit rejected this argument, concluding that the specification's reference to "modified cellulose derivatives," which would include microcrystalline cellulose as an example of a disintegrating agent and the use of microcrystalline cellulose in an example of an unsuccessful prior art formulation outside the scope of the claims were not disclosures of "subject matter . . . specifically identified as being an alternative to a claim limitation."[523] The Federal Circuit stated that "the public notice function of patents suggests that before unclaimed subject matter is deemed to have been dedicated to the public, that unclaimed subject matter must have been identified by the patentee as an alternative to a claim limitation."[524]

§ 7:3.4 Patent Validity

[A] Obviousness

[A][1] Combinations of Excipients

Patents claiming pharmaceutical formulations often recite combinations of known excipients having known functions. These patents may be subjected to attack based on the argument that the substitution of excipients needed to achieve the claimed formulation would have been obvious to one of ordinary skill in the art.

The Federal Circuit, in *Abbott Laboratories v. Andrx Pharmaceuticals, Inc.*,[525] vacated a grant of a preliminary injunction because it concluded that the defendant had raised substantial questions as to the validity of Abbott's patents directed to an extended release formulation of the antibiotic clarithromycin.

One aspect of the case is illustrative. Abbott's '718 patent included claims to "a pharmaceutical composition for extended release of an erythromycin derivative" and a "pharmaceutically acceptable polymer" that achieved certain pharmacokinetic parameters. The term

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522. *Id*. at 1378.
523. *Id*. at 1379.
524. *Id*.
525. Abbott Labs. v. Andrx Pharm., Inc., 452 F.3d 1331 (Fed. Cir. 2006).

"erythromycin derivative" was construed to include clarithromycin, but to exclude a related macrolide antibiotic, azithromycin, sold by Pfizer as the drug Zithromax®.[526] The term "pharmaceutically acceptable polymer" was construed to cover a group of water-soluble hydrophilic polymers selected from a group of polymers set forth in the specification, including HPMC.[527]

The Federal Circuit found that substantial questions as to the validity of the formulation claims were raised by two prior art references. One prior art reference, a Patent Cooperation Treaty (PCT) published application by Pfizer (the '422 publication), described controlled-release formulations of azithromycin (as noted above, a macrolide antibiotic outside the scope of the '718 patent) with HPMC (the preferred polymer of the '718 patent). A second prior art reference, a patent owned by Abbott (the '190 patent), described a controlled release pharmaceutical formulation of clarithromycin (a macrolide antibiotic within the scope of the '718 patent) combined with a water soluble alginate salt (an ingredient outside the scope of the polymers like HPMC covered by the claims of the '718 patent).[528] Based on the disclosures of these prior art references, the Federal Circuit concluded that "there exists a substantial argument that a person of ordinary skill in the art would be motivated to combine the '422 publication, namely the use of HPMC in extended release macrolide compositions, with the '190 patent with a reasonable expectation of success."[529]

The Federal Circuit found the evidence for the motivation to combine set forth in Abbott's own prior art '190 patent, notwithstanding Abbott's arguments that "the compounds azithromycin and clarithromycin are so different that the '422 publication would not reasonably motivate a person of skill in the art to interchange the components of the formulations in the '422 publication with those of the '190 patent with a reasonable expectation of success."[530] In particular, the court noted that "[n]ot only does the '190 patent claim compositions with clarithromycin, but claim 14 of the '190 patent claims '[t]he composition of claim 4, wherein the macrolide is selected from the group consisting of erythromycin, dirithromycin, *azithromycin*, roxithromycin, and ABT-229.'"[531] Thus, although the '190 patent only explicitly described controlled-release formulations of clarithromycin, the Federal Circuit concluded from Abbott's attempt to also

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526. *Id*. at 1337–39.
527. *Id*.
528. *Id*. at 1340.
529. *Id*. at 1341–42.
530. *Id*. at 1341.
531. *Id*. (emphasis added).

claim in that patent azithromycin controlled-release formulations that:

> Abbott ha[d] represented to the U.S. Patent and Trademark Office ('PTO') that the differences between clarithromycin and azithromycin were such that azithromycin could be substituted into a controlled release clarithromycin composition by a person of ordinary skill in the art without undue experimentation. . . . As a result, based on Abbott's own '190 patent, there exists a substantial argument that a person of ordinary skill in the art would be motivated to combine the '422 publication, namely the use of HPMC in extended release macrolide compositions, with the '190 patent with a reasonable expectation of success.[532]

In other words, Abbott's prior art '190 patent provided a sufficient suggestion that the formulation of a controlled-release composition of azithromycin would also work for clarithromycin such that one skilled in the art would have been motivated to use HPMC described in the azithromycin formulation of the '422 publication with clarithromycin.

[A][2] Combination Therapies

Pharmaceutical products may also involve the combination of two or more active ingredients. Patents directed to formulations combining two previously known active ingredients raise typical issues, including validity over the prior art.

[A][2][a] Obvious Combination

A patent claiming the combination of the analgesic ibuprofen and the decongestant pseudoephedrine was held obvious over prior art teaching the combination of other analgesics (aspirin or acetaminophen) and pseudoephedrine, the interchangeability of ibuprofen with either aspirin or acetaminophen, and the fact that doctors had prescribed administering ibuprofen with acetaminophen.[533] The court found that these prior art teachings, along with a motivation to make the combination, rendered obvious the claimed combination formulation.[534]

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532. *Id*. at 1341–42.
533. Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476 (Fed. Cir. 1997).
534. *Id*. at 1483–85; *see also* McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1369–70 (Fed. Cir. 2003) (affirming judgment of obviousness of claim to combination of the drugs loperamide and simethicone to treat respectively diarrhea and gas based on prior art teaching: (a) the concurrence of the two conditions, (b) the use of other anti-diarrheal agents together with simethicone, and (c) the use of loperamide to treat diarrhea

A patent in another case claiming the combination of two known diuretics in a ten to one ratio was found obvious over a prior art patent disclosing a genus of 1200 different combinations including the claimed combination.[535] The limitation of a ten to one ratio in the claim did not save it from obviousness because that proportion could be "[r]eached by means of routine procedures, and produc[ed] only predictable results."[536]

[A][2][b] Nonobvious Combination

The Federal Circuit reversed and remanded a district court's grant of summary judgment holding a claimed combination of hydrocodone (an opioid) and ibuprofen, which is a non-steroidal anti-inflammatory drug (NSAID) obvious over the prior art.[537] The district court had improperly refused to consider evidence of unexpected results using the combination of the two compounds because those results were discovered after the issuance of the patent. The patent's specification contained evidence that supported the "surprising" benefit from the combination.[538] The Federal Circuit also held that additional data developed by the patent owner that showed, for example, "the synergistic interaction of hydrocodone and ibuprofen when administered together for pain relief" and "enhanced muscle repair after exercise" from the combination therapy should have been considered by the district court:

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as providing recourse to the doctrine of equivalents motivation to make the claimed combination); Allergan, Inc. v. Sandoz Inc., 726 F.3d 1286 (Fed. Cir. 2013).

535. Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 805–06 (Fed. Cir. 1989).

536. *Id*. at 809.

537. Sanofi-Aventis Deutschland v. Glenmark Pharm. Inc., 748 F.3d 1350, 1361 (Fed. Cir. 2014) (affirming judgment based on jury verdict of nonobviousness because there was substantial evidence "that persons skilled in the art in 1986 would not have predicted the longer-lasting hypertension control demonstrated by the double-ring structures of quinapril and trandolapril in combination with calcium antagonists, because of the widespread belief that double-ring inhibitors would not fit the pocket structure of the ACE"); Pozen Inc. v. Par Pharm., Inc., 696 F.3d 1151 (Fed. Cir. 2012) (claims to combination therapy were not obvious over prior art reference that disclosed use of drug A "+" drug B, because one skilled in the art would have understood reference as describing sequential dosing, and reference did not disclose the relative efficacy of the combined therapy); Knoll Pharm. Co. v. Teva Pharm. USA, Inc., 367 F.3d 1381 (Fed. Cir. 2004).

538. *Id*. at 1384.

> Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application. It is not improper to obtain additional support consistent with the patented invention, to respond to litigation attacks on validity. There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work . . . to be introduced into evidence in response to litigation attack.[539]

As shown above, the validity of formulation patents directed to combination products having multiple active ingredients over the prior art will turn on traditional tests for patentability, including non-obviousness, discussed in this book.[540]

[A][3] Pharmacokinetic/Pharmacodynamic Limitations

The Federal Circuit reversed a district court's finding that a claim to a method of providing a "therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm" and dependent claims specifying cyclobenzaprine hydrochloride as the drug and specific pharmacokinetic[540.1] values was obvious over prior art teaching an immediate-release formulation of cyclobenzaprine hydrochloride.[540.2] The district court found that a skilled artisan could calculate the formulation needed to achieve the claimed pharmacokinetic values based on available data from the immediate-release formulation of cyclobenzaprine.[540.3] The Federal Circuit, however, held that without a known relationship between the pharmacokinetic and pharmacodynamic[540.4] values for any formulation of cyclobenzaprine, the skilled artisan had no way to know if a sustained-release formulation would achieve the required therapeutic efficacy.[540.5] The court rejected defendants' argument that it was obvious to try a bioequivalent formulation based on an assumption that an extended-release formulation of cyclobenzaprine would have the same effect on the body as an immediate-release formulation because their expert's testimony

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539. *Id*. at 1385.
540. *See supra* section 5:3.
540.1. "Pharmacokinetics is the study of what a person's body does to a drug after administration." *In re* Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063 (Fed. Cir. 2012).
540.2. *Id*. at 1066–67, 1073.
540.3. *Id*. at 1071.
540.4. Pharmacodynamics refers to what a drug "does to the body." *Id*. at 1070.
540.5. *Id*. at 1071–72.

failed to shed "light on why a skilled artisan would have chosen a bioequivalent PK profile in the absence of a known PK/PD relationship for cyclobenzaprine."[540.6] "[T]he absence of such testimony suggests that skilled artisans would not have encountered finite, small, or easily traversed options in developing a therapeutically effective, extended-release formulation."[540.7]

[B] Written Description

A claim requiring administration of a dosage form for an opioid that provides the patient a "maximum plasma concentration of the opioid [that is] more than twice the plasma level of the opioid twenty-four hours after administration of the drug" was held not to have adequate support in the specification to satisfy the written description requirement.[541] The specification only described the invention as possessing a "generally flat" or "substantially flat" morphine plasma concentration curve, therefore it failed to support limitation in claims that maximum plasma concentration was to be more than twice the plasma level of the opioid twenty-four hours after it was dispensed.[542] "[A] person skilled in the art would not necessarily interpret the term 'flat' to be limited to a concentration level ratio less than or equal to two."[543] The court noted that, "[a]lthough the examples provide the data from which one can piece together the C_{max}/C_{24} limitation, neither the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasizes the C_{max}/C_{24} ratio."[544]

Upon reviewing a "district court's determination that the asserted claims of [two formulation patents] are not invalid for lack of an inadequate written description," the Federal Circuit reversed because "the shared specification does not adequately describe the claimed effectiveness of uncoated PPI."[544.1] The asserted claims cover "uncoated PPI effective to raise the gastric pH to at least 3.5," but the patentee argued in support of its obviousness analysis "that ordinarily skilled artisans would not have expected uncoated PPIs to be effective," and the defendant argued that "nothing in the specification would teach a person of ordinary skill in the art otherwise."[544.2]

540.6. *Id*. at 1073.
540.7. *Id*.
541. Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1327 (Fed. Cir. 2000).
542. *Id*. at 1324–25.
543. *Id*. at 1325.
544. *Id*. at 1326.
544.1. Nuvo Pharm. v. Dr. Reddy's Labs., 923 F.3d 1368, 1384 (Fed. Cir. 2019).
544.2. *Id*. at 1377.

[C] Enablement

Enablement depends in part on the breadth of the claim.[544.3] A claim to a pharmaceutical formulation that defines some of the excipients in functional terms, such as any surfactant, and does not limit it to particular concentrations, may be very broad.[544.4] Broad claims increase the importance of examples using a variety of excipients.[544.5]

Arguing in the specification or during prosecution history that the invention is not obvious over the prior art because the art is unpredictable, or because the results are unexpected, can make it more difficult to achieve a favorable determination on enablement in subsequent litigation.[544.6]

§ 7:3.5 *Bibliography of Pharmaceutical Formulation Treatises and Texts*

The following is a non-exhaustive list of treatises and texts on pharmaceutical formulation science and technology that may assist in analyzing formulation patents:

Aulton, Michael E. ed., 2001. *Pharmaceutics: The Science of Dosage Form Design*. London: Churchill Livingston.

Banker, Gilbert S. and Christopher T. Rhodes eds., 2002. *Modern Pharmaceutics*. London: CRC Press.

544.3. *See supra* section 5:5.8[A][5]; ALZA Corp. v. Andrx Pharm., LLC, 603 F.3d 935, 943 (Fed. Cir. 2010) (finding patent not enabled where the claims required both osmotic and nonosmotic dosage forms and "the quantity of experimentation, lack of guidance in the specification, absence of working embodiments, and breadth of the claims demonstrate[d] that the . . . specification fail[ed] to enable a person of ordinary skill to make and use non-osmotic oral dosage forms").

544.4. Pharm. Res., Inc. v. Roxane Labs., Inc., 253 F. App'x 26, 30 (Fed. Cir. 2007) ("The claims allow the choice of *any* surfactant in *any* concentration . . . . We thus conclude that the district court properly determined that the claims at issue 'have an extraordinarily broad scope.'").

544.5. *Id*. ("Par's specification discloses only three working examples, utilizing only one new surfactant. Given the highly unpredictable nature of the invention and the extremely broad scope of the claims, these three working examples do not provide an enabling disclosure commensurate with the entire scope of the claims.").

544.6. *Id*. at 29 (arguing in the specification that the "surfactants . . . need to be selected carefully and be used within a critical range" and in prosecution that the skilled artisan "would not have any reasonable expectation of success in maintaining a stable flocculated suspension of megestrol acetate once a change in the type or amount of surfactant or wetting agent is made" supported summary judgment of nonenablement).

Gennaro, Alfonso R. ed., 2000. *Remington: The Science and Practice of Pharmacy* 858, 860–63. Philadelphia: University of the Sciences.

Lachman, Leon, Herbert A. Lieberman, and Joseph L. Kanig, 1986. *The Theory and Practice of Industrial Pharmacy*. Philadelphia: Lea & Febiger.

Lieberman, Herbert A., Leon Lachman, and Joseph B. Schwartz eds., 1989. *Pharmaceutical Dosage Forms: Tablets, Vol. 1*. Informa Healthcare.

Lieberman, Herbert A., Leon Lachman, and Joseph B. Schwartz eds., 1990. *Pharmaceutical Dosage Forms: Tablets, Vol. 2*. Informa Healthcare.

Rowe, Raymond C., Paul J. Sheskey, and Paul J. Weller eds., 2003. *Handbook of Pharmaceutical Excipients*. Washington, DC: APhA Publications.

Rowe, Raymond C., Paul J. Sheskey, and Sian C. Owen eds., 2005. *Handbook of Pharmaceutical Excipients*. Washington, DC: APhA Publications.

§ 7:4 Method of Treatment*

§ 7:4.1 What Is a Method of Treatment Claim?

A method of treatment claim is a type of process claim. Section 101 of the Patent Act permits inventors of "any new and useful process" to obtain a patent.[545] Method of treatment claims can be written in the following form: administering an effective amount of compound *X* to a patient to treat disease *Y*.[546] Some other possibilities are shown below:

- administering a specified amount of compound *X* to treat disease *Y*[547]

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* Written by Daniel L. Reisner and Seth Simpson.

545. 35 U.S.C. § 101.

546. Merck & Co. v. Teva Pharm. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003) ("A method of treatment of urolithiasis and inhibiting bone reabsorption which consists of administering to a patient in need thereof an effective amount of 4-amino-1-hydroxybutane-1,1-biphosphonic acid.").

547. Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1366 (Fed. Cir. 2005) ("A method for treating osteoporosis in human comprising orally administering about 70 mg of alendronate monosodium trihydrate, on an alendronic acid basis, as a unit dosage according to a continuous schedule having a dosing interval of once-weekly.").

- administering an effective amount of a compound selected from genus *X* to treat disease *Y*[548]
- administering an effective amount of any compound that is capable of performing a specified function in the body to treat disease *Y*[549]
- administering an effective amount of a combination of *X* and *Y* to treat disease *Z*[550]
- performing procedure *X* on a subject to treat disease *Y*.[551]

The following provides some illustrations of the kinds of issues raised by patents claiming methods of treatment.

§ 7:4.2 Patentability of Method of Treatment Claims

The inventor of a novel, unobvious compound useful for treating a disease is generally entitled to a patent on both the compound and its use.[552] If, however, the same entity obtains separate patents on the compounds and any use disclosed in the compound patent, there is a substantial risk of obviousness-type double patenting because a

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548. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1351 (Fed. Cir. 2003) ("A method for treating neurodegenerative diseases which comprises administering a therapeutically effective amount of a compound of formula [H_2N-CH_2-C(CH2)n-CH_2COOR_1] wherein R_1 is hydrogen or a lower alkyl and n is 4, 5, or 6 or a pharmaceutically acceptable salt thereof, in unit dosage form, to a mammal in need of said treatment.").

549. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 918 (Fed. Cir. 2004) ("A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment.").

550. Knoll Pharm. Co. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 1383 (Fed. Cir. 2004) ("A process for treating pain in a mammal which comprises administering to the mammal one part by weight of hydrocodone or a pharmaceutically acceptable acid addition salt thereof and about 20 to 80 parts by weight of ibuprofen or a pharmaceutically acceptable salt thereof.").

551. Manning v. Paradis, 296 F.3d 1098, 1099 (Fed. Cir. 2002) ("A method of treating a subject in cardiac arrest comprising: blocking the descending aorta of said subject; and then perfusing the aortic arch of said subject with an oxygen-carrying protective solution in an amount effective to deliver oxygen to the heart of said subject.").

552. *See, e.g.*, *In re* Pleuddemann, 910 F.2d 823, 825–26 (Fed. Cir. 1990) (discovery of "a new and useful compound . . . having a *particular use*" can be claimed as "the method or process *of using* the compounds for their intended purpose").

court will consider both the compound and the utility disclosed in the compound patent when evaluating potential obviousness-type double patenting of the use patent over the compound patent.[552.1] Discovering a new use for an old compound, however, can entitle the discoverer to a patent on the new use.[553] A method of using a new compound—even if structurally close to a prior art compound—can be patented if it has an unexpected property of being useful as a treatment.[554] On the other hand, merely discovering the scientific principle that explains why an old compound produces a known effect, such as the reason aspirin reduces inflammation, does not provide a basis for patenting a method of treatment.[555]

Method of treatment claims have been permitted even where the compound and a method of using it are both known if the claimed method is limited to a specific purpose not taught by the prior art. For example, the Court of Customs and Patent Appeals reversed a

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552.1. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1386 (Fed. Cir. 2003) ("The Fleming patent's claim describes a compound, and Fleming's written description discloses a single utility of that compound as administration to a human in amounts effective for inhibiting β-lactamase. The '720 patent claims nothing more than Fleming's disclosed utility as a method of using the Fleming compound. Thus, the claims of the Fleming and '720 patents are not patentably distinct."); Pfizer, Inc. v. Teva Pharm. USA, Inc., 518 F.3d 1353, 1363 (Fed. Cir. 2008) (holding that method of treatment claims invalid for obviousness-type double patenting over patent claiming compound and disclosing therapeutic utility claimed by the method patent).

553. *See, e.g.*, *In re* Hack, 245 F.2d 246, 248 (C.C.P.A. 1957) (discoverer of "a new use of a known . . . composition" can be protected by a use claim).

554. *See, e.g.*, *In re* May, 574 F.2d 1082, 1090–92 (C.C.P.A. 1978) (upholding claims that "recite the use of a novel compound" despite similarity to prior art compounds because of "an unexpected beneficial result").

555. EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1349 (Fed. Cir. 2001) ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.") (citation omitted); *see also infra* section 7:4.5[A] (further discussion of inherent anticipation of method of treatment claims); Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("Santarus is also incorrect that the claims reciting specific blood serum concentrations of PPI would have been nonobvious. The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. . . . To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.").

Patent Office rejection of a claim covering a method for stimulating growth in livestock by feeding them aspirin over prior art that disclosed testing the use of aspirin to see if it inhibited normal growth.[556] The court found the method claims nonobvious over the prior art because the art did not disclose taking aspirin for the purpose of promoting growth.[557]

Ordinary skill in the art for a method of treatment is not limited to the skills of a treating physician and can include the skills of a person who develops new drugs and treatments.[558]

Where the invention is predicated on the discovery of a correlation between dosing and an effect on a subject, a limitation that ties the correlation to the method of administering the treatment can overcome patent ineligible subject matter concerns.[558.1] On the other hand, the additional of instructions to the patient or doctor which do not affect the method of administration do not by themselves confer patentability over the prior art.[558.2]

§ 7:4.3 Conception

Conception of an invention for a method of treatment claim may be considered complete when the inventor has the idea of using a specific compound or class of compounds for a specific treatment. Lack of a reasonable basis for believing the method of treatment will be successful does not detract from the completeness of the conception, and testing to prove the utility of the method is not part of the conception of the method.[559]

§ 7:4.4 Claim Construction Issues

Claim construction often determines the outcome of patent infringement litigation. Although the general principles of claim

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556. *In re* Caldwell, 319 F.2d 254 (C.C.P.A. 1963).
557. *Id*. at 257.
558. Daiichi Sankyo Co. v. Apotex, Inc., 501 F.3d 1254 (Fed. Cir. 2007). See *supra* section 5:3.6[B] for a further discussion of skill in the art.
558.1. *See supra* section 3:8.1.
558.2. *See infra* section 7:4.5[C][3].
559. Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1231 (Fed. Cir. 1994) ("The question is not whether Burroughs Wellcome reasonably believed that the inventions would work for their intended purpose, the focus of the evidence offered by [the defendants], but whether the inventors had formed the idea of their use for that purpose in sufficiently final form that only the exercise of ordinary skill remained to reduce it to practice. Whether or not Burroughs Wellcome believed the inventions would in fact work based on the mouse screens is irrelevant.") (citation omitted).

construction are discussed elsewhere, a review of some cases involving treatment claims will be helpful.[560]

[A] Preambles

Method of treatment claims frequently have preambles.[561] In appropriate circumstances, courts will construe these preambles to be limiting.

[A][1] Preambles Can Be Limiting

The preamble of a claim consists of the introductory language that appears before the transition phrase, the latter often identified by the words "comprises" or "comprising."[562] In construing a method of treatment claim, courts must determine whether the preamble is merely a non-limiting statement of intended treatment or whether it was meant to limit the scope of the claim.[563]

"If the body of the claim sets out the complete invention, and the preamble is not necessary to give 'life, meaning and vitality' to the claim, 'then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.'"[564] A statement of intended use in a claim preamble is non-limiting if it "is only a statement of purpose and intended result" and "does not result in a manipulative difference in the steps of the claim."[565] In any event, the intended result stated in a method of treatment preamble will not be construed "as limited to those instances of practicing the claimed method that achieve the stated result for purposes of validity, but as encompassing all instances of carrying out the physical steps for purposes of infringement."[566]

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560. *See infra* chapter 9.

561. *See, e.g.*, Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1322 (Fed. Cir. 2005); Knoll Pharm. Co. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 1383 (Fed. Cir. 2004); Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1371 (Fed. Cir. 2001); *Burroughs Wellcome*, 40 F.3d at 1225 n.3.

562. *See* Rapoport v. Dement, 254 F.3d 1053, 1059 (Fed. Cir. 2001) ("First, we note that the disputed phrase 'treatment of sleep apneas' is technically part of the preamble of the interference count, because it appears before the transition word 'comprising.'").

563. See *infra* section 9:3.1 for further discussion of preambles.

564. *Bristol-Myers Squibb*, 246 F.3d at 1373–74 (quoting Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999)).

565. *Bristol-Myers Squibb*, 246 F.3d at 1375, 1376.

566. *Id.* at 1376 ("Moreover, Bristol would have us construe the claims as limited to those instances of practicing the claimed method that achieve the stated result for purposes of validity, but as encompassing all instances of carrying out the physical steps for purposes of infringement. Again, Bristol cannot have it both ways.").

[A][2] Construing Preambles in Method of Treatment Claims

Where the claim preamble sets out the purpose of the treatment and the body of the claim directs that the method be performed on someone "in need" of such treatment, courts may find the purpose stated in the preamble as a claim limitation.[567] When the purpose of treatment recited in a claim's preamble is a limitation, practicing the method of treatment for a different purpose is not practice of the claimed invention.[568] However, where the preamble merely expresses an intended purpose, such as "reducing hematologic toxicity" or "treating a cancer patient to effect regression of a taxol-sensitive tumor," at least one court has construed the preamble as non-limiting.[569]

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567. Jansen v. Rexall Sundown, Inc., 342 F.3d 1329, 1333 (Fed. Cir. 2003) ("[T]he claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' . . . [T]he claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed.") (citation omitted); *Rapoport*, 254 F.3d at 1059 (construing the preamble of a patent interference count, holding "without treating the [preamble] phrase 'treatment of sleep apneas' as a claim limitation, the phrase 'to a patient in need of such treatment' would not have a proper antecedent basis"); *see also In re* Caldwell, 319 F.2d 254, 257 (C.C.P.A. 1963) (finding the claim preamble language "stimulating growth of ruminants, poultry and swine" limiting, and explaining, "the *real* novelty is as defined in all of the appealed claims—stimulating the growth of ruminants, poultry, or swine *by feeding them aspirin* for that purpose . . . the 'real novelty' . . . reside[s] in . . . the feeding of aspirin for the stated purpose [in the claim preamble]").

568. *Jansen*, 342 F.3d at 1334 ("In other words, administering the claimed vitamins in the claimed doses for some purpose other than treating or preventing [the condition stated in the claim preamble] is not practicing the claimed method, because Jansen limited his claims to treatment or prevention of that particular condition in those who need such treatment or prevention.").

569. *Bristol-Myers Squibb*, 246 F.3d at 1375, 1376 (explaining that the preamble language, a method "'for reducing hematologic toxicity' . . . [is] non-limiting, and merely express[es] a purpose of reducing hematologic toxicity relative to the toxicity experienced by a patient undergoing a twenty-four-hour infusion. The steps of the three-hour infusion method are performed in the same way regardless whether or not the patient experiences a reduction in hematologic toxicity. . . . [T]he expression '[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity' . . . is only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claim.").

[A][3] Adding Method of Treatment Preamble Language by Amendment Can Render Preamble Limiting

"[C]laims are not construed in a vacuum, but rather in the context of the intrinsic evidence, *viz.*, the other claims, the specification, and the prosecution history."[570] Addition of language to a preamble in order to gain allowance of a method of treatment claim during prosecution was found by one court to weigh in favor of finding the preamble limiting.[571]

[B] Specific Claim Terms

[B][1] "Treat"

As explained above, the words "treatment" or "treating" used in the preamble of a method of treatment claim may be construed as claim limitations.

One court construed the word "treat" in a patent interference count as a limitation, requiring the claimed invention to administer an amount of a substance necessary to achieve a therapeutic effect on the subject, rather than simply providing any amount of the substance to the subject.[572]

When the plain language of a claim refers to treating a particular disorder, treatment may be construed as limited to the stated disorder and not to the treatment of symptoms associated with the disorder.[573]

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570. *Jansen*, 342 F.3d at 1333.

571. *Id.* at 1333–34 ("In this case, the 'treating or preventing macrocytic-megaloblastic anemia' phrase and the 'to a human in need thereof' phrase were added to gain allowance of the claims after almost twenty years of repeatedly unsuccessful attempts to gain allowance of claims without those phrases. We must therefore give them weight, for the patentability of the claims hinged upon their presence in the claim language.").

572. Manning v. Paradis, 296 F.3d 1098, 1102–04 (Fed. Cir. 2002) ("Here the preamble defines the intended purpose of the invention because unless oxygen were delivered to the heart of the subject in a therapeutic amount the invention would have no purpose. . . . The plain meaning of the word 'treat' requires that the invention of the count is used to seek or to achieve a therapeutic effect on the subject, rather than simply providing [any amount of] oxygen to the subject's heart.").

573. L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co., 849 F.3d 1049, 1060 (Fed. Cir. 2017) (holding that the Board erred in construing the phrase "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis" to mean an "individual hav[ing] symptoms that may be associated with penile fibrosis, such as [erectile dysfunction]" because erectile dysfunction is merely a symptom); Rapoport v. Dement, 254 F.3d 1053, 1059–60 (Fed. Cir. 2001) ("[T]he

The patentee may also choose to define in the patent's specification what it means to "treat" a particular disorder.[573.1]

[B][2] "Effective Amount"

The Federal Circuit has determined "that 'effective amount' is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation."[574]

When a method of treatment claim requires an "effective amount" and also recites an express dosage amount, the "effective amount" language does not limit the claim.[575]

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plain language of the interference count unambiguously refers to 'treatment of sleep apneas' narrowly defined, and does not also include by its plain terms 'treatment of symptoms associated with sleep apneas.'" The court further relied on the specification of the senior party's patent application to support its count construction, finding the description of the invention "consistent with treatment of the underlying sleep apnea disorder . . . and inconsistent with treatment of anxiety and other symptoms commonly associated with sleep apnea . . . .").

573.1. Allergan, Inc. v. Apotex Inc., 754 F.3d 952, 957–58 (Fed. Cir. 2014) ("All parties, as well as the district court, agreed that the specification provides an express definition for the term: '"Treating hair loss" includes arresting hair loss or reversing hair loss, or both, and promoting hair growth.' . . . Reading the patentee's own lexicography in light of the whole specification, we conclude that a method of 'treating hair loss' may include a method of promoting hair growth without also arresting or reversing hair loss.").

574. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1383–84 (Fed. Cir. 2003); *see also In re* Caldwell, 319 F.2d 254, 258 (C.C.P.A. 1963) (finding "effective amount" means in common terms, "enough to work but not too much. 'Effective amount' admirably states what is to be derived from the disclosure of the specification as to amount and we can see nothing 'critical' about the amount in determining the existence of patentable invention."); Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1277–78 (Fed. Cir. 2003) ("At the outset, this court notes that the term 'effective amount' has a customary usage . . . mean[ing] 'a sufficient amount of the specified component to [attain a result] having the specified properties under the specified conditions, if any.'") (quoting Minn. Mining & Mfg. Co. v. Chemque, Inc., 303 F.3d 1294, 1299, 1304 (Fed. Cir. 2002)); Key Pharm. v. Hercon Labs. Corp., 161 F.3d 709, 718 (Fed. Cir. 1999) (considering fact that "the FDA considered 2.5 to 15 mg/day to be pharmaceutically effective" as of the filing date when construing "pharmaceutically effective amount" to be that amount "plus an excess amount to ensure that the desired amount is delivered.").

575. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1375 (Fed Cir. 2001) ("[T]he expression 'an antineoplastically effective

[B][3] "Co-Administration"

The Federal Circuit construed a method of treatment involving "co-administering" of two pharmaceuticals to include three scenarios: (1) administering two drugs at the same time (concomitant administration); (2) adding treatment of drug B after treatment with drug A has already begun (adjunctive administration); and (3) adding treatment of drug A after treatment with drug B has already begun (adjunctive administration).[575.1]

§ 7:4.5 Anticipation and Obviousness

Method of treatment inventions can be based on known compounds, and even on compounds that were previously known to be useful in treating other diseases. Numerous cases have dealt with the issue of when such prior art anticipates a method of treatment.

Method of treatment inventions can also be based on uses of new compounds. Numerous cases have dealt with whether the claims are obvious by determining whether the new compound itself is nonobvious,[575.2] however, even if the new compound is obvious, one must still determine if the use is also obvious.[575.3]

[A] Inherent Anticipation

Prior art "may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference."[576]

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amount' . . . essentially duplicates the dosage amounts recited in the claims that are also described in the specification as 'antineoplastically effective.' . . . The express dosage amounts are material claim limitations; the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim.").

575.1. AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1371, 1377 (Fed. Cir. 2014) (court construed "'co-administering' to mean that treatment with the antibody can be: (1) started at approximately the same time as treatment with methotrexate (concomitant administration); (2) added after treatment with the methotrexate has already begun (adjunctive administration); or (3) begun first, with the methotrexate treatment later added (adjunctive administration)"; court explicitly rejected a fourth scenario, "administration of the antibody alone after discontinuing the administration of methotrexate").

575.2. See *supra* section 7:2.2 for a discussion of chemical compound obviousness law.

575.3. *See infra* section 7:4.5[C].

576. As described in section 5:2.2[D]. Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003); *see also* Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc., 344 F.3d 1186, 1192 (Fed. Cir.

[A][1] Examples of Inherency

Integra LifeSciences I Ltd. v. Merck KGaA[577]

Claim: Method for inhibiting animal cell proliferation by using a solution containing a polypeptide with the amino acid sequence Arg-Gly-Asp.[578]

Prior Art: Nature article taught that polypeptides with Arg-Gly-Asp will interfere with the attachment of rat kidney fibroblast cells to the fibronectin coated substrates.[579]

Inherent Property: inhibition of cell proliferation

Holding: Article anticipates "because the application of Arg-Gly-Asp peptides to certain cells blocked attachment of those cells to certain substrates, it naturally follows that the Arg-Gly-Asp peptides would also halt any future proliferation of or reattachment within the same cells thereafter."[580]

MEHL/Biophile International Corp. v. Milgraum[581]

Claim: Method for removing hair by applying a laser "substantially vertically" over a hair follicle opening.[582]

Prior Art: (1) Manual for a laser used to remove tattoos;

(2) Article describing tissue damage in guinea pigs caused by a laser.

2003) ("A claim limitation is inherent in the prior art if it is necessarily present in the prior art, not merely probably or possibly present."); EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1349 (Fed. Cir. 2001) ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.") (citation omitted).

577. Integra LifeSciences I Ltd. v. Merck KGaA, 50 U.S.P.Q.2d (BNA) 1846 (S.D. Cal. 1999), *aff'd in relevant part, rev'd in part*, 331 F.3d 860 (Fed. Cir. 2003), *vacated*, 545 U.S. 193 (2005).

578. 50 U.S.P.Q.2d (BNA) at 1849.

579. *Id.*

580. *Id.* at 1849–50 (relying on other prior art that suggested "a general recognition in the field that the successful proliferation of animal cells requires the duplication of appropriate stromal (attachment) requirements of the cell").

581. MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362 (Fed. Cir. 1999).

582. *Id.* at 1364.

Inherent Property: removal of hair

Holding: (1) Manual did not anticipate because it did not disclose aligning the laser "substantially vertically over a hair follicle opening" and there was "no necessary relationship between the location of a tattoo and the location of hair follicles."[583] (2) Article did inherently disclose every limitation because by placing the laser in contact with the skin of the guinea pig, which is hairy, the laser would be aligned "perpendicular to the skin surface and therefore substantially vertically over follicle openings."[584]

In re May[585]

Claim: Method for treating pain without producing physical dependence by administering specific compounds.

Prior Art: Compound within the genus of compounds listed in claim disclosed in prior art as useful in effecting analgesia.

Inherent Property: non-addictiveness of the compound

Holding: Rejected claims because the non-addictiveness was merely an "unknown property . . . of the species disclosed by [prior art, and] such discovery does not constitute a new use."[586]

Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.[587]

Claim: Method for treating cancer patient comprising (1) premedicating with medicament that treats hypersensitivity reactions; and (2) administering 135–175 mg/m^2 paclitaxel over about three hours.

Prior Art: Disclosed treatment of patients with three-hour infusions of paclitaxel within the claimed dosage ranges (without observing any tumor reduction) and referred to pretreatment as a potential means to reduce hypersensitivity reactions.

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583. *Id.* at 1365.
584. *Id.* at 1366.
585. *In re* May, 574 F.2d 1082 (C.C.P.A. 1978).
586. *Id.* at 1090.
587. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368 (Fed. Cir. 2001).

Inherent Property: tumor regression

Holding: Claimed method of treatment anticipated; court refused to read the claim preamble of language requiring efficacious amounts as claim limitations because it found this to be an inherent result of the prior art method.[588]

Ex parte Novitski[589]

Claim: Method for protecting a plant from pathogenic nematodes by inoculating the plant with a nematode-inhibiting strain of *Pseudomonas cepacia*.

Prior Art: A patent disclosed a method that comprises "the step of inoculating a plant with *Pseudomonas cepacia* type Wisconsin 526" to protect a plant from fungal diseases.[590]

Inherent Property: the nematode-inhibiting activity

Holding: "[W]e find that *Pseudomonas cepacia* type Wisconsin 526 inherently possesses nematodeinhibiting activity and that Dart's step of inoculating with [it] inherently and necessarily constitutes a method for protecting a plant from plant pathogenic nematodes."[591] While the patent referred to a cutoff value of 40% inhibitory activity in the specification, the claims did "not specify any degree of nematode-inhibiting activity . . . [and] [w]e shall not read into these claims limitations from the specification."[592]

In re Kao[592.1]

Claim: A method of relieving pain using controlled release oxymorphone "wherein the oxymorphone C_{max} is at least about 50% higher when the dosage form is administered to the subject under fed versus fasted conditions."

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588. *Id.* at 1376–77.
589. *Ex parte* Novitski, 26 U.S.P.Q.2d (BNA) 1389 (B.P.A.I. 1993).
590. *Id.* at 1390.
591. *Id.*
592. *Id.* at 1391.
592.1. *In re* Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Prior Art: "Maloney 'teaches oral sustained release preparations of opioid analgesics' with the use of oxymorphone as a preferred opioid." It also teaches "using calcium sulfate (a cross linking agent), lactose (a filler), and hydrogenated vegetable oil (a hydrophobic material) in his formulation. Based on these disclosures, the Board determined that it would have been obvious . . . to formulate the claimed oral dosage form and to administer the form to the subject as claimed."

Inherent Property: "[T]he claimed 'food effect' is an inherent property of oxymorphone itself, present both in controlled release and immediate release formulations of that drug."

Holding: "This is not a case where the Board relied on an unknown property of prior art for a teaching. Rather, Maloney's express teachings render the claimed controlled release oxymorphone formulation obvious, and the claimed 'food effect' adds nothing of patentable consequence."

[A][2] Examples of No Inherency

Griffin v. Bertina[593]

Claim: Method for diagnosing increased risk for thrombosis comprising obtaining specified nucleic acid from subject and assaying for a specified point mutation.

Prior Art: Prior reduction to practice by "identifying the point mutation."

Inherent Property: correlation of the point mutation with increased risk of thrombosis

Holding: "Griffin only offered evidence concerning performance of the manipulative steps in which it was discovered that [one individual] possessed the point mutation of the count. He did not demonstrate that the inventors diagnosed that [the individual] had an increased risk of thrombosis . . . ."[594]

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593. Griffin v. Bertina, 285 F.3d 1029 (Fed. Cir. 2002).
594. *Id.* at 1034.

Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc.[595]

Claim: Equipment for delivering gas, abrasive, and liquid to tooth surface to remove plaque and stain without causing damage.

Prior Art: Patent disclosed a blasting and spraying gun using pressurized liquid that could be set to any water pressure.

Inherent Property: EMS argued that the prior patent inherently anticipated the limitations of "substantially unpressurized flow of liquid" and "continuous liquid curtain surrounding the pressurized jet of particle-laden gas."[596]

Holding: "The mere fact that a certain thing may result from a given set of circumstances is insufficient to prove anticipation. EMS was required to prove that an unpressurized flow is necessarily present in the Ruemelin disclosure . . . ."[597]

Rapoport v. Dement[598]

Claim: Method of treating sleep apnea, by administration of a "therapeutically effective regimen of buspirone or a pharmaceutically effective acid addition salt thereof."[599]

Prior Art: Article taught administrating 10 mg of Buspirone three times daily to relieve anxiety.

Inherent Property: successful treatment of sleep apnea

Holding: Article did not anticipate because (1) it was directed towards treating anxiety not sleep apnea; (2) it did not teach dosing before bedtime; and (3) it did not teach a dose that would necessarily be a "therapeutically effective amount."[600]

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595. Electro Med. Sys., S.A. v. Cooper Life Scis., Inc., 34 F.3d 1048 (Fed. Cir. 1994).
596. *Id.* at 1052.
597. *Id.* (citations omitted).
598. Rapoport v. Dement, 254 F.3d 1053 (Fed. Cir. 2001).
599. *Id.* at 1056.
600. *Id.* at 1060–63.

Allergan, Inc. v. Apotex Inc.[600.1]

Claim: Method of treating hair loss by administering one of a group of compounds including bimatoprost by locally administering on the skin once per day.

Prior Art: Patent discloses use of various compounds "including bimatoprost" as eyedrops to treat glaucoma but "does not refer to hair growth or treating hair loss, nor does it disclose topical application of any compounds."[600.2]

Inherent Property: Defendant argued that the application of eyedrops containing bimatoprost results in the growth of eyelashes. "At issue is whether promoting hair growth through topical application on bimatoprost on the skin is necessarily present or inherent in the method of applying eyedrops containing bimatoprost."[600.3]

Holding: The Federal Circuit affirmed the district court's finding of noninherency based on its crediting "appellee's expert witness" who "had persuasively testified that a 'properly applied drop' would not transfer to the skin."[600.4]

Par Pharm., Inc. v. TWi Pharm., Inc.[600.5]

Claim: "A method of increasing the body mass in a human patient . . . comprising administering . . . a megestrol formulation . . . wherein after a single administration . . . there is no substantial difference in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus fasted state."

Prior Art: "all of the substantive limitations in the independent claims are present in the various prior art references"

Inherent Property: "food effect limitations"

600.1. Allergan, Inc. v. Apotex Inc., 754 F.3d 952 (Fed. Cir. 2014).

600.2. *Id.* at 960.

600.3. *Id.*

600.4. *Id.* at 960–61.

600.5. Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186, 1196 (Fed. Cir. 2014) (reversing finding of obviousness based on inherency); *see also* Par Pharm., Inc. v. TWi Pharm., Inc., No. CCB-11-2466, 2015 WL 4577737, at *5 (D. Md. July 28, 2015) (on remand: "In sum, TWi has shown by clear and convincing evidence that the food effect limitations are inherent in the prior art.").

Holding: Vacated inherent obviousness determination for failure to apply the proper standard and remanded. On remand, the food effect was found to be inherent.

[B] Prior Art Need Not Disclose Efficacy to Anticipate

"[A] prior art reference need not disclose 'proof of efficacy' to anticipate" a "method for treating a disease."[600.6] "A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis."[601] Similarly, a prior art reference disclosing an experiment that performs every step in a method of treatment claim anticipates the claim whether or not the performance of those steps resulted in a failed experiment.[602] Furthermore, the steps described in the prior art reference do not have to be performed as long as they are suggested and are enabling to one of skill in the art.[603] On the other hand, one court held that a prior art reference that did not suggest the use of aspirin to promote growth and that reported an experiment showing that giving aspirin to rats and children did not have an effect on their growth did not anticipate a claim to a method of using aspirin to promote growth in livestock.[604]

600.6. *In re* Gleave, 560 F.3d 1331, 1335 (Fed. Cir. 2009).

601. Celeritas Techs., Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361 (Fed. Cir. 1998).

602. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001) (explaining that the scientist performing the experiment disclosed in a prior art reference "simply performed the claimed method on patients who did not show any antitumor effect. [The] performance of these same steps today would literally infringe the '803 claims; it is axiomatic that that which would literally infringe if later anticipates if earlier. Moreover, [the scientist] enabled the performance of those steps even though he did not achieve a favorable outcome, which was not a requirement of the claim.") (citation omitted); *see also* Ciba-Geigy Corp. v. Alza Corp., 864 F. Supp. 429, 437 (D.N.J. 1994) (rejecting argument that use of the word "might" fails to teach anything because the "tenor" of the disclosure "is not relevant" and all that matters is whether the reference identifies the invention), *aff'd in relevant part, rev'd in part*, 68 F.3d 487 (Fed. Cir. 1995) (unpublished).

603. *Bristol-Myers Squibb*, 246 F.3d at 1379 ("[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art.").

604. *See In re* Caldwell, 319 F.2d 254, 255–56 (C.C.P.A. 1963) ("Insofar as stimulating the growth of any animals by feeding them aspirin is concerned, there does not appear to be any prior art. . . . [I]t does not appear

[C] Obviousness

[C][1] Methods of Using New Compounds

Methods of treatment using new compounds must still satisfy the obviousness requirement, either because the compound itself is nonobvious or because the claimed use of that new compound is nonobvious. Although determining whether a claim covering the use of a novel compound is obvious requires consideration of both structural obviousness of the new compound and the particular claimed use, the cases tend to focus on the obviousness of the compound itself. (The next section includes relevant authority.)

[C][2] New Methods of Using Old Compounds

New methods of using old compounds include claims limiting their use to the treatment of new diseases, new dosing regimens, and combination treatments.

A court found that the claimed method of using old compounds to treat pain was inherently anticipated by the prior art despite the discovery of unexpected nonaddictive properties.[604.1] The court rejected the argument that the prior art could be distinguished because the claims at issue covered a method for effecting nonaddictive analgesia, because it found this is not a "new use."[604.2]

A court found claims to 40 mg 3x / week obvious over prior dosing amounts of 20 mg and 40 mg based on art that "encouraged POSITAs to pursue a less frequent than daily dosing regimen" and an "already-approved daily 20mg injection—120mg/week" regimen.[604.3] The court explained that in view of this motivation, "a POSITA had only a limited number of permutations of dose and frequency to explore that were not already disclosed in the prior art."[604.4] The "already-approved" regimen was "120mg/week versus 140mg/week" in the

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from anything of record that [aspirin's] use as a growth promoter for any animal, human or otherwise, has ever been even suggested. . . . It seems pretty clear that the [prior art] reference stands for, and suggests, only one thing as far as the present case goes. That is, that feeding aspirin to children and rats over prolonged periods does not interfere with or retard growth of these two species of animals. . . . Our reaction to the disclosure of the sole reference is that anyone reading it would extract from it only the impression that aspirin in reasonable or practical dosages has no affect whatever on animal growth.").

604.1. *In re* May, 574 F.2d 1082, 1090 (C.C.P.A. 1978) ("While appellants have discovered a hitherto unknown property, to wit, nonaddictiveness, of the species disclosed by May, such discovery does not constitute a new use.").

604.2. *Id*. at 1090–93.

604.3. *In re* Copaxone Consol. Cases, 906 F.3d 1013, 1025–29 (Fed. Cir. 2018).

604.4. *Id*. at 1025.

claimed dose.[604.5] "Although the universe of potential GA doses is theoretically unlimited, the universe of dosages in the prior art that had clinical support for being effective and safe consisted of only two doses: 20mg and 40mg. Even if there were multiple injection frequencies not yet tested in the prior art—1x, 2x, 3x a week etc.—these still represent a limited number of discrete permutations."[604.6]

Another court found that although the claim covering the use of atenol to treat hypertension covered the use of a novel compound, the prior art taught that it was part of a general class of compounds known to be beta-blockers and was useful in treating hypertension.[604.7] The art also taught "not only the requisite structure necessary for beta-blocking activity but the portions of this structure which can tolerate modification without a resultant loss of beta-blocking activity."[604.8] "The Court concludes that the prior art, taken as a whole, creates a reasonable expectation that atenolol would be a beta-blocker and, thus, be useful in the treatment of hypertension."[604.9]

In *Amgen v. Sandoz*,[604.10] Amgen cross-appealed the district court's determination that claims 2, 19, and 21 of its U.S. Patent 10,092,541, directed to a dosing schedule for the branded drug product Otezla® (apremilast), indicated for treating psoriasis, would have been obvious over the prior art. Amgen argued that the district court's analysis was flawed, as it relied on generalized characterizations of a dose-titration schedule and failed to adequately address why a skilled artisan would have been motivated to achieve the claimed dosage schedule. Amgen also contended that the lower court's obvious-to-try statements did not rectify these errors and that the evidence provided by Sandoz did not establish a finite set of options for dose-titration schedules.[604.11]

Sandoz, however, countered by asserting that the district court appropriately determined that the claims in question would have been obvious over the prior art. Sandoz argued that modifying the dosing schedule in the prior art reference to reduce known side effects would have been within the skill of a person in the art. Additionally, Sandoz contended that the estimated number of possible dose-titration

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604.5. *Id*.
604.6. *Id*. at 1026.
604.7. Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 369–70 (D. Del. 1991).
604.8. *Id*.
604.9. *Id*.
604.10. Amgen Inc. v. Sandoz Inc., 66 F.4th 952 (Fed. Cir. 2023).
604.11. *Id*. at 967.

schedules provided by Amgen was inflated and that correcting the assumptions reduced the possible options to eighteen.[604.12]

The Federal Circuit agreed with Sandoz on Amgen's cross-appeal, affirming the district court's decision. The court found that the prior art supported the conclusion that varying doses in response to side effects was a standard medical practice, making the claimed invention obvious. The court concluded that a skilled artisan would have been motivated to use the prior art schedule as a starting point and adjust it to titrate the dosing up in smaller amounts. Therefore, the court found no error in the district court's determination that claims 2, 19, and 21 of the '541 patent would have been obvious over the prior art.[604.13]

[C][3] Genus of Methods of Treatment Could Render Included Species Obvious

"The genus-species distinction may have particular relevance in the field of personalized medicine, where, for example, a particular treatment may be effective with respect to one subset of patients and ineffective (and even harmful) to another subset of patients."[605] "Singling out a particular subset of patients for treatment (for example, patients with a particular gene) may reflect a new and useful invention that is patent eligible despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally. An obviousness rejection likely would not be appropriate where the new patient subset displayed unexpected results."[606] Where, however, the species is admittedly contained within a prior art genus and each limitation defining the species was taught by the prior art and constitute a limited set of parameters, the species may be found obvious.[607]

[C][4] Instructional Limitations

Method of treatment claims sometimes include "instructional limitations" which may require someone to provide specific information

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604.12. *Id*. at 967–68.

604.13. *Id*. at 968.

605. Prometheus Labs., Inc. v. Roxane Labs, Inc., 805 F.3d 1092, 1098 (Fed. Cir. 2015).

606. *Id*.

607. *Id*. at 1101 (claimed species of administering alosetron to IBS patients who satisfied the following parameters: women with IBS-D; who experienced symptoms for at least six months; and have had moderate pain, rendered obvious over method of administering alosetron to IBS patients because prior art disclosed each of these limiting parameters and "there was a limited number of known parameters" rendering it obvious to combine these known parameters).

to the patient about the treatment. Such methods can be tied to the FDA-mandated package inserts that accompany approved drugs. These limitations raise specific issues for claims to methods that are otherwise known in the prior art but for the "instructional limitation." The question (in both an obviousness and anticipation analysis) becomes whether the additional instructional limitation "has a 'new and unobvious functional relationship' with the known method of administering" the drug.[608] Unless there is a requirement that the informing step somehow changes the manner in which the drug is administered, the instructional limitation cannot save the claim because to hold otherwise would allow anyone to "continue patenting a product indefinitely provided that they add a new instruction sheet to the product."[609]

§ 7:4.6 Written Description

[A] Examples of Method of Treatment Cases Involving Written Description

Several examples illustrate patents claiming method of treatment inventions that failed to satisfy the written description requirement.[610] Other examples illustrate satisfaction of the written description requirement.[611]

[B] Field of Use Claim

A field of use claim is a type of method of treatment claim defined in terms of the biological function of the drug (for example, antibiotic or beta-blocker) instead of its chemical structure. At a minimum, the Federal Circuit has made clear that a person of ordinary skill must be able to identify such a compound based on the specification's

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608. King Pharm., Inc. v. Eon Labs, Inc., 616 F.3d 1267, 1279 (Fed. Cir. 2010) (holding there was no functional relationship between the informing and administering steps because "[i]nforming a patient about the benefits of a drug in no way transforms the process of taking the drug with food"); *In re* Kao, 639 F.3d 1057, 1072 (Fed. Cir. 2011) ("Though the correlation between the renal impairment and bioavailability was not known, informing someone of the correlation cannot confer patentability absent a functional relationship between the informing and administering steps.").
609. *In re* Ngai, 367 F.3d 1336, 1339 (Fed. Cir. 2004).
610. *See* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004); Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320 (Fed. Cir. 2000).
611. Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963 (Fed. Cir. 2006); *In re* Cortright, 165 F.3d 1353 (Fed. Cir. 1999).

disclosure. In the case of antibiotics, that functional language identifies many known drugs. On the other hand, referring to inhibitors of a new receptor "X" as "X-inhibitors" may not be itself sufficient to satisfy the written description requirement.

The Federal Circuit, in *University of Rochester v. G.D. Searle & Co.*,[612] invalidated a claim reciting a method for selectively inhibiting the cyclooxygenase-2 (COX-2) enzyme by administering "a non-steroidal compound that selectively inhibits activity" of the COX-2 enzyme. The patent disclosed no compounds that could be used in the claimed method and there was no evidence that "the ordinarily skilled artisan would be able to identify any compound based on [the patent's] vague functional description."[613] The court held that absent a disclosure of what compounds would have the desired characteristics of selectively inhibiting COX-2, "the claimed methods cannot be said to have been described."[614]

[C] Dosing

A claim requiring administration of a dosage form for an opioid that provides the patient with a "maximum plasma concentration of the opioid [that is] more than twice the plasma level of the opioid twenty-four hours after administration of the drug" did not have adequate support in the specification to satisfy the written description requirement.[615] The specification only described the invention as possessing a "generally flat" or "substantially flat" morphine plasma concentration curve, therefore it failed to support a limitation in claims that maximum plasma concentration was to be more than twice the plasma level of the opioid 24 hours after it was dispensed.[616]

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612. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004); *see also* Ariad Pharm., Inc. v. Mass. Inst. of Tech., 560 F.3d 1366 (Fed. Cir. 2009) (invalidating claims reciting methods for reducing NF-κB activity); *In re* Alonso, 545 F.3d 1015, 1018, 1021 (Fed. Cir. 2008) (rejecting claims reciting methods for treating neurofibrosarcoma by administering "monoclonal antibodies idiotypic to the neurofibrosarcoma"—a class of antibodies that target malignant nerve sheath tumor). See *supra* section 5:4.5[A] for a discussion of the written description requirements application to compound and composition claims and to method claims that require use of compounds and compositions.
613. *Univ. of Rochester*, 358 F.3d at 927–28.
614. *Id*. at 927; *Ariad*, 560 F.3d at 1373 ("Regardless of whether the asserted [method of treatment] claims recite a compound, Ariad still must describe some way of performing the claimed methods.").
615. *Purdue*, 230 F.3d at 1327.
616. *Id*. at 1324–25.

"[A] person skilled in the art would not necessarily interpret the term 'flat' to be limited to a concentration level ratio less than or equal to two."[617] The court noted that, "[a]lthough the examples provide the data from which one can piece together the C_{max}/C_{24} limitation, neither the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasizes the C_{max}/C_{24} ratio."[618]

§ 7:4.7 Enablement

[A] Compound Needed to Practice Claim Must Be Enabled

Method of treatment claims for pharmaceutical inventions are not enabled when a way to make a compound needed to practice the claimed method is not disclosed and not taught by the prior art.[619]

[B] Dosing

A method of treatment claim is not enabled when the specification and the art fail to teach the dose required for the treatment

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617. *Id*. at 1325.
618. *Id*. at 1326.
619. Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 232–33 (W.D.N.Y. 2003) (patent not enabled because it "essentially calls for the use of trial and error to attempt to find a compound that will selectively inhibit PGHS-2 activity in a human host, which is the method claimed by the patent"), *aff'd on other grounds*, 358 F.3d 916 (Fed. Cir. 2004); *see In re* Collier, 427 F.2d 831, 832–33 (C.C.P.A. 1970) (method claims not enabled because neither applicant's specification nor the art disclosed "how to make the epoxy silane starting material" recited in the claim); *see also Ex parte* Kropp, 143 U.S.P.Q. (BNA) 148, 152 (B.P.A.I. 1959) (method claim not enabled because "the starting material [in claim] obviously cannot be reproduced from the written description, nor does the specification give any source where it can be found"); Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380, 1382–86 (Fed. Cir. 2013) (no enablement where "the specification . . . disclose[d] only a starting point for further iterative research in an unpredictable and poorly understood field. Synthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry. . . . The specification offer[ed] no guidance or predictions about particular substitutions that might preserve the immunosuppressive and antirestenotic effects observed in sirolimus. The resulting need to engage in a systematic screening process for each of the many rapamycin candidate compounds [was] excessive experimentation" and therefore, "practicing the full scope of the claims . . . required undue experimentation").

without undue experimentation.[620] However, dosing instructions setting forth both the dose amount and the time in which to expect results have been found sufficient to enable one of ordinary skill to practice the claimed invention.[621]

§ 7:4.8 Best Mode

The best mode requirement has been applied to patents claiming method of treatment inventions.[622]

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620. *In re* Gardner, 427 F.2d 786, 788–90 (C.C.P.A. 1970) ("We consider the [dose] range so great [10 to 450 mg] as not to be an enabling or how-to-use disclosure as contemplated by the statute."); *In re* Colianni, 561 F.2d 220, 222 (C.C.P.A. 1977) ("The application of 'sufficient' ultrasonic energy is essential to appellant's claimed method, yet his specification does not disclose what a 'sufficient' dosage of ultrasonic energy might be or how those skilled in the art might make the appropriate selection of frequency, intensity, and duration. There is not a single specific example or embodiment by way of an illustration of how the claimed method is to be practiced."); Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 374 (D. Del. 1991) (claims invalid because the disclosed dose range of 25 to 1,200 mg and more preferably 200 to 600 mg is broad "and is very high in comparison to the dose range of 50 mg to 100 mg approved by the FDA" and because "the patent disclosure would not offer guidance but misdirect one attempting to determine an effective dose").

621. *In re* Cortright, 165 F.3d 1353, 1359 (Fed. Cir. 1999) ("[O]ne of ordinary skill would not construe 'restoring hair growth' to mean 'returning the user's hair to its original state,' as the board required. To the contrary, consistent with Cortright's disclosure and that of other references, one of ordinary skill would construe this phrase as meaning that the claimed method increases the amount of hair grown on the scalp but does not necessarily produce a full head of hair. Properly construed, claim 1 is amply supported by the written description because Example 1 discloses the amount of Bag Balm® to apply (about one teaspoon daily) and the amount of time (about one month) in which to expect results. These dosing instructions enable one of ordinary skill to practice the claimed invention without the need for any experimentation.").

622. Cardiac Pacemakers, Inc. v. St. Jude Med., Inc., 381 F.3d 1371, 1375, 1379 (Fed. Cir. 2004) (holding nondisclosure of a particular type of battery used in an implantable heart stimulator for the treatment of a detected arrhythmia did not violate the best mode requirement, stating "[t]here was evidence before the jury that persons knowledgeable in the field of the invention would know the sources of batteries for pacemakers and related devices. There was no evidence of concealment, and the jury had evidence that the Honeywell battery was published in a publication for battery specialists."). For further discussion of the best mode requirement see *supra* section 5:6.

§ 7:4.9 Infringement

[A] Suing the Maker of the Therapeutic: Indirect Infringement

Proving infringement of a method of treatment claim often involves theories of indirect infringement. Depending on the nature of the claim, a method of treatment claim may only be directly infringed by medical personnel or a patient and not the maker of the therapeutic agent or device. For a variety of reasons, however, a patentee may prefer to sue the company that makes the therapeutic in preference to the doctor and patients who may practice the method. The Patent Act covers two forms of indirect infringement known as inducing infringement and contributory infringement.[623]

[B] Suing on Method of Treatment Claims Against an ANDA Defendant

Patentees can assert claims for inducing infringement of method of treatment claims against generic drug manufacturers under section 271(e)(2) of title 35 based on the filing of an Abbreviated New Drug Application (ANDA) if the ANDA is for an FDA-approved use claimed by the patent.[624] The holder of a method of use patent, however, may not sue an ANDA applicant for inducement, "if the ANDA applicant is not seeking FDA approval for the use claimed in the patent and if the use claimed in the patent is not FDA-approved."[625] Even if the ANDA applicant seeks approval for claimed use, proof of infringement is not automatic. "[M]ere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven."[626]

There must be evidence that the ANDA filer "has or will promote or encourage doctors to infringe" the asserted method of treatment patent.[627]

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623. See *infra* sections 10:2.2 and 10:2.3 describing indirect infringement under 35 U.S.C. § 271(b) & (c).
624. Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1330–32 (Fed. Cir. 2003) ("[A] patent holder asserting infringement of a patent that claims a FDA-approved method of use for which an ANDA seeks approval will, in many instances, have to prove induced infringement. Therefore, section 271(e)(2) may support an action for induced infringement.").
625. *Id*. at 1332; Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1354 (Fed. Cir. 2003) ("it is not an act of infringement [under section 271(e)(2)] to submit an ANDA for approval to market a drug for use when neither the drug nor that use is covered by an existing patent").
626. *Warner-Lambert*, 316 F.3d at 1364.
627. *Id*. For further discussion of bringing inducement claims against ANDA filers, see section 8:1.4[B][3][b].

§ 7:5 Pharmaceutical Manufacturing*

Intellectual property rights in a pharmaceutical product may be protected by patents directed to methods of making the product, either in addition to, or as an alternative to patents that are directed to the active pharmaceutical ingredient itself or to a pharmaceutical formulation of the active ingredient. The Patent Act specifies that a "new and useful process" is patentable subject matter.[628] Thus, a patent may be granted that claims the steps used to synthesize a pharmaceutical compound or the steps used to make a pharmaceutical formulation.

Patents may also be issued that are directed to intermediates in the synthesis of a pharmaceutical compound as long as the final compound is demonstrated to have a practical utility.[629]

Patents may also be issued that claim pharmaceutical compositions at least in part by the process steps used to make the compositions. Such claims, called "product-by-process" claims have raised issues regarding how the recited process steps affect determinations of patent infringement and validity.

This section focuses on patents that relate to the processes used to make pharmaceutical compositions.[630]

§ 7:5.1 Intermediates

[A] Definition and Purpose

Chemical compounds used as intermediates to synthesize other compounds may be patentable if the final compound has a "substantial" or "real world" utility.[631] The value of a patent to a chemical

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* Written by David K. Barr.

628. 35 U.S.C. § 101.

629. *Cf. In re* Kirk, 376 F.2d 936, 945 (C.C.P.A. 1967) ("[I]f a process for producing a product of only conjectural use is not itself 'useful' within§ 101, it cannot be said that the starting materials for such a process—*i.e.*, the presently claimed intermediates—are 'useful.'"); *In re* Joly, 376 F.2d 906 (C.C.P.A. 1967) (stating that claims to intermediates for making steroids of unknown utility do not satisfy the utility requirement).

630. Process claims also implicate 35 U.S.C. § 271(g), which makes the importation into the U.S. of a product that is made by a process patented in the United States an act of infringement. Section 271(g) is discussed *supra* in section 7:1.4[B].

631. Courts have at various times stated that the utility requirement means that the invention has a "substantial" or a "practical" utility. According to the U.S. Patent Office, a "substantial utility" defines a "real world" use. "Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities." U.S. Patent and Trademark Office, Revised Interim

intermediate is limited by the value of the final product and the importance of the intermediate to making the final product. The patent on an intermediate does not prevent one from making the final product using different intermediates.

[B] Utility Required

The utility requirement of section 101 of title 35[632] was applied by the Supreme Court to a process for making a chemical compound in *Brenner v. Manson*.[633] The Supreme Court held unpatentable for failure to satisfy the utility requirement a process for making a steroid compound because no use was disclosed. The Court rejected the arguments that the utility requirement for the claimed process was satisfied "because it works—*i.e.*, produces the intended product" or "because the compound yielded belongs to a class of compounds now the subject of serious scientific investigation."[634] In addition, based on the recognized unpredictability in the field, the Court was not persuaded by evidence of the utility of a homologous compound.[635]

Thus, the Court concluded that the utility requirement should act as a substantive limitation to the patenting of chemical compounds:

> [A] process patent in the chemical field, which has not been developed and pointed to the degree of *specific utility*, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, without compensating benefit to the public.

Utility Guidelines Training Materials 6, www.uspto.gov/web/menu/utility.pdf (last visited Jan. 16, 2007) [hereinafter Training Materials]. *See also supra* chapter 3.

632. 35 U.S.C. § 101 states:

> "Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

(Emphasis added.)

633. Brenner v. Manson, 383 U.S. 519 (1966).

634. *Id*. at 532.

635. *Id*. (arguing that "[r]espondent himself recognized that the presumption that adjacent homologues have the same utility has been challenged in the steroid field because of a 'greater known unpredictability of compounds in that field'").

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with *substantial utility*. Unless and until a process is refined and developed to this point—where *specific benefit* exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.[636]

Although the claim at issue in *Brenner* was directed to a process, the Court stated that its reasoning with respect to the utility requirement "would apply equally to the patenting of the product produced by the process."[637]

After *Brenner*, the courts have attempted to define the parameters of the utility requirement as it applies to chemical compounds, including compounds having a stated utility as intermediates for the manufacture of pharmaceutical compounds.[638]

In re Kirk,[639] like *Brenner*, involved the patentability of novel steroid compounds. In *Kirk*, applicants stated that the claimed compounds had "biological activity," based on the activity of analogous steroidal compounds, and that the compounds were useful "as

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636. *Id*. at 534–35 (emphasis added).

637. *Id*. at 535. In concluding, the *Brenner* Court stated that the Patent System was intended to reward what is shown to be useful, not what may prove to be useful in the future: "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Id*. at 536.

638. The courts have noted that the utility requirement is closely related to the enablement requirement of 35 U.S.C. § 112. Thus, it has been held that an invention that lacks utility under section 101 also fails to satisfy the enablement requirement. *In re* Brana, 51 F.3d 1560, 1564 (Fed. Cir. 1995) ("Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it."); *In re* Ziegler, 992 F.2d 1197, 1200–01 (Fed. Cir. 1993) ("The how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention. . . . If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112."); *In re* Kirk, 376 F.2d 936, 942 (C.C.P.A. 1967) ("Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention."). *See also* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (Jan. 5, 2001) (stating that claims rejected under section 101 should also be rejected "under § 112, first paragraph, on the basis that the disclosure fails to teach how to use the invention as claimed").

639. *In re* Kirk, 376 F.2d 936 (C.C.P.A. 1967).

intermediates in the preparation of compounds with useful biological properties."[640] Relying on *Brenner*, the court affirmed a rejection for lack of utility, rejecting applicants' assertion of utility based on the similarity of the claimed compounds to compounds of known utility: "It seems to us that the nebulous expressions 'biological activity' or 'biological properties' appearing in the specification convey no . . . explicit indication of the usefulness of the compounds and how to use them . . . ."[641] The court also rejected applicants' contention that the claimed compounds were useful as "intermediates in the production of aromatic steroidal hormones and other biologically useful compounds."[642] Again relying on *Brenner*, the court found that applicants had failed to establish the utility of the final compounds for which the claimed compounds were asserted to be intermediates: "It seems clear that, if a process for producing a product of only conjectural use is not itself 'useful' within § 101, it cannot be said that the starting materials for such a process—*i.e.*, the presently claimed intermediates—are 'useful.'"[643]

Similarly, in *In re Joly*,[644] a companion case to *Kirk*, the court held that claims to intermediates to compounds of unknown utility do not satisfy the utility requirement. The claims were directed to compounds stated to be "'useful as intermediates' in the preparation of certain 2,3-diketo steroids," but "no specific utility [was] stated" for the named final steroid compounds.[645] The applicant argued that "[the] disclosure of a steroid as useful as an intermediate to make other steroids by specific disclosed reactions is an adequate disclosure of utility."[646] The court disagreed:

> the *practical* utility of the compound, or compounds, produced from a chemical "intermediate," the "starting material" in such a process, is an essential element in establishing patentability of that intermediate. It seems clear that, if a process for producing a product of only conjectural use is not itself "useful" within

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640. *Id*. at 938.
641. *Id*. at 941.
642. *Id*. at 939, 945.
643. *Id*. at 945. *Kirk* relied on the court's prior decision in *In re* Diedrich, 318 F.2d 946, 949, 951 (C.C.P.A. 1963), in which a parent application was found to provide insufficient support under 35 U.S.C. §§ 112, 120 because it merely stated that "the claimed compounds are useful for 'technical and pharmaceutical purposes'" and one skilled in the art would not know how to use the compounds, notwithstanding later-developed evidence of their use as X-ray contrast agents.
644. *In re* Joly, 376 F.2d 906 (C.C.P.A. 1967).
645. *Id*. at 908.
646. *Id*.

> § 101, it cannot be said that the starting materials for such a process—*i.e.*, the presently claimed intermediates—are "useful."[647]

Accordingly, the patentability of a compound that is useful as an intermediate for making a final compound is premised on a showing of a practical utility of the final compound. It is not sufficient that the patent disclose how to use the intermediate to make the final compound, there must be a disclosure of a utility for the final compound.[648]

§ 7:5.2 Product-By-Process Claims

[A] Definition and Purpose

A patent claim that describes a product in terms of the process used to make the product is called a "product-by-process" claim. A product-by-process claim may recite, for example, "A pharmaceutical compound X made by reacting compound Y with compound Z in an aqueous medium having a pH of 5 at a temperature between 70 and 80° C."

Product-by-process claims are not listed among the kinds of patentable inventions specifically set out in the Patent Act.[649] Product-by-process claims were first permitted in order to claim products that were not readily susceptible to physical description, but which could be described by the process used to make them.[650] Over time,

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647. *Id*. (quoting *Kirk*, 376 F.2d 936) (emphasis added). Judges Rich and Smith filed vigorous dissents in *Kirk* and *Joly*. Their dissents distinguished *Brenner* and argued that new and unobvious chemical compounds have utility in the conduct of further research. *Kirk*, 376 F.2d at 947, 966–68; *Joly*, 376 F.2d at 909–10, 926.

648. Training Materials, *supra* note 631, at 6–7, provides a list of examples that do not define "substantial" utilities, which includes "[a] claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility."

649. 35 U.S.C. § 101 sets out specific categories of patentable subject matter: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." As the Federal Circuit stated in *In re* Thorpe, 777 F.2d 695, 697 (Fed. Cir 1985), "[p]roduct-by-process claims are not specifically discussed in the patent statute."

650. Atl. Thermoplastics Co. v. Faytex Corp., 970 F.2d 834, 843 (Fed. Cir. 1992) ("For years, the PTO, with the approval of the CCPA, limited this exception to those instances where the applicant could describe an invention in no way other than in terms of its manufacturing process.") (citations omitted); *Thorpe*, 777 F.2d at 697 ("Product-by-process claims

product-by-process claims became accepted even if the claimed product was capable of physical description.[651]

[B] Construction of Product-By-Process Claims

[B][1] Patent Office Examination of Pending Product-By-Process Claims

The Federal Circuit has acknowledged that, in the examination of patent applications, the Patent Office may treat a pending product-by-process claim as a product claim and determine its patentability without regard to the process terms recited in the claim.[652] According to Patent Office practice, in determining the patentability of a product-by-process claim "[o]nce the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product."[653] As a predecessor court to the Federal Circuit noted, "[a]s a practical matter, the Patent Office is not equipped to manufacture products produced by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith."[654]

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are not specifically discussed in the patent statute. The practice and governing law have developed in response to the need to enable an applicant to claim an otherwise patentable product that resists definition by other than the process by which it is made.").

651. *Atl. Thermoplastics*, 970 F.2d at 844 ("As product-by-process claiming became more common, the CCPA moved toward accepting product-by-process claims without a showing of necessity.").

652. *See id*. at 846 ("The PTO's treatment of product-by-process claims as a product claim for patentability is consistent with policies giving claims their broadest reasonable interpretation. The same rule, however, does not apply in validity and infringement litigation."); *Thorpe*, 777 F.2d at 697 ("[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. . . . If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.") (citations omitted); *accord In re* Brown, 459 F.2d 531, 535 (C.C.P.A. 1972) (For product-by-process claims, "it is the patentability of the *product* claimed and *not* of the recited process steps which must be established.").

653. U.S. PATENT & TRADEMARK OFFICE, U.S. DEP'T OF COMMERCE, 2 MANUAL OF PATENT EXAMINING PROCEDURE § 2113 (8th ed. 2006) (citing *In re* Marosi, 710 F.2d 798, 802 (Fed. Cir. 1983).

654. *Brown*, 459 F.2d at 535.

[B][2] Construction of Issued Product-By-Process Claims in Patent Infringement Litigation

In a 1991 decision in *Scripps Clinic & Research Foundation v. Genentech, Inc.*,[655] a panel of the Federal Circuit held that in infringement litigation, product-by-process claims should be construed without regard to whether the accused product was made by the recited process steps.[656] *Scripps* also held that "claims must be construed the same way for validity and infringement,"[657] so that the recited process terms would not be considered in determining either validity or infringement. In 1992, a different panel of the Federal Circuit in *Atlantic Thermoplastics Co. v. Faytex Corp.*[658] disagreed with *Scripps* and held that infringement of a product-by-process claim requires proof that the accused product was made by recited process steps.[659] As in *Scripps*, the Federal Circuit in *Atlantic Thermoplastics* held that "claims mean the same for infringement and validity."[660]

In a 2006 decision in *SmithKline Beecham Corp. v. Apotex Corp.*,[661] a divided panel of the Federal Circuit, while declining to resolve or address the conflict between *Scripps* and *Atlantic Thermoplastics*, held that the process terms of a product-by-process claim did not prevent anticipation where the same product was in the prior art, stating that "anticipation by an earlier product patent cannot be avoided by claiming the same product more narrowly in a product-by-process claim."[662] However, the court stated that anticipation could be avoided if the recited process steps produced a product that distinguished over the prior art: "If those product-by-process claims produced a different product than that disclosed by the [prior

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655. Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991), *overruled by* Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282 (Fed. Cir. 2009).
656. *Id*. at 1583 ("the correct reading of product-by-process claims is that they are not limited to product prepared by the process set forth in the claims").
657. *Id*.
658. Atl. Thermoplastics Co. v. Faytex Corp., 970 F.2d 834 (Fed. Cir. 1992).
659. *Id*. at 846–47 ("process terms in product-by-process claims serve as limitations in determining infringement").
660. *Id*. at 846. The *Atlantic Thermoplastics* panel explained that product-by-process claims are construed differently in administrative proceedings before the Patent Office than they are in patent infringement and validity litigation: "The PTO's treatment of product-by-process claims as a product claim for patentability is consistent with policies giving claims their broadest reasonable interpretation. The same rule, however, does not apply in validity and infringement litigation." *Id*.
661. Abbott Labs. v. Sandoz, Inc., 439 F.3d 1312 (Fed. Cir. 2006).
662. *Id*. at 1318.

art] patent, there would be an argument that the [prior art] patent disclosure did not anticipate."[663] Since only validity was at issue, the court did not have to consider whether the process terms should be given effect in determining infringement.

In 2009, the Federal Circuit in *Abbott Laboratories v. Sandoz, Inc.*,[664] sitting en banc, addressed the conflict between *Scripps* and *Atlantic Thermoplastics* and held that in patent infringement litigation, "process terms limit product-by-process claims."[665] The en banc court in *Abbott Laboratories* adopted the rule of the *Atlantic Thermoplastics* decision in which the court "construed product-by-process claims as limited by the process,"[666] and overruled the contrary *Scripps* decision.[667] *Abbott Laboratories* cited Supreme Court authority, including *Warner Jenkinson Co. v. Hilton Davis Chemical Co.*,[668] for the principle that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention."[669] *Abbott Laboratories* accordingly restated the rule of *Atlantic Thermoplastics* that "process terms in product-by-process claims serve as limitations in determining infringement."[670]

Subsequent to the en banc decision in *Abbott Laboratories*, a panel decision of the Federal Circuit in *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*[671] marked the first time the Federal Circuit addressed both the infringement and validity of a product-by-process claim.

In *Amgen*, the claim at issue claimed a pharmaceutical composition of human erythropoietin (EPO) "wherein said erythropoietin is purified from mammalian cells grown in culture."[672] At issue was whether EPO derived in the prior art from a urinary source anticipated the claim. The court concluded that the claimed EPO, which was construed to be recombinantly produced, was structurally different than the prior art urinary-derived EPO and that there was

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663. *Id*. at 1319. The Federal Circuit held that SmithKline had waived this argument on appeal by relegating it to a footnote in its opening appeal brief. *Id*. at 1319–20.
664. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282 (Fed. Cir. 2009).
665. *Id*. at 1293.
666. *Id*. at 1291.
667. *Id*. at 1293.
668. Warner Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17 (1997).
669. *Abbott Labs.*, 566 F.3d at 1293 (quoting *Warner-Jenkinson*, 520 U.S. at 19). Accordingly, the Federal Circuit in Abbott stated that, "[a]s applied to product-by-process claims, *Warner-Jenkinson* thus reinforces the basic rule that the process terms limit product-by-process claims." *Id*.
670. *Id*. (quoting *Atlantic Thermoplastics*, 970 F.2d at 846–47).
671. Amgen Inc. v. F. Hoffmann-La Roche Ltd., 580 F.3d 1340 (Fed. Cir. 2009).
672. *Id*. at 1364.

therefore no anticipation.[672.1] However, the court also concluded that the same structural features of the claimed recombinantly produced EPO which avoided anticipation by the prior art urinary-derived EPO, were not required to be present in the accused EPO product in order to find infringement.[672.2] Rather, the court held that under *Abbott v. Sandoz*, infringement of a product-by-process claim is determined by whether the accused product was made by the recited process steps without regard to whether the accused product possessed the same features that avoided anticipation by the prior art.[672.3]

In so holding, the *Amgen* panel acknowledged that its opinion conflicted with "the axiom that 'claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses,'"[672.4] which, as mentioned above, both the prior *Scripps* and *Atlantic Thermoplastics* decisions had agreed upon. Thus, the *Amgen* panel applied different claim constructions for its validity and infringement determinations. In addition, the *Amgen* panel acknowledged that its decision created an exception to the established principle that "that which infringes if later" must "anticipate if earlier."[672.5]

> For product-by-process claims, that which anticipates if earlier does not necessarily infringe if later. That is because a product in the prior art made by a different process can anticipate a product-by-process claim, but an accused product made by a different process cannot infringe a product-by-process claim. Similarly, that which infringes if later does not necessarily anticipate if earlier.

672.1. *Id*. at 1352–53.

672.2. *Id*. at 1353–54.

672.3. *Id*.

672.4. *Id*. at 1369 (quoting Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1351 (Fed. Cir. 2001) ("Because the claims of a patent measure the invention at issue, the claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses.")). Other Federal Circuit decisions are to the same effect. *See, e.g.*, Kim v. ConAgra Foods, Inc., 465 F.3d 1312, 1324 (Fed. Cir. 2006) ("The same claim construction governs for validity determinations as for infringement determinations."); Beachcombers v. WildeWood Creative Prods., Inc., 31 F.3d 1154, 1163 (Fed. Cir. 1994) ("We have already interpreted the claims for purposes of assessing their validity. The same interpretation of course applies to the infringement analysis.") (citations omitted).

672.5. *See* Miller v. Eagle Mfg. Co., 151 U.S. 186, 203 (1894); Knapp v. Morss, 150 U.S. 221, 228–29 (1893); Commercial Mfg. Co. v. Fairbank Canning Co., 135 U.S. 176, 194 (1890); Peters v. Active Mfg. Co., 129 U.S. 530, 537 (1889); Upsher-Smith Labs. v. Pamlab, L.L.C., 412 F.3d 1319, 1322 (Fed. Cir. 2005); Lisle Corp. v. A.J. Mfg. Co., 398 F.3d 1306, 1315 (Fed. Cir. 2005); Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003).

> That is because an accused product may meet each limitation in a claim, but not possess the features imparted by a process limitation that might distinguish the claimed invention from the prior art.[672.6]

However, if subject matter that "infringes if later" does not also "anticipate if earlier," it could seemingly result in a situation in which a product that existed in the prior art could infringe a later patent, although the patent would be valid over that prior art product. Whether in view of such a result the Federal Circuit will revisit the construction of product-by-process claims in infringement and validity determinations, including by the court sitting en banc, remains to be seen.

§ 7:5.3 *Process Claims*

[A] Definition and Purpose

Processes for making chemical compounds or biologic molecules may be patented if the general requirements for obtaining a patent are satisfied.[673] Process claims can protect particular methods for making a pharmaceutical product, requiring competitors to use alternative non-infringing methods which may be less efficient than the patented method. Proving infringement of method claims may present evidentiary problems for the patentee who has to prove that a competitor's product is made by an infringing process. Part of such proof may be a forensic analysis of an accused product for a "marker" as evidence that the patented process was used by the defendant.

[B] Patentability of Process Claims

The patentability of claims to processes for making chemical compounds has been the subject of much litigation. An important question is whether the nonobviousness of the starting materials and end products of the claimed process can be considered in determining the patentability of the claimed process. This was answered in the affirmative by the Federal Circuit in its 1995 decision in *In re Ochiai*.[674] In *Ochiai*, the Federal Circuit reversed a Patent Office Board of Appeals rejection of a claim to a process for making a

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672.6. *Amgen Inc.*, 580 F.3d at 1370.

673. Section 7:5.3[B], *infra*, addresses patentability of process claims. See *supra* chapter 5 for a general discussion of patentability for all types of claims. See *infra* sections 7:6 and 7:7 in this chapter for a discussion on the patentability of nucleic acids and antibodies, including methods for making these biological molecules.

674. *In re* Ochiai, 71 F.3d 1565 (Fed. Cir. 1995).

particular cephem compound having antibiotic properties. The court noted that the claimed process requires the use of a new, nonobvious acid as a starting compound and that "[o]ne having no knowledge of this acid could hardly find it obvious to make any cephem using this acid . . . , much less the particular cephem recited in [the] claim" at issue.[675] In so finding, the court rejected the Patent Office's position that processes used were "standard" or "conventional" without regard to the novelty and nonobviousness of the starting materials.[676] The court concluded:

> The prior art . . . contains nothing at all to suggest that one seek this concededly nonobvious final product. The examiner erred by indulging in an essentially hindsight comparison of the functioning of the new acid in [the] claim . . . as a precursor to the claimed cephem with that of other acids in the prior art processes that produced other cephems.[677]

Thus, the Federal Circuit has held that prior art teaching a general chemical reaction does not render prima facie obvious a claim to using that general reaction to make a particular compound, unless the prior art also suggests the desirability of modifying the general process in order to make the particular compound recited in the claim.[678]

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675. *Id*. at 1569.

676. *Id*. at 1567–69. In deciding *Ochiai*, the Federal Circuit limited its prior, and arguably contrary, decision in *In re* Durden, 763 F.2d 1406 (Fed. Cir. 1985), to its facts. *Ochiai*, 71 F.3d at 1571–72. In *Durden*, the Federal Circuit affirmed the final rejection of a claim to a process for making a novel compound using a novel starting compound as obvious over a prior art disclosure of a chemical process using similar reactants. The court noted that the patent applicants in *Durden* had conceded the obviousness of their claimed process "apart from the fact of employing a novel and unobvious starting material and apart from the fact of producing a new and unobvious product. . . ." *Durden*, 763 F.2d at 1408.

677. *Ochiai*, 71 F.3d at 1570.

678. *See In re* Brouwer, 77 F.3d 422 (Fed. Cir. 1995) ("Although the prior art references the examiner cited teach a general chemical reaction of a compound containing an active methylene group with an ester of vinylsulfonic acid, we have made clear that '[t]he mere fact that a device or process utilizes a known scientific principle does not alone make that device or process obvious.' Moreover, the mere possibility that one of the esters or the active methylene group-containing compounds disclosed [in the prior art] could be modified or replaced such that its use would lead to the specific sulfoalkylated resin recited in claim 8 does not make the process recited in claim 8 obvious 'unless the prior art suggested the desirability of [such a] modification' or replacement.") (citations omitted).

[C] Biotechnological Processes

With regard to patents directed to biotechnological processes, in 1995 Congress amended the patent laws to provide that "a biotechnological process using or resulting in a composition of matter that is novel . . . and nonobvious . . . shall be considered nonobvious if (A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and (B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person."[679] This provision is consistent with the case law discussed above that in determining the patentability of a process claim, the patentability of starting materials and end products may be considered.

§ 7:6 Nucleic Acid Patents*

Appendices at the end of the treatise contain a glossary of terminology (Appendix A) and a primer (Appendix B) on concepts useful for understanding nucleic acid based technologies.

§ 7:6.1 The Promise of Genomics

[A] First Recombinant DNA Organism

In 1973, Stanley Cohen and Herbert Boyer created the first recombinant DNA organism using recombinant DNA techniques pioneered a year earlier by Paul Berg.[680] Their success is widely credited as laying the foundation for the biotechnology industry. But science alone does not account for biotechnology's success. From its inception, patents played a big role in the industry's growth. Even today, the vast majority of biotechnology companies are small businesses with fifty or fewer employees.[681] In many cases, they have no marketed

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679. 35 U.S.C. § 103(b)(1)(A) & (B). Section 103(b)(2) further provides that the process patent also contain the claims to the composition of matter used in or made by the process or, if the composition of matter claims are contained in a different patent, the process patent and composition of matter patent be set to expire on the same date. *See* 35 U.S.C. § 103(b)(2)(A) & (B); *see also supra* section 5:3.1[B].

* Written by Patricia Carson.

680. A recombinant DNA organism is a non-naturally occurring organism created by modifying the organism's genetic information using techniques that allow combing DNA sequences from different sources and inserting the modified sequence into the organism in its first stage of development.

681. *See* Key Biotechnology Indicators at 1, Dec. 2011, http://www.oecd.org/science/inno/49303992.pdf.

products. These companies rely heavily on their intellectual property to entice investors to fund their research and discovery processes. In large part, that intellectual property involves the manipulation of nucleic acid sequences using recombinant techniques.[682]

[B] Cellular Factors for Making Proteins

The earliest patents aimed at the use of biological processes to make useful products were directed to cloned genes.[683] Inventors isolated genes that encoded proteins that might be useful for treating diseases. After cloning a gene, it can be introduced to host cells to create cellular factories that express the protein encoded by that gene.[684] Today, drug makers use host cells transformed with different cloned human genes to manufacture a variety of human therapeutics:

insulin for diabetes

factor VIII for hemophilia A

human growth hormone for treatment of dwarfism

erythropoietin for the treatment of anemia

granulocyte colony stimulating factor for stimulating white blood cell production

tissue plasminogen activator for dissolving blood clots

Patents for all of these genes have been obtained to protect the technology surrounding the recombinant production of these therapeutic proteins. These patents have been the subject of numerous patent litigations.

[C] Genetic Basis of Disease

Recombinant DNA technology and its applications have now gone far beyond the creation of cellular factories. The majority of human diseases originate in our genes. Every year, scientists discover new links between individual genes and specific diseases. Once these links have been discovered, scientists can develop a variety of diagnostic tests based on the gene. Carrier screening can help couples assess their risk for passing on inherited genetic disorders. Fetal testing can

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682. *See* Robert Cook-Deegan and Christopher Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. GENOMICS & HUMAN GENETICS 383, 395–96 (Sept. 22, 2010), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2935940/.

683. A cloned gene is an isolated copy of a gene.

684. *See infra* App. B:5.2[E].

detect abnormal or missing genes indicating potential birth defects. Predictive gene tests allow doctors to identify individuals at risk for particular diseases, identify telltale DNA changes in cancer or pre-cancer cells, provide for early detection of certain cancers, and assist in cancer prognosis. To date, predictive gene tests have been developed for a number of diseases including Tay-Sachs disease, cystic fibrosis, and certain types of breast cancer.

[D] Gene Therapy

Gene therapy is a cutting edge technology that uses genes or other nucleic acid sequences to treat diseases. For example, in a disease caused by a defective gene making a mutant protein, the genetic defect can be corrected by introducing a non-defective gene. This is referred to as "gene replacement" therapy. Non-hereditary genetic disorders can be treated through "transient gene" therapy. In transient gene therapy, genes encoding therapeutic proteins are temporarily introduced to the patient. The first commercial gene therapy product, Gendicine, delivers the P53 tumor suppressor gene and is used to treat squamous cell carcinoma of the head and neck.

[E] Our Expanding Knowledge of Genes

In October 1990, the Human Genome Project was formally initiated to identify all of the approximately 20,000–25,000 genes in human DNA and determine the sequences of the 3 billion chemical base pairs that make up human DNA. It was originally estimated that the effort would take fifteen years. Technological advances, however, allowed for completion of the sequence of the human genome in the Spring of 2003, two years ahead of schedule. Key among the technological advances was methodology developed in 1990 by J. Craig Venter. While working at the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH), Venter developed methods for finding ESTs.[685] ESTs represented a new strategy that revolutionized the process of gene discovery.

Increased knowledge of the human genome greatly advanced efforts to characterize the nature of gene variation in human populations. A major goal in human genetics is to understand the role of common genetic variants in susceptibility to common diseases. Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation. SNPs are stable mutations consisting of a change at a single base in a DNA molecule. These small genetic variations can point the way to genetic disease diagnosis and cures.

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685. An EST is a short nucleotide sequence generated from an expressed gene in an organism that represents a fragment of a cDNA clone, produced by reverse transcribing mRNA.

EST and SNP technology has contributed to the growing number of patents drawn to nucleic acid sequences. In 1992, the NIH rocked the scientific community by filing two patent applications claiming more than 4,000 human genes, based on Venter's EST strategy. This action by NIH is widely credited with precipitating a rush to patent incomplete gene sequences and the ensuing controversy regarding whether or not such sequences should be patented.

By 2002, more than three million gene-related patent applications were filed by academic, government, and corporate researchers.[686] Numerous patents to nucleic acids have been issued by the PTO. Several Federal Circuit decisions have addressed the patentability of various nucleic acid patents.[687]

Gene patents are not limited to human genes. Nucleic acids isolated from disease causing organisms allow for the development of valuable diagnostic tools for disease detection and prevention. The entire human immunodeficiency virus (HIV) genome has been sequenced and patented. This sequence information has provided the basis for better diagnostic tests and allowed physicians to track drug resistance mutations.

Gene patents are also key assets in agricultural biotechnology. In 2002, Japanese scientists reported finding the enzyme in onions that makes our eyes water.[688] The identity of the enzyme is the first step in isolating the gene and subsequent engineering of the plants to create tearless onions. Patented genes conferring insect resistance have been introduced to plants such as corn, soybeans, cotton and rice. These crop plants have also been genetically engineered to possess superior nutritional properties through the introduction of appropriate genes. Competitors holding patents in this field have been embroiled in frequent patent disputes over the course of a decade.

[F] Biotechnology Patents

Biotechnology patents come in a wide variety of types and have applications to all aspects of drug development and treatment. Types of biotech patents include claims directed to nucleic acid sequences, organisms with modified nucleic acid sequences, amino acid sequences, and various methods of making and using the foregoing, such as methods of purifying proteins, screening drugs, and treating patients. The table below provides a non-exhaustive list of types of biotech patents.

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686. Jeanne Andrea Di Grazio, *Patenting Human Genes*, BRYN MAWR S&T (Apr. 2002), http://www.brynmawr.edu/sandt/2002_april/.

687. *See infra* section 7:6.2.

688. S. Imai, *Plant Biochemistry: An Onion Enzyme that Makes the Eyes Water, in* NATURE 419, 685 (Oct. 2002).

Table 7-2

Some Types of Biotech Patents

nucleic acid sequences	isolated, naturally occurring nucleic acid sequences from an animal, plant, microorganism, or virus
	isolated and purified short fragments of naturally occurring nucleic acid sequences (known as expressed sequence tags or ESTs)
	modified or synthesized (that is, non-naturally occurring) nucleic acid sequences organisms that incorporate modified nucleic acid sequences
	methods of making or using any of the above
amino acid sequences	isolated proteins comprising a specified amino acid sequence

The following table provides a non-exhaustive list of applications for biotechnology patents.

Table 7-3

Some Applications of Biotechnology Patents

Drug Research, Development, and Manufacture	drug screening to identify potentially useful treatments
	animal mode (such as transgenic mice) for testing potential treatments
	biotechnology-based methods for making drugs
Treatment	diagnosis (for example, HIV nucleic acid probe for detecting HIV infection)
	drug therapy (for example, gene therapies, protein-based drugs)
	drug delivery

§ 7:6.2 Eligibility of Nucleic Acid Sequences for Patenting

Among the patent issues of particular importance in the area of biotechnology is the requirement that an invention be "new."[689] DNA,

689. This requirement is found in 35 U.S.C. § 101, which states that "Whoever invents or discovers any *new* and useful process, machine, manufacture, or composition of matter, or any *new* and useful improvement thereof,

ribonucleic acid (RNA), and the proteins they encode, all the subject of intense patenting efforts, were around long before humans and their patent systems. The PTO nevertheless has issued numerous patents to nucleic acids and amino acids.

[A] Product of Nature Exception to Patentability

The patent statute permits the patenting of "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[690] A true "product of nature" does not fall within these four categories, therefore products of nature are generally held unpatentable.[691] Until the Supreme Court issued its decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, it had not decided the patentability of natural DNA sequences.[691.1] Decisions addressing living organisms and purified chemicals (discussed below) had provided some guidance as to circumstances under which DNA sequences would no longer be considered a "product of nature." The Supreme Court, however, took up the issue in *Myriad* and ruled that isolated, naturally occurring DNA is not patent-eligible subject matter.[691.2]

[A][1] Patentability of Man-Made Living Organisms: Diamond v. Chakrabarty

In *Diamond v. Chakrabarty*,[692] one of the first cases involving biotechnology, the Supreme Court faced the question of whether a living thing was patentable. The Court reviewed the appellate court's determination that an applicant who claimed "a bacterium from the genus *Pseudomonas* containing therein at least two stable plasmids, each of said plasmids providing a separate hydrocarbon genetic pathway," was entitled to a patent. The invention consisted of a new strain of bacteria that was capable of degrading multiple elements of crude oil.[693] The bacteria had been altered by "genetic engineering" to gain this characteristic, and no naturally occurring bacteria possessed this

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may obtain a patent thereof, subject to the conditions and requirements of this title." (Emphasis added.) 35 U.S.C. § 102 more fully delineates what qualifies as new or novel.

690. 35 U.S.C. § 101.

691. M.P.E.P. § 706.03(a) (2006).

691.1. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

691.2. *Id.*; *see supra* section 3:8.2[B][2].

692. Diamond v. Chakrabarty, 447 U.S. 303 (1980).

693. *Id.* at 305.

property.[694] The bacteria was believed to be useful for dealing with oil spills.[695]

The patent examiner had allowed Chakrabarty's claims for the method of production of the bacteria, and claims for the means of using the bacteria in conjunction with a carrier.[696] However, the examiner rejected the claims for the bacteria itself because: (1) microorganisms are "products of nature," and (2) that as living things they are not patentable subject matter.[697]

The Court held that the living, human-made microorganism was patentable under section 101 of title 35 because it constituted a "manufacture" or "composition of matter."[698] Congress's inclusion of the word "any" in the statute convinced the Court "that the patent laws [should] be given wide scope."[699] The Committee reports accompanying the 1952 Act indicate that Congress intended patentable subject matter to include "anything under the sun that is made by man."[700] The Court acknowledged that not every discovery is patentable under section 101 of title 35, but Chakrabarty's invention was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character, [and] use.'"[701]

Though the Plant Patent Act had long afforded patent protection to certain types of both sexually and asexually reproduced plants, it had specifically excluded bacteria from protection.[702] The Court found that Congress did not make a distinction between living and inanimate things, but instead, consistent with the Court's own opinion, Congress had chosen to draw a line between "products of nature, whether living or not, and human made inventions."[703]

The Court rejected arguments that the statute was ambiguous with respect to patenting living organisms, and that microorganisms could not qualify as patentable subject matter without Congress's express authorization.[704]

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694. *Id*.
695. *Id*.
696. *Id*. at 306.
697. *Id*.
698. *Id*. at 309–10.
699. *Id*. at 308.
700. *Id*. at 309.
701. *Id*. at 309–10.
702. *Id*. at 310–11. An interesting exception because bacteria clearly are not plants.
703. *Id*. at 313.
704. *Id*. at 314.

Though petitioner and various amici tried to warn of the "grave risks that may be generated by [such] research endeavors," the Court was not swayed.[705] These briefs presented a "gruesome parade of horribles," including the spread of pollution and disease, the loss of genetic diversity, and a depreciation of the value of human life itself.[706] The Court explained that "the grant or denial of patents on micro-organisms is not likely to put an end to genetic research or to its attendant risks."[707] Whether these arguments were "fantasies generated by fear of the unknown," or genuine concerns, the Court held that the concerns would more properly be dealt with by the Executive and Legislative branches of the government.[708]

[A][2] Purified and Isolated (Prior to Myriad*)*

Although *Chakrabarty* settled the issue of patenting living things where the DNA of the organism had been altered by the inventor, it did not address the patentability of *natural* DNA sequences. *Chakrabarty*'s reasoning that "anything under the sun that is made by man" is patentable might appear to lead to the conclusion that natural DNA sequences could not be patented since they certainly exist in nature without any human action to create them. However, a long line of cases has given support to the argument that natural DNA sequences are patentable when they are purified and isolated.

[A][2][a] *Kuehmsted v. Farbenfabriken of Elberfeld*

In 1910, the Seventh Circuit in *Kuehmsted v. Farbenfabriken of Elberfeld*[709] was the first court to find that a substance previously known could be patented if it could be isolated into a pure and therapeutically useful product.[710] A researcher, Hoffmann, had obtained a patent on acetyl salicylic acid, or aspirin. In an infringement suit, defendants alleged that Hoffmann had merely obtained a more purified version of a product previously produced by Kraut.[711] The court found that the two substances had the same chemical formula, but found that Hoffmann's product was therapeutically distinct from the earlier versions.[712] The court explained:

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705. *Id*.
706. *Id*.
707. *Id*. at 317.
708. *Id*.
709. Kuehmsted v. Farbenfabriken of Elberfeld Co., 179 F. 701 (7th Cir. 1910).
710. *Id*. at 702.
711. *Id*. at 703.
712. *Id*. at 704.

> It was long known that salicylic acid was the best remedy for rheumatism . . . that when taken internally in a free state it was injurious to the stomachs of all patients . . . and that for a long time attempts were made to overcome this pernicious quality of salicylic acid and at the same time retain its beneficent effects, but without ultimate success until the discovery by Hoffmann of the resulting product of the patent in suit . . . Hoffmann has produced a medicine indisputably beneficial to mankind—something new in a useful art, such as our patent policy was intended to promote. Kraut and his contemporaries, on the other hand, had produced only, at best, a chemical compound in an impure state.[713]

Key to the court's view was that Hoffmann's version was "therapeutically available," while earlier versions were not.[714]

[A][2][b] *Merck & Co. v. Olin Mathieson*

The exception to the product of nature rule based on purity and therapeutic usefulness was refined in *Merck & Co v. Olin Mathieson*.[715] In *Merck*, the patentees claimed "vitamin B(12)-active compositions" derived from specified fermentates and used to treat pernicious anemia. This vitamin existed in minute quantities in nature, and the administration of the natural substance was far less effective than the patented substance.[716] As found in the natural fermentates, the substance had "no utility, therapeutically or commercially, until converted into compositions comparable to the accused products."[717]

Defendants objected that each step in a purification process is not a patentable advance, if the new product differs from the old one "merely in degree and not in kind."[718] The Fourth Circuit found that the compositions of the patent were patentable, as "they never existed before; there was nothing comparable to them. If we regard them as a purification of the active principle in natural fermentates, the natural fermentates are quite useless, while the patented compositions are of great medicinal and commercial value."[719] The new products were not the same as the old ones, but instead were new and useful compositions entitled to patent protection. Though the products were otherwise available in nature, their therapeutic usefulness in a purified state made them separately patentable.

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713. *Id*.
714. *Id*. at 705.
715. Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 160 (4th Cir. 1958).
716. *Id*. at 161.
717. *Id*.
718. *Id*. at 162.
719. *Id*. at 164.

In the biotechnology world, patent prosecutors seized upon the reasoning in *Kuehmsted* and *Merck*, and have used the language "purified and isolated" in claims to naturally occurring DNA to secure claims to DNA sequences.[720] While it is true that the DNA exists in nature without human intervention, a single gene, purified and isolated from surrounding DNA, and other nuclear and cellular components, only exists by the efforts of the inventor, and is therefore patentable.

[B] Cases Suggesting Natural DNA Sequences Not Patentable (Prior to *Myriad*)

In contrast to *Kuehmsted* and *Merck*, courts have sometimes denied patent claims to products found in nature even where the inventor was able to isolate the natural products, or use them in unique combinations, making them much more commercially useful.

[B][1] Funk Bros. v. Kalo

The Supreme Court, in *Funk Bros. v. Kalo*,[721] found invalid claims to certain combinations of isolated natural products.[722] The inventor conceived of a way to isolate and combine certain forms of a *Rhizobia* bacteria that could be used to assist certain leguminous plants in fixing nitrogen from the air.[723] It was well known that the bacteria had nitrogen-fixing properties, and that different species were effective with different varieties of plants. Therefore, a combination of species that could be used by farmers on all their plants was desired in order to make buying and storing easier for farmers and retailers. The problem was that the different species of bacteria produced an inhibitory effect upon one another when used in combination.[724] The patentee ascertained that there existed in nature particular strains of each individual species of bacteria that were non-inhibitive, and

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720. *See, e.g.*, Amgen Inc. v. Chugai Pharm. Co., 13 U.S.P.Q.2d (BNA) 1737, 1759 (D. Mass. 1989) (discussed in *infra* section 7:6.4[A]) ("The invention claimed . . . is not . . . the DNA sequence encoding human EPO since that is a nonpatentable natural phenomenon 'free to all men and reserved exclusively to none. . . . Rather the invention as claimed . . . is the 'purified and isolated DNA sequence encoding erythropoietin.'"), *aff'd in part, rev'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1991); *see also In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995) (claiming isolated and purified HBGF from bovine uterine tissue).
721. Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 128 (1948).
722. *Id*. at 128.
723. *Id*. at 129.
724. *Id*. at 129–30.

he used known techniques to isolate these non-inhibitive forms. He then combined them into a useful mixture.[725]

Despite the fact that the patentee isolated the non-inhibitive strains of the bacteria from a mixture of all strains of each species, much as the scientists in *Merck* isolated a purer version of vitamin B_{12}, the Court was unconvinced that the patentee had created anything new.[726] "The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men."[727] The court recognized that the patentee did more than discover a law of nature, as he made a new and different composition of the non-inhibitive strains that was commercially useful and economical.[728] However, this "fell short of invention within the meaning of the patent statutes," because it was merely the "discovery of [the bacteria's] qualities of non-inhibition."[729] The discovery of the bacteria's non-inhibitory qualities was "ingenious," and "may well have been an important commercial advance."[730] "But once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step."[731]

It might well be asked why the isolation of aspirin and vitamin B_{12} from impurities allows these natural substances to be patented, while strains of bacteria isolated from a combination of all strains are not patentable.[732] Perhaps the unspoken difference is that *Funk Bros.* involved living organisms while *Kuehmsted* and *Merck* involved chemicals. The Supreme Court may not have been willing to allow patents to bacteria or other non-plant living organisms until presented with the creation of new bacteria not found in nature in *Diamond v. Chakrabarty*[733] in 1980.

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725. *Id.* at 130.
726. *Id.*
727. *Id.* at 130.
728. *Id.* at 130–31.
729. *Id.* at 131.
730. *Id.*
731. *Id.* at 132.
732. It could be argued that the patentee in *Funk Bros.* had a stronger case for patentability than the inventors in *Kuehmsted* or *Merck* because he not only isolated the natural product, but he combined them in a unique way to create new mixtures not found in nature.
733. Diamond v. Chakrabarty, 447 U.S. 303 (1980).

[B][2] General Electric v. De Forest Radio Co.

Also presenting an interesting contrast to *Merck* is *General Electric v. De Forest Radio Co.*,[734] in which the Third Circuit found that an inventor could not claim a purified version of tungsten, even though tungsten had hitherto not been found in pure form in nature. The inventor, Coolidge, claimed "substantially pure tungsten having ductility and high tensile strength," which was useful in the creation of filaments for light bulbs.[735] Tungsten in nature was always found as tungsten oxide, a hard and brittle form that could not be drawn into wires. Coolidge's process produced pure tungsten, which contrary to common opinion turned out to be highly ductile and could easily be formed into wires.[736] In denying patentability, the court stated, "If it is a natural thing then clearly, even if Coolidge was the first to uncover it and bring it into view, he cannot have a patent for it because a patent cannot be awarded for a discovery or for a product of nature, or for a chemical element."[737] Since Coolidge did not give tungsten its ductile nature, but merely discovered characteristics given by nature, the court held that the patent was invalid.[738] It was acknowledged that Coolidge was "the first to discover that when pure it has characteristics . . . wholly different from the impure oxide of tungsten."[739] He was not entitled to a patent, however, because "[m]anifestly he did not create pure tungsten, nor did he create its characteristics. These were created by nature[.]"[740]

§ 7:6.3 Utility Requirement for Nucleic Acid Patents

In the 1990s, the discovery of new nucleic acid sequences outpaced the ability of science to identify their function. Researchers filed large numbers of patent applications claiming nucleic acids eager to protect the fruits of their EST and SNP research. In response, the PTO focused on the utility requirement as a potential check upon the patentability of these sequences. The PTO was concerned that

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734. Gen. Elec. Co. v. De Forest Radio Co., 28 F.2d 641, 643 (3d Cir. 1928). Since the Supreme Court in *Chakrabarty* seemed to follow the product of nature doctrine, this case has not been implicitly overruled but it is distinguishable on the facts. Coolidge did not produce a new product with different characteristics from any found in nature, but merely discovered a natural product possessing natural properties inherent in it.
735. *Id*. at 643.
736. *Id*. at 642–43.
737. *Id*. at 642.
738. *Id*. at 644.
739. *Id*. at 643.
740. *Id*.

claims to ESTs and SNPs might preclude later work by others to identify a function for these sequences. The PTO explained:

> A patent on a composition gives *exclusive* rights to the composition for a limited time, even if the inventor disclosed only a single use for the composition. Thus, a patent granted on an isolated and purified DNA composition confers the right to exclude others from *any* method of using that DNA composition, for up to 20 years from the filing date.[741]

There is a concern that a patent granted on a DNA fragment encoding a polypeptide of unknown function—and therefore of doubtful practical value—could interfere with the development of technology based on a full-length DNA sequence encoding a protein of known function if the full-length sequence contained the patented fragment.

Section 101 of title 35 of the U.S. Code requires that an invention be useful to be patentable.[742] In general, the law for pharmaceuticals compositions requires an applicant to have evidence of pharmacological activity for new compounds to satisfy the utility requirement.[743] The evidence need not be of *in vivo* human pharmacological activity as long as the *in vitro* or *in vivo* animal data of pharmacological activity has a reasonable correlation with human *in vivo* activity.

As a general matter, the Federal Circuit has applied the patent jurisprudence relating to chemical compounds to nucleic acid sequences.[744] The PTO has done likewise.[745]

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741. Utility Examination Guidelines ("2001 Utility Guidelines"), 66 Fed. Reg. 1092, 1095 (Jan. 5, 2001) (emphasis in original).

742. See *supra* chapter 3 for an explanation.

743. *In re* Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995); *see also* Fujikawa v. Wattanasin, 93 F.3d 1559, 1564 (Fed. Cir. 1996) ("In the pharmaceutical arts, . . . practical utility may be shown by adequate evidence of pharmacological activity.").

744. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it."); Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229 (Fed. Cir. 1994) ("DNA encoding a human protein [is] a chemical compound."). *See also* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 925 (Fed. Cir. 2004) (with respect to written description requirement of 35 U.S.C. § 112, the distinction between genetic and non-genetic materials is "irrelevant; the statute applies to all types of inventions").

745. In response to comments regarding its 2001 Utility Guidelines, the PTO stated that, "[l]ike other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or synthesized in a laboratory from chemical starting materials." 66 Fed.

[A] PTO Board of Patent Appeals Decisions

The Patent and Trademark Office Board of Patent Appeals and Interferences (the "Board") has issued few opinions discussing the application of the utility requirement to nucleic acid sequences. Many of these cases have close parallels to the chemistry cases that find no utility where the compound being claimed has no known useful properties, or is an intermediate to a chemical that has no known useful properties.[746] In general, they evidence an increasing willingness to declare patents invalid for lack of utility, perhaps as a reaction to a perception that there is an overabundance of questionable patents.

In a relatively early decision, *Ex parte Maizel*,[747] the Board raised concern regarding a claim to a DNA sequence encoding a protein because its biological function was unknown at the time of filing. The claims on appeal were directed to a DNA sequence encoding the B-cell growth factor (BCGF). Although the examiner had not issued a rejection based on lack of utility, the Board *sua sponte* raised the issue because "[a]ppellant's specification clearly states that as of its filing date, the actual function of BCGF protein was unknown."[748] Thus, the Board stated that "[s]hould this application be prosecuted further we urge the examiner to specifically consider whether or not the application complies with the utility requirements."[749]

In *Lee v. Barr*,[750] the Board found that Lee and other assignors to Genentech, Inc. had failed to establish a "practical utility" for an interference count directed to "a DNA construct comprising a

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Reg. 1092, 1093. In addition, the PTO stated that "Patents for genes are treated the same as for other chemicals," and that "Patent law provides no basis for treating DNA differently from other chemical compounds that are compositions of matter." *Id*. at 1094, 1095.

746. *See, e.g.*, Brenner v. Manson, 383 U.S. 519 (1966); *In re* Kirk, 376 F.2d 936 (C.C.P.A. 1967); *In re* Joly, 376 F.2d 906 (C.C.P.A. 1967).

747. *Ex parte* Maizel, 27 U.S.P.Q.2d (BNA) 1662 (B.P.A.I. 1992).

748. *Id*. at 1668.

749. *See also Ex parte* Deuel, 27 U.S.P.Q.2d (BNA) 1360, 1365 (B.P.A.I. 1993) ("Because there is no statement of use in the specification, no description in the specification regarding how to use the claimed growth factor, and no exemplification of a use, it would appear that the growth factors claimed herein may lack practical utility and may be unpatentable under §§ 101 and 112 of our patent code."); *Ex parte* Anderson, 30 U.S.P.Q.2d (BNA) 1866, 1870 (B.P.A.I. 1993) (suggesting lack of utility rejection if application is further prosecuted because "the specification does not describe how to use the claim[ed] compounds 'in vivo' and does not exemplify or otherwise describe successful utilization of the proteins prepared from the claimed DNAs.").

750. Lee v. Barr, 1994 Pat. App. LEXIS 12 (B.P.A.I. July 19, 1994).

sequence coding for human insulin-like growth factor-I (IGF-I)."[751] Noting that the intended use of IGF-I was therapeutic, the Board was not persuaded that positive results in either a radioimmunoassay (RIA) or a radioreceptor assay (RRA) established biological activity. The Board based its conclusion on the testimonies of one of the inventors as well as defendant's expert witnesses indicating that because the RIA is an *in vitro* assay, it is not a measure of biological or pharmacological activity.[752] Similarly, the RRA, which measures the binding of a protein to a receptor *in vitro*, does not demonstrate *in vivo* biological activity.[753] The Board also rejected Lee's argument that the IGF-I fusion protein was useful as a secondary reference standard for the RIA and RRA assays, because such utility was "not disclosed in the application or contemplated by the inventors."[754]

In *Ex parte Lindstrom*,[755] the Board *sua sponte* entered a new ground of rejection based on lack of utility under sections 101 and 112 for a claim to a DNA sequence encoding a subunit of a protein.[756] The Board noted that the specification merely stated that "the present invention provides critical groundwork for practical applications and future studies of neuronal 4BgtBPs."[757] Citing *Brenner*, the Board found that usefulness for "future studies" does not satisfy the requirement for a specific utility.[758]

[B] The PTO's Utility Examination Guidelines and Training Materials

In 2001, the PTO issued revised "Utility Examination Guidelines" (2001 Utility Guidelines). The Guidelines covers the review of patent applications for compliance with the utility requirement.[759]

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751. *Id*.
752. *Id*. at 14.
753. *Id*. at 21–22.
754. *Id*. at 19. In the initial litigation relating to this interference, neither the district court pursuant to 35 U.S.C. § 146, nor the Federal Circuit on appeal, reached the utility issue. Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 499 (Fed. Cir. 1997). Subsequently, Genentech submitted new evidence of a correlation between positive RRA test results and biological activity. However, on appeal of a district court decision in Genentech's favor, the Federal Circuit reversed because the recognition of practical utility was not made by the inventors, but rather by a consultant. Genentech, Inc. v. Chiron Corp., 220 F.3d 1345 (Fed. Cir. 2000).
755. *Ex parte* Lindstrom, 1994 WL 1709508 (B.P.A.I. Sept. 28, 1994).
756. *Id*. at *1.
757. *Id*. at *3.
758. *Id*.
759. 66 Fed. Reg. 1092 (Jan. 5, 2001).

The 2001 Utility Guidelines superseded the PTO's prior guidelines issued in 1995[760] and 1999.[761] Many commentators agree that the 2001 Utility Guidelines seek to impose a substantive limitation on an applicant's ability to patent nucleic acid sequences, and, more particularly, ESTs.[762]

[B][1] The 1995 Utility Guidelines

The 1995 Utility Guidelines, which were superseded in 2001, provided that the utility requirement could be met if the invention had either a "well-established" utility or a showing of a "specific" utility that was "credible." An invention had a "well-established utility if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (for example, properties of a product or obvious application of a process)."[763] An invention also met the utility requirement "[i]f the applicant has asserted that the claimed invention is useful for any particular purpose (*i.e.*, a 'specific utility') and that assertion would be considered credible by a person of ordinary skill in the art . . . ."[764] This fairly low standard for utility was criticized as being inconsistent with the case law in not requiring a showing that the asserted utility was "substantial" or "practical."[765]

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760. 60 Fed. Reg. 36,263 (July 14, 1995).
761. 64 Fed. Reg. 71,440 (Dec. 21, 1999).
762. *See, e.g.*, Leslie G. Restaino, *Patenting DNA-Related Inventions in the European Union, United States and Japan*, 2003 UCLA J.L. & TECH. 2 (2003) ("Under the new Guidelines, . . . a mere assertion of the utility of an EST as a probe without further disclosure of its specific function is considered not enough by USPTO to satisfy the utility and enablement requirement."); Lawrence T. Kass & Michael N. Nitabach, *A Roadmap for Biotechnology Patents?*, 30 AIPLA Q.J. 233, 261 (2002) ("Thus, under the PTO's understanding of the 'specific and substantial utility' requirement, patent claims will only be granted to the first person who demonstrates some understanding of the function of the gene or encoded protein."); Timothy A. Worrall, *The 2001 Utility Examination Guidelines and DNA Patents*, 16 BERKELEY TECH. L.J. 123, 135 ("The 2001 Utility Guidelines may limit claims to DNA compositions having only speculative utility.").
763. 60 Fed. Reg. 36,263–64 (July 14, 1995).
764. *Id.*
765. *See, e.g.*, Mary Smith, *Comment: An End to Gene Patents?*, 73 U. COLO. L. REV. 747, 768 (2002) ("By analogy, under *Brenner*, EST sequences having no use other than as a research tool to find the full-length gene, itself of unproven utility, would not have utility either. Despite *Brenner's* holding, under the 1995 Guidelines ESTs would be patentable.").

[B][2] The 1999 Revised Utility Guidelines

In 1997, the PTO announced that it would begin allowing patents on ESTs based on their utility as probes.[766] In 1998, the first EST patent issued.[767] Subsequently, the PTO was confronted by a wave of applications directed to ESTs.[768]

In 1999, the PTO issued the Revised Utility Guidelines. The 1999 Revised Utility Guidelines were in direct response to public comments expressing concern regarding the patentability of ESTs. In particular, the PTO stated that it had received comments that the 1995 Utility Guidelines would permit the patenting of ESTs "when the sole disclosed use of an EST is to identify other nucleic acids whose utility was not known, and the function of the corresponding gene is not known."[769] The 1999 Revised Utility Guidelines also responded to comments that "PTO examination procedures would result in granting patents based on nonspecific and nonsubstantial utilities, contrary to established case law."[770] Accordingly, the 1999 Revised Utility Guidelines provided that a "claimed invention must have a specific and substantial utility."[771] The 1999 Revised Utility Guidelines retained the provisions of the 1995 Utility Guidelines with respect to "credibility" and "well-established" utility.

[B][3] The 2001 Utility Guidelines

In January 2001, the PTO issued another version of the Utility Guidelines.[772] The 2001 Utility Guidelines represented a substantial change from the 1995 version. In particular, the 2001 Utility Guidelines provide that "[a]n invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (2) the utility is specific, substantial, and credible."[773] The 2001 Utility Guidelines instruct patent examiners that "[i]f at any time during the

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766. Ed Susman, *U.S. PTO to Allow Patents on Gene Fragments Called ESTs*, BIOTECH. NEWSWATCH, 1997 WL 8790500 (Mar. 3, 1997).
767. U.S. Patent No. 5,817,479, "Human Kinase Homologs," issued on October 6, 1998, to Incyte Pharmaceuticals, Inc.
768. *See* Eliot Marshall, *The Patent Office Faces a 90-Year Backlog*, 272 SCI. 643 (1996) (PTO official projected that "it could take a single senior staffer more than 90 years to examine the DNA sequences already in the queue").
769. 64 Fed. Reg. 71,441.
770. *Id*.
771. *Id*.
772. 66 Fed. Reg. 1092.
773. 66 Fed. Reg. 1098.

examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility."[774]

The 2001 Utility Guidelines provide that "[a] claimed invention must have a specific and substantial utility. This requirement excludes 'throw-away,' 'insubstantial,' or 'non-specific' utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. § 101."[775]

> The 2001 Utility Guidelines also state that
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> [c]redibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.[776]

[B][4] The Utility Guidelines Training Materials

In 2000, the PTO issued the Revised Interim Utility Guidelines Training Materials (Training Materials) to provide patent examiners with guidance in assessing whether the utility requirement of section 101 is met.[777] The Training Materials provide that: (1) "[f]or method claims that recite more than one utility, if at least one utility is credible, specific, and substantial, a rejection under 35 U.S.C. § 101 should not be made," and (2) "[f]or product claims that do not recite any utilities, disclosure or assertion of one specific, substantial and credible utility meets the criteria of 35 U.S.C. § 101."[778] The Training Materials also provide definitions for the terms "credible," "specific," and "substantial" utilities.

[B][4][a] "Specific" Utility

A "specific" utility is a "utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention." According to the Training Materials, "a claim to a polynucleotide whose use is disclosed simply as a 'gene probe' or 'chromosome marker' would not be considered to be *specific* in the absence of a disclosure of a specific DNA target."[779]

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774. *Id*.
775. *Id*.
776. *Id*.
777. Training Materials, *supra* note 631.
778. *Id*. at 3–4.
779. *Id*. at 5.

In addition, a "general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed."[780]

[B][4][b] "Substantial" Utility

A "substantial" utility "defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities."[781] Thus, if the claimed invention is merely useful for further research, or a method for making (or an intermediate for making) a final product that has no known specific, substantial utility, the asserted utility is not substantial.[782] The Training Materials list the following as examples that do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition.

C. A method of assaying for or identifying a material that itself has no "specific and/or substantial utility."

D. A method of making a material that itself has no specific, substantial and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

[B][4][c] "Credible" Utility

The "credibility" of an asserted utility is measured by "whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided."[783] An assertion of utility is "credible" unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion."[784] The Training Materials provide "perpetual motion machines" as an example of a claimed invention that would lack credibility while the credibility of the use of nucleic acids as probes, chromosome markers, or forensic or diagnostic markers "would not be questioned."[785]

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780. *Id.* at 5–6.
781. *Id.* at 6.
782. *Id.*
783. *Id.* at 5.
784. *Id.*
785. *Id.*

[B][4][d] "Well-Established" Utility

A well-established utility is "a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art."[786]

[B][5] The Nucleic Acid Examples of the Training Materials

The Training Materials provide two examples examining satisfaction of the utility requirement by claims to DNA sequences.

[B][5][a] "DNA Fragments"

The first example, Example 9, entitled "DNA Fragments," is directed to a specification that discloses DNA fragments that are stated to be useful as probes to obtain the full-length genes that correspond to the sequences. However, "no use is disclosed for any of the putative proteins other than the possibility of using them to identify and study the cellular mechanisms and activities in which the proteins are involved."[787] The Training Materials conclude that the claimed invention does not have a "well-established" utility, noting that there is no art that points to the activity of the cDNA or proteins that can be obtained using the cDNA. The claimed invention also lacks "specific" and "substantial" utility based on the lack of knowledge regarding the full length gene. In particular, the Training Materials state that there is no "specific" utility because the only asserted utility—the use of the sequence as a probe—"is not particular to the sequence being claimed because it would be applicable to the general class of cDNAs. Any partial nucleic acid prepared from any cDNA may be used to [*sic*] as a probe in the preparation and or identification of a full-length cDNA."[788] Moreover, there is no "substantial" utility because where "the only utility asserted for the protein is for identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved" the invention does not define a "real world" use.[789]

Notwithstanding Example 9 of the Training Materials, in response to comments regarding the 2001 Utility Guidelines, the PTO stated that "ESTs which meet the criteria for utility, novelty, and nonobviousness are eligible for patenting when the application teaches

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786. *Id*. at 7.
787. *Id*. at 50.
788. *Id*. at 51.
789. *Id*. at 51–52.

those of skill in the art how to make and use the invention."[790] For example, the PTO stated that "[a]n isolated and purified DNA molecule may meet the statutory utility requirement if, *e.g.*, it can be used to produce a useful protein or it hybridizes near and serves as a marker for a disease gene."[791]

[B][5][b] "DNA Fragment Encoding a Full Open Reading Frame (ORF)"

The second example, Example 10, is entitled "DNA Fragment Encoding a Full Open Reading Frame (ORF)." In this example, the specification discloses a nucleic acid sequence that has a high degree of homology to a DNA ligase.[792] In addition, the sequence encodes an amino acid sequence that has 95% similarity to the consensus sequence of the known DNA ligases and there is a high level of sequence conservation among DNA ligases. Moreover, the PTO's prior art search reveals that the next highest level of homology is 50%. Under these facts, the PTO concluded that a "well-established" utility is shown: "Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that [the claimed sequence] encodes a DNA ligase" and "DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA."[793]

Example 10 is consistent with the position taken by the PTO in its response to comments regarding the 2001 Utility Guidelines. There the PTO stated that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion."[794] Moreover, the PTO stated that "[w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein."[795] Finally, the PTO cautioned that there "is no *per*

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790. 66 Fed. Reg. 1094.
791. *Id*.
792. DNA ligase is an enzyme that can link together DNA strands that have double-strand breaks by forming new chemical bonds.
793. Training Materials, *supra* note 631, at 54.
794. 66 Fed. Reg. 1096.
795. *Id*.

se rule regarding homology, and each application must be judged on its own merits."[796]

[C] Expressed Sequence Tags and Single Nucleotide Polymorphs

One type of DNA fragment that has received considerable attention is ESTs. Clearly, ESTs were behind the changes to the 2001 Utility Guidelines.[797] The Federal Circuit has made clear that when the EST codes for part of a gene whose function is unknown, the claim to the EST does not meet the utility requirement and should be rejected by the PTO.[798]

The applicant in *In re Fisher* tried to claim five ESTs that encode part of certain proteins in maize plants.[799] When Fisher filed the patent application, he "did not know the precise structure or function of either the genes or the proteins encoded for by those genes."[800] The application listed seven uses of the claimed ESTs in an attempt to satisfy the utility requirement.[801] The Federal Circuit found that "none of Fisher's seven asserted uses meets the utility requirement of § 101."[802] An "application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research," and "must disclose a use which is not so vague as to be meaningless."[803]

ESTs coding parts of proteins with unknown function are merely "objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end."[804] The court noted that Fisher had not actually used them for any of these

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796. *Id*.
797. *In re* Fisher, 421 F.3d 1365, 1372 (Fed. Cir. 2005) (noting that Example 9 of the 2001 Utility Guidelines is applicable to ESTs).
798. *Id*. at 1378.
799. *Id*. at 1367.
800. *Id*. at 1368.
801. The seven disclosed uses are: (1) serving as a molecular marker for mapping the entire maize genome, which consists of ten chromosomes that collectively encompass roughly 50,000 genes; (2) measuring the level of mRNA in a tissue sample via microarray technology to provide information about gene expression; (3) providing a source for primers for use in the polymerase chain reaction (PCR) process to enable rapid and inexpensive duplication of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *Id*. at 1368.
802. *Id*. at 1370.
803. *Id*. at 1371.
804. *Id*. at 1373.

uses in the real world.[805] Fisher's invention thus lacks "substantial" utility.[806] Fisher's invention also lacks a "specific" utility because "[a]ny EST transcribed from any gene in the maize genome has the potential to perform any one of the alleged uses," and "nothing about Fisher's seven alleged uses set the five claimed ESTs apart from . . . any EST derived from any organism."[807]

§ 7:6.4 Written Description of Nucleic Acids

Section 112, paragraph 1 of the Patent Act sets forth three distinct disclosure requirements of a valid invention:

> The specification shall contain a *written description* of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the *best mode* contemplated by the inventor of carrying out his invention.[808]

For rapidly changing technologies, courts must apply these written description, enablement, and best mode disclosure requirements to strike an effective balance between encouraging competition and rewarding inventions.[809]

A heated debate continues to simmer at the Federal Circuit. All on the court as of this writing agree that section 112, paragraph 1 requires inventors to make disclosures to the public as part of the *quid pro quo* for receiving patent protection. The Federal Circuit also has made clear that the three statutory disclosure requirements are separate and distinct, each independently reporting different aspects of the invention that further the dualistic goals of the patent

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805. *Id*. at 1374.
806. *Id*.
807. *Id*. The court was careful to stress that "[t]he claimed ESTs themselves are not an end of Fisher's research effort, but only tools to be used along the way in the search for a practical utility." *Id*. This distinguishes Fisher's claims from claims for research tools such as the PCR reaction, which are the end product of the invention, even though they are tools that allow further research.
808. 35 U.S.C. § 112, ¶ 1 (emphasis added). See *supra* sections 5:4 to 5:6 for a further explanation of these requirements.
809. *See* Markman v. Westview Instruments, Inc., 517 U.S. 370, 390 (1996) ("The limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others and the assurance that the subject of the patent will be dedicated ultimately to the public.").

system.[810] Opinions differ, however, on whether the enablement requirement or a robust written description requirement best determines adequate disclosure.

[A] Satisfying the Written Description Requirement

In cases involving nucleic acid sequences, the Federal Circuit has applied the patent jurisprudence relating to chemical compounds.[811] Normally, chemical compounds can be distinguished from one another based on differences in atomic composition and structure.[812] The principal distinguishing characteristic of one DNA segment over another is its nucleotide sequence. The Federal Circuit established in two early cases that adequate written description of a novel DNA segment generally requires disclosure of its nucleic acid sequence.

[A][1] Amgen, Inc. v. Chugai Pharmaceutical Co.

The Federal Circuit first established the importance of an isolated nucleotide sequence in fulfilling the disclosure requirements of section 112, paragraph 1 in *Amgen, Inc. v. Chugai Pharmaceutical Co.*[813] Amgen owned a patent that claimed a purified and isolated DNA sequence encoding the human erythropoietin (EPO) gene. Defendant Chugai alleged that another inventor had conceived the strategy that was ultimately found by the district court to result "in the successful identification and isolation of the EPO gene."[814] Chugai further argued that the inventor was diligent in reducing the invention to practice, and therefore, he should be considered a prior

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810. The Federal Circuit reaffirmed and explained through example that 35 U.S.C. § 112, requires a "written description of the invention" that is separate and distinct from the enablement requirement. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991). A specification that discusses only compound *A* can still enable one skilled in the art to make and use compounds *B* and *C*. However, the class consisting of *A, B*, and *C* has not been described. *Id*. at 1561–62 (citing *In re* DiLeone, 436 F.2d 1404, 1405 n.1 (C.C.P.A. 1971); *see also In re* Ahlbrecht, 435 F.2d 908, 911 (C.C.P.A. 1971) (finding that although disclosure of parent application may have enabled production of claimed esters having 2-12 methylene groups, it only described esters having 3-12 methylene groups).

811. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.").

812. *See, e.g.*, *In re* Dillon, 919 F.2d 688, 702 (Fed. Cir. 1990).

813. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991).

814. *Id*. at 1205.

inventor over Amgen under section 102(g) of the Patent Act. The Federal Circuit disagreed with Chugai's argument and held that conception of a DNA sequence, which an inventor is unable to describe with specificity sufficient to distinguish it from other materials, is not achieved prior to reduction to practice. According to the court, conception may be properly claimed once the isolation of the gene (that is, reduction to practice) has occurred. The court stated that conception is not achieved without the precondition of reduction to practice in these circumstances, because an inventor may have difficulty envisioning the composition of a gene to sufficiently distinguish it from other such materials.[815]

The district court invalidated a claim covering a "potentially enormous" number of EPO analogs for lack of enablement.[816] The Federal Circuit held that the claims were not enabled, not because of the number of EPO analogs, but because of the lack of enablement of the underlying *DNA sequences* that were the subject of the claim.[817] According to the Federal Circuit,

> it is not necessary that a patent applicant test all the embodiments of this invention; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, that means disclosing *how to make and use enough sequences to justify grant of the claims sought*. Amgen has not done that here.[818]

The court held that since Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs, Amgen has failed to disclose sufficient sequence information to enable a person of ordinary skill in the art to practice the claimed invention.[819] Although *Amgen* did not deal with the written description requirement as described below, it created the conceptual framework for

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815. *Id*. at 1206. The alleged prior inventor's "conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. . . . Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene." *Id*. at 1207.
816. *Id*. at 1213. The district court determined that the specification could not support the number of analogs within the scope of the claims because their individual biological properties could not be known without undue experimentation. *See id*.
817. *Id*.
818. *Id*. (citation omitted) (emphasis added).
819. *Id*. at 1204.

later written description cases concerning nucleotide sequence disclosure.

[A][2] Fiers v. Revel

In *Fiers v. Revel*,[820] the Federal Circuit held that an application covering DNA, which did not disclose the nucleotide sequence of that DNA, did not satisfy the written description requirement by merely reciting a general strategy for isolating DNA.[821] The court stated that

> [a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself.[822]

The *Fiers* court used the reasoning of *Amgen*, in which conception was at issue, and expanded it to demand the same high degree of specificity for compliance with the written description requirement:

> As we stated in *Amgen* and reaffirmed above, such a disclosure just represents a wish, or arguably a plan, for obtaining the DNA. If a conception of a DNA requires a *precise definition, such as by structure, formula, chemical name, or physical properties*, as we have held, then a description also requires that degree of specificity.[823]

The Federal Circuit added that "[c]laiming all DNA's that achieve a result without defining what means will do so is not in compliance with the written description requirement; it is an attempt to preempt the future before it has arrived."[824] Thus, after *Fiers*, it is clear that adequate written description, and possession of a novel DNA segment, at least under the current state of technology, requires disclosure of its nucleotide sequence or, as explained below, a deposit of the DNA segment in an acceptable depository for biological material.

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820. Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993).
821. *Id*. at 1171.
822. *Id*. at 1170.
823. *Id*. (emphasis added).
824. *Id*.

[B] Heightened Written Description Requirement for Biotechnology and DNA Sequence Patents?

[B][1] Regents of University of California v. Eli Lilly & Co.

In *Regents of University of California v. Eli Lilly & Co.*,[825] the Federal Circuit affirmed the district court's judgment after a bench trial that claims asserted against Lilly were invalid for lack of adequate written description. The University of California owned a patent that disclosed cDNA sequences for proinsulin and preproinsulin in rats, and general methods that might be used to obtain the human DNA sequence.[826]

In invalidating claims that generically recite cDNAs encoding vertebrate insulin, the *Lilly* panel relied on its conclusion in *Fiers* that only the exact sequence can provide an adequate written description of a claimed piece of DNA.[827] The court explained that because the patent merely described the function of the cDNA, but conveyed no distinguishing information about its identity, such as relevant structural or physical characteristics, one skilled in the art could not "visualize or recognize" the genus members.[828] Furthermore, it concluded that the description requirement could be satisfied for the genus claim by recitation of (a) a representative number of cDNAs (nucleotide sequences), or (b) "structural features common to the members of the genus."[829]

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825. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).

826. *Id*. at 1563.

827. *Id*. at 1566 (citing *Fiers*, 984 F.2d at 1171) ("An adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention."). Significantly, *Lilly* deviated from the traditionally restricted view of the application of the written description requirement as articulated in *Vas-Cath*. *See supra* note 810. In Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991), Judge Rich wrote that the written description requirement only "comes into play" in three circumstances: (1) examination of new claims not contained in the original application; (2) when a patentee seeks the benefit of a filing date under 35 U.S.C. §§ 119 or 120; and (3) in the interference context where priority is disputed between parties. *Vas-Cath*, 935 F.2d at 1560.

828. *Lilly*, 119 F.3d at 1568 ("A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. . . . It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result.").

829. *Id*. at 1569.

Lilly, according to some, articulated a heightened standard in biotechnology inventions drawn to genes. Patents that claimed genes or functional DNA segments without disclosing the claimed nucleotide sequence were now vulnerable to invalidity challenges. Even patents that disclosed specific sequences but broadly claimed generic subject matter were at risk after *Lilly*. Inventors, too, were left with few options for repairing deficient applications while still retaining the benefit of an early priority date.[830]

[B][2] Enzo Biochem, Inc. v. Gen-Probe, Inc. (Enzo I)

The Federal Circuit momentarily extended the reach of *Lilly* in *Enzo Biochem, Inc. v. Gen-Probe, Inc. (Enzo I)*.[831] Affirming summary judgment, the court held that reference in the specification to deposits in public depositories of nucleic acid probes whose sequences were not disclosed in the specification, but which possessed a known functionality, may not satisfy the written description requirement for claims directed to the probes.[832]

The claims at issue in *Enzo I* were drawn to nucleic acid probes that were specific for bacteria that cause gonorrhea. The patent described the binding affinity of claimed sequences, and deposited three probes that met the claim limitations.[833] According to the court, this disclosure was "purely functional" because the hybridization conditions did not identify the sequences but merely described what they do.[834] Also, the functional description failed to meet the written description guidelines promulgated by the PTO,[835] even though these Guidelines, like the MPEP, are not binding on the court in the first place.[836] The court acknowledged that these inventors, unlike those in *Lilly*, had achieved more than "a mere wish or a plan for obtaining the claimed invention."[837] But in this case, the absence of sequence information could not be cured by public deposit.[838]

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830. *See* 35 U.S.C. §§ 102, 120.
831. Enzo Biochem, Inc. v. Gen-Probe, Inc., 285 F.3d 1013 (Fed. Cir.) (*Enzo I*), *vacated*, 323 F.3d 956 (Fed. Cir. 2002) (*Enzo II*).
832. *Enzo I*, 285 F.3d at 1020.
833. *Id*.
834. *Id*. at 1018.
835. Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001) [hereinafter WD Guidelines].
836. *Enzo I*, 285 F.3d at 1019; *see also* Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10 (Fed. Cir. 1995) (noting that the MPEP is not binding on this court but is "entitled to judicial notice as an official interpretation of statutes or regulations as long as it is not in conflict therewith").
837. *Enzo I*, 285 F.3d at 1018 (quoting *Lilly*, 119 F.3d at 1566).
838. *Enzo I*, 285 F.3d at 1021.

Judge Dyk's dissenting opinion focused squarely on *Lilly*. He stated that *Lilly* "is open to serious question" since it imposes a "unique written description requirement in the field of biotechnology" and departs from the general rule of "possession" of the invention.[839] In addition, he suggested that reference to a deposit "is an ideal way of satisfying the written description requirement."[840] Indeed, the many PTO regulations governing biological deposits contemplate satisfaction of the written description requirement, and in deciding otherwise, the majority opinion imposes new restrictions that are inconsistent with the statutory and regulatory scheme.[841]

[B][3] Enzo Biochem, Inc. v. Gen-Probe, Inc. (Enzo II)

Perhaps in response to the outcry of the biotech community, in *Enzo Biochem, Inc. v. Gen-Probe, Inc.* (*Enzo II*),[842] the same three judge panel reconsidered *Enzo I*, and vacated its earlier decision. Taking judicial notice of the PTO's Written Description Guidelines, the panel reversed course and placed greater emphasis on the fact that, in some cases, a functional description of genetic material can satisfy the written description requirement:

> [T]he PTO has determined that the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'[843]

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839. *Id*. at 1025 (dissenting opinion).
840. *Id*. at 1027 ("The primary purpose of the statutory written description requirement is to provide notice to competitors and the public of the scope of the patent claims.").
841. *Id*. at 1028–29.
842. Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956 (Fed. Cir. 2002) (*Enzo II*).
843. *Id*. at 964 (citing WD Guidelines, *supra* note 835) (emphasis in original). In general, the WD Guidelines are consistent with Federal Circuit case law, as they require an applicant "permit a person skilled in the art to clearly recognize [the] applicant had possession of the claimed invention." 66 Fed. Reg. 1105. With respect to nucleotide sequences, however, the Guidelines did not fully embrace the heightened written description requirement as it was first established in *Lilly*. Perhaps presaging the Federal Circuit's more permissive conclusion in *Enzo II*, the Guidelines assert that multiple identifying properties short of an actual sequence, including functional characteristics, may be sufficient to show possession of an invention. *See* 66 Fed. Reg. 1110, n.42 (listing relevant identifying characteristics for biomolecules, including sequence, structure, binding

Applying these principles to *Enzo II*, the court remanded to the district court to determine whether one skilled in the art would find enough in the specification to "demonstrate possession of the generic scope of the claims" by the inventors.[844] The remand order also instructed the district court to consider whether one skilled in the art would consider the claimed subject matter to be adequately described, recognizing the significance of the deposits and the scope of the claims.[845]

The court adhered to its "possession plus" analysis from *Enzo I*. Enzo argued that because it reduced three sequences within the scope of the claims to practice, it had shown "possession" of the claimed invention sufficient to meet the requirements of section 112, paragraph 1. The court disagreed, stating that possession is merely "ancillary to the statutory mandate," and without more renders disclosure insufficient.[846]

The *Enzo II* court also reversed the decision in *Enzo I* refusing to consider a biological deposit referenced in the specification as part of the written description. It held that "reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1."[847]

Although the Federal Circuit granted a rehearing, the court rejected a petition to rehear the appeal en banc.[848] Dissenting from this denial, Judge Rader argued that outside the context of resolving priority, no statute or precedent supports an independent written description requirement.[849] Now *Enzo II*, like *Lilly* before it,

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affinity, binding specificity, molecular weight, length, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, and antibody cross-reactivity]; *accord Enzo II*, 323 F.3d at 964.

844. *Id*. at 966.

845. *Id*. at 967.

846. *Id*. at 969.

847. *Enzo II*, 323 F.3d 965.

848. *Id*. at 970.

849. *Id*. at 978 (dissenting opinion) ("'The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him.' In sum, WD was a new matter doctrine, a priority policeman.") (citing *In re* Wertheim, 541 F.2d 257, 262 (C.C.P.A. 1976)) (emphasis added in opinion). Based on the historical genesis of the written description requirement, Judge Rader concluded that the requirement's sole purpose served the "very clear function [of] preventing new matter from creeping into the claim amendments." *Id*. Judge Linn's dissenting opinion raised similar arguments. *Id*. at 987.

"depart[s] from decades of established case law,"[850] and creates a "new free-standing disclosure requirement" that replaces enablement.[851] As a result, *Lilly*'s new rule requires "a far more demanding disclosure," while simultaneously "jeopardizing a sizeable percentage of claims filed before" *Lilly*.[852] Thus, the court's written description jurisprudence improperly encroaches on the territory of enablement, which is better suited for measuring the adequacy of a disclosure, among other functions.[853] Judge Lourie's concurring opinion rejected this criticism, observing that "[n]ew interpretations of old statutes in light of new fact situations occur all the time."[854] According to the opinion, a robust written description requirement will guarantee that in exchange for a monopoly to practice an invention, a patentee will declare both what the invention is *and* how to make and use it.[855]

[B][4] Amgen, Inc. v. Hoechst Marion Roussel, Inc.

In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*,[856] the Federal Circuit had yet another opportunity to revisit *Lilly*. Amgen alleged that Transkaryotic Therapies (TKT) infringed claims of five patents covering EPO, a hormone that stimulates red blood cell formation in mammals.[857] Asserted claims were drawn to methods of expressing EPO in vertebrate and mammalian cells, but the specification disclosed expression only in monkey and hamster cells.[858] TKT, relying on *Enzo II* and *Lilly*, argued that these generic claims lacked an adequate written description.[859] The district court disagreed, and the

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850. *Id*. at 983.
851. *Id*. at 980.
852. *Id*. at 982–83. Unanswered by the majority opinion is Judge Rader's reliance on Supreme Court cautionary statements "against the disruption of the settled expectations of the inventing community." *Id*. at 982. Ironically, Judge Rader cited Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002), to support this proposition. There are likely many applicants across diverse technological arts who would like a second chance to respond to office actions and draft claim amendments in the wake of the Festo cases. Indeed, Judge Rader even suggested as much in his recent concurrence in that same case on remand to the Federal Circuit. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 344 F.3d 1359, 1376 (Fed. Cir. 2003).
853. *Enzo II*, 323 F.3d at 982.
854. *Id*. at 971.
855. *Id*. at 971–72, 974–75. Judge Newman labeled description as the "foundation of the patent specification."
856. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003).
857. *Id*. at 1319.
858. *Id*. at 1338.
859. *Id*.

Federal Circuit affirmed its finding that the challenged claims were valid.[860]

The Federal Circuit distinguished *Enzo II* and *Lilly*, concluding that "the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend."[861] The court applied a written description rule that requires one of ordinary skill in the art "to recognize" that the inventor invented what is claimed.[862] In the opinion of the court, "the words 'mammalian' and 'vertebrate' readily convey distinguishing information concerning their identity such that one of ordinary skill in the art could visualize or recognize the identity of those members of the genus."[863]

Even though the court did not apply *Lilly* or *Enzo II* in this case, it acknowledged that the written description requirement can be subject to a higher standard than enablement.[864] The court traced the evolution of its jurisprudence limiting and clarifying the original holding in *Lilly*:

> We held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself—not merely a recitation of its function or a reference to a potential method for isolating it.[865] [citation omitted]
>
> More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.[866] [citation omitted]
>
> Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of

860. *Id*. at 1319.
861. *Id*. at 1332. The court concluded that TKT's *Lilly* argument could only apply to host cells for EPO expression, because EPO itself would have been well known to one of skill in the art.
862. *Id*. at 1330.
863. *Id*. at 1332 (quoting *Lilly*, 119 F.3d at 1568).
864. *See Amgen*, 314 F.3d at 1334 ("The enablement requirement is often more indulgent than the written description requirement."). Disapproving of the district court's refusal to apply the principles of *Lilly*, Judge Clevenger would have required the district court to reconsider whether the disclosure sufficiently described the broad genus claimed. *Id*. at 1360.
865. *Id*. at 1332 (citing *Lilly*, 119 F.3d at 1566–67).
866. *Amgen*, 314 F.3d at 1332 (citing *Enzo Biochem*, 296 F.3d at 1324).

> cells that can be used to produce recombinant human EPO. [The patent sequence for the EPO gene]. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell-not the human DNA itself.[867]

[B][5] University of Rochester v. G.D. Searle & Co.

The Federal Circuit's decision in *University of Rochester v. G.D. Searle & Co.*[868] demonstrated the court's willingness to invalidate claims even if there was evidence that the inventors possessed the idea embodied by the claims.[869] The University of Rochester patent is directed to a method of selectively inhibiting the enzyme COX-2 by administering a non-steroidal compound that selectively inhibits its activity of the COX-2 gene product.[870] On the date of issue, the University of Rochester sued several pharmaceutical companies (collectively, "Pfizer") for patent infringement based on Pfizer's sale of non-steroidal COX-2 inhibitor drugs.[871] Pfizer moved for summary judgment of invalidity on the grounds that, inter alia, the patent failed to meet the written description requirement of section 112, paragraph 1 of title 35. The district court found the claims to be invalid

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867. *Id*.

868. Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir.), *reh'g denied by and reh'g en banc denied by* 375 F.3d 1303 (Fed. Cir. 2004).

869. Prior to *Univ. of Rochester*, the Federal Circuit revisited the law of written description in Moba B.V. v. Diamond Automation Inc., 325 F.3d 1306 (Fed. Cir. 2003). Instead of expounding upon the written description requirement in the context of nucleic acid sequences, the court resolved the issue in the context of high-speed egg processing machines. In *Moba*, declaratory judgment plaintiff Moba alleged that the specification failed to adequately describe a claimed mechanism for lifting eggs. Although *Moba* concerned the mechanical arts, the court still considered *Lilly* in its analysis. The court stated that two applications of 35 U.S.C. § 112, ¶ 1 are cognizable. First, the written description requirement polices priority by preventing applicants from adding new matter to the claims. *Moba*, 325 F.3d at 1319–20. Second, outside of a priority dispute, the written description requirement mandates sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing. *Id*. at 1320. The second application, as envisioned by *Moba*, was previously outlined in *Lilly*. The Federal Circuit in *Moba* rejected a heightened written description standard since *Lilly* did not mandate any "particular form of disclosure." *Id*. at 1321. Thus, the written description requirement is satisfied under the court's reasoning in *Moba* if one skilled in the art "would discern possession of the invention at the time of filing." *Id*.

870. *Univ. of Rochester*, 358 F.3d at 918.

871. *Id*. at 919. Pfizer markets two anti-inflammatory agents that are COX-2 inhibitors: Celebrex® and Bextra®.

for lack of an adequate written description, concluding that the patent did not disclose a specific compound, and provided no guidance on how to make or obtain any compound that fell within the scope of the patent's claims beyond trial-and-error research.[872]

On appeal, the University of Rochester argued the district court erroneously held that a claim drawn to a method of obtaining a biological effect in a human by administering a compound cannot, as a matter of law, satisfy the written description requirement without disclosing the identity of any such compound.[873] The Federal Circuit disagreed, and stated that an adequate written description requirement would "describe the claimed invention so that one skilled in the art can recognize what is claimed."[874] Generalized language may be inadequate if it fails to convey the detailed identity of an invention. The court stated that "[r]egardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."[875]

The Federal Circuit's analysis in *University of Rochester* acknowledged the often significant overlap between the written description, enablement and best mode requirements set forth in section 112, paragraph 1. In this context, the court also pointed out that the written description requirement applies to original claims and, as it did in *Enzo II*, rejected the University's attempt to limit the written description requirement to the priority context. The court confirmed that the statute requires meaningful disclosure to the public in exchange for exclusive rights to practicing the invention.[876]

The court rejected the University of Rochester's argument that the *Lilly* written description standard should be limited to inventions claiming genetic material or to composition of matter claims to biotechnology inventions.[877] The court made clear that its decisions in *Fiers*, *Lilly*, and *Enzo II* differed only with respect to the subject matter of the claims and not the rule for compliance with the written

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872. *Id*.
873. *Id*. at 920.
874. *Id*. at 922–23.
875. *Id*. at 926.
876. *Id*. at 922.
877. *Id*. at 925 ("[35 U.S.C. § 112 ¶ 1] applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue."); *but cf. Hoechst*, 314 F.3d at 1332 (suggesting that the more demanding written description requirement of *Lilly* may be restricted to "new or unknown *biological* materials").

description requirement. The Federal Circuit explained that the "patent specification [must] set forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed."[878]

The Federal Circuit again denied a petition for rehearing *en banc*,[879] although the members of the court agreed that the "bourgeoning conflict in pronouncements" must eventually be resolved.[880] But in the view of Judge Dyk, "this is neither the right time, nor the right case" in which to resolve the difficult issued surrounding the court's current written description jurisprudence.[881]

[C] Practical Implications of the Federal Circuit's Written Description Jurisprudence

The final disposition of *University of Rochester* at the Federal Circuit is indicative of the lack of consensus on the written description requirement.[882] Voting for rehearing, Judges Rader, Linn and Gajarsa indicated they would no longer interpret section 112, paragraph 1 to require a separate "written description" that is more than an "enablement" requirement.[883] Judge Newman, however, supported the concept of a separate written description requirement, but voted for rehearing the case to clarify the law.[884] In explaining his vote to deny rehearing, Judge Lourie contended that the court's precedent was "clear and consistent and necessitates no revision of written description law."[885]

Lilly's reputation as a biotechnology patent killer may be misplaced. If *Lilly* indeed imposes a heightened written description standard, it should have rendered biotechnology patents as a group more vulnerable to invalidity attacks. Widespread invalidation, however, does not appear to have taken place.[886] Furthermore, patents in arts

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878. *Univ. of Rochester*, 358 F.3d at 928.
879. Univ. of Rochester v. G.D. Searle & Co., 375 F.3d 1303, 1304 (Fed. Cir. 2004).
880. *Id*. at 1304 (dissenting opinion).
881. *Id*. at 1327 (concurring opinion).
882. *Univ. of Rochester*, 375 F.3d 1303.
883. *Id*. at 1307 (Linn, J., dissenting, with whom Judges Rader and Gajarsa concur). *Id*. at 1308 (Rader, J., dissenting, with whom Judges Linn and Gajarsa concur).
884. *Id*. at 1304.
885. *Id*. at 1307.
886. An absence of widespread invalidation does not reveal the impact on business decisions on whether to license or for how much, decisions not to assert patents, or decisions to settle because of uncertainties regarding potential claim validity.

other than biotechnology have not been spared from written description challenges.[887] If enablement is a lower standard, one would also expect to see biotechnology patents surviving enablement challenges more frequently than written description challenges. Again, no clear evidence supports this expectation.

In fact, biotech patents are not immune from enablement attacks. In *Plant Genetic Systems v. DeKalb Genetics Corp.*,[888] the Federal Circuit affirmed an invalidity judgment for asserted claims of a patent owned by Plant Genetic Systems. The claims were directed to cells and plants that had been genetically modified for resistance to herbicides that kill weeds. The specification disclosed modification of dicot plants, but did not disclose a working example using monocot plants.[889] Claims, however, embraced both classes. In holding these claims invalid for lack of enablement because they failed to teach modification of monocots, the district court rejected the patent holder's position that its status of "pioneer" entitled it to a lower standard of enablement.[890]

In another decision involving the written description requirement as applied to nucleic acid sequences, the Federal Circuit upheld rejection of pending claims drawn to nucleic acids encoding a protein whose amino acid sequence was only partially disclosed.[891] Armed with the amino acid sequence of a protein, the court agreed that an inventor could claim all nucleic acid sequences that could give rise to that sequence.[892] Without the complete amino acid sequence, however, an inventor "had no more than a wish to know the identity of the DNA encoding" the protein.[893] The court rejected the applicant's

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887. *See, e.g.*, PIN/NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235 (Fed. Cir. 2002) (composition for inhibiting tubers); TurboCare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co., 264 F.3d 1111 (Fed. Cir. 2001) (shaft ceiling system for fluid turbine); Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473 (Fed. Cir. 1998) (sectional sofa); Tronzo v. Biomet, Inc., 156 F.3d 1154 (Fed. Cir. 1998) (artificial hip sockets); *but see* Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352 (Fed. Cir. 2003) (expandable stent); Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc., 291 F.3d 1317 (Fed. Cir. 2002) (sub-sea wellheads); Union Oil Co. of Cal. v. Atl. Richfield Co., 208 F.3d 989 (Fed. Cir. 2000) (gasoline composition).

888. Plant Genetic Sys. v. DeKalb Genetics Corp., 315 F.3d 1335 (Fed. Cir. 2003).

889. *Id*. at 1338.

890. *Id*. at 1339.

891. *In re* Wallach, 378 F.3d 1330, 1335–36 (Fed. Cir. 2004).

892. *Id*. at 1334. The court acknowledged that "the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it." *Id*. at 1333.

893. *Id*. at 1335.

Enzo II-styled argument that a functional description can satisfy the written description requirement in some cases, and reaffirmed its conclusion that any functional description must be "coupled with a known or disclosed correlation between function and structure."[894]

The Federal Circuit is uniquely tasked as the final arbiter of interpreting the patent statutes to strike the best balance between countervailing goals of encouraging innovation and competition, except in those rare cases where the Supreme Court entertains a patent issue. Inventors must be adequately protected to ensure continued risk-taking and investment in new ideas. Relaxed enablement and written description disclosure rules can lead to overly broad patent claims, which are believed to stifle competition, and reduce incentives for firms to try to design around or improve existing inventions. On the other hand, unreasonably strict disclosure rules can also suffocate innovation and discourage prompt disclosure, since inventors will wait to gather as much data as possible for their applications, depriving the public of potentially groundbreaking advances or life-saving breakthroughs.

Much of the outcry about written description case law is due to a perception that the Federal Circuit's standards are far from certain. In some self-critical moments, the court has acknowledged the chaotic situation resulting from its shifting standards. When announced, rule changes that followed from these landmark rulings had the effect of instantly invalidating already issued claims for lack of adequate disclosure. Should this pattern continue, interested parties will have a difficult time determining which patents are likely to withstand future scrutiny over their full term.

§ 7:6.5 Other Grounds for Invalidity of Nucleic Acid Inventions

In addition to the case law on written description set forth in the preceding section, a number of cases involve issues concerning the potential invalidation of nucleic acid-related inventions based on anticipation, obviousness, indefiniteness, best mode, and enablement. Several cases also address inventorship and conception of nucleic acid inventions.

[A] Anticipation

In *Novo Nordisk Pharmaceuticals, Inc. v. Bio-Technology General Corp.*,[895] a case involving pituitary-derived HGH, prior art anticipated

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894. *Id*. (citing WD Guidelines, 66 Fed. Reg. 1106).

895. Novo Nordisk Pharm., Inc. v. Bio-Tech. Gen. Corp., 424 F.3d 1347 (Fed. Cir. 2005).

a claim covering "a 191-amino acid sequence identical to that of pituitary-derived HGH and that the protein have the full biological activity of pituitary-derived HGH."[896] The prior art disclosed the protein sequence based on the DNA found by the authors and indicated that it "appears identical in all respects to the major form of pituitary HGH" and reported test results specifying that their protein "had the same structure and chemical properties as pituitary-derived HGH."[897]

In *Enzo Biochem, Inc. v. Gen-Probe, Inc.*,[898] the Federal Circuit has also affirmed the invalidation of claims relating to DNA probes for gonorrhea based on prior sale because the "polynucleotide probe is a tangible item or product that can be sold or offered for sale,"[899] and a prior provision in an agreement "could not be considered to be only a research and development provision relating to an undeveloped process."[900] On the other hand, the Federal Circuit has held that the secret use of recombinant "cells internally to develop future products that were never sold, without more, is insufficient to create a public use bar to patentability."[901]

In *In re Gleave*, the Federal Circuit affirmed the Board's rejection of claims to a "bispecific antisense oligodeoxynucleotide . . . complementary to" the human genes for IGFBP-2 and IGFBP-5 "of sufficient length to act as an antisense inhibitor" of these proteins as anticipated.[901.1] It rejected applicants' argument that the prior art reference was deficient on the grounds that it did not demonstrate antisense activity because the "composition claims do not require antisense activity either."[901.2]

[B] Obviousness

[B][1] Amino Acid Sequences

Claims directed at amino acid sequences where the prior art discloses a similar sequence that varies only by individual amino acid components that are structurally similar can be invalid as obvious. For instance, the disclosure of Phe-Pro-Ile rendered Phe-Pro-Leu sequence prima facie obvious because "[t]he structure of Leu and Ile

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896. *Id*. at 1355.
897. *Id*.
898. Enzo Biochem, Inc. v. Gen-Probe, Inc., 424 F.3d 1276 (Fed. Cir. 2005).
899. *Id*. at 1282.
900. *Id*.
901. Invitrogen Corp. v. Biocrest Mfg., L.P., 424 F.3d 1374, 1383 (Fed. Cir. 2005).
901.1. *In re* Gleave, 560 F.3d 1331, 1333 (Fed. Cir. 2009).
901.2. *Id*. at 1336.

alone suggest their functional equivalency."[902] A claim to a "method for producing a predetermined protein . . . in a transformed host species of bacteria" was rendered obvious by a reference teaching a method for producing ribosomal RNA (not a protein) in a transformed bacteria because the reference "explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins."[903]

[B][2] Nucleic Acid Sequences

[B][2][a] Post-*KSR*

After *KSR*, the Federal Circuit held that claims to a specified nucleic acid sequence were invalid over a prior reference disclosing the protein encoded by that sequence, a monoclonal antibody specific to that protein and "a five-step protocol for cloning nucleic acid molecules encoding" this protein using the antibody.[903.1] The court explained that "[t]he record shows the well-known and reliable nature of the cloning and sequencing techniques in the prior art, not to mention the readily knowable and obtainable structure of an identified protein."[903.2]

[B][2][b] Pre-*KSR*

Prior to *KSR*, claims to DNA sequences were not necessarily rendered obvious when prior art discloses the amino acid sequence expressed by the DNA and general methods for isolating DNA sequences. For instance, claims to nucleic acid molecules coding for a type of insulin were found not obvious over "general method for isolating genes," because the claims were aimed at compositions, "and the issue is the obviousness of the claimed compositions, not of the method by which they are made."[904] Disclosed amino acid sequences expressed by the claimed nucleic acids also did not render the claims obvious because "of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein."[905]

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902. *In re* Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997).
903. *In re* O'Farrell, 853 F.2d 894, 901 (Fed. Cir. 1988).
903.1. *In re* Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009); *cf. In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995) (holding (pre-*KSR*) that DNA encoding HBGFs not rendered obvious by partial amino acid sequence for HBGF).
903.2. *Id*.
904. *In re* Bell, 991 F.2d 781, 785 (Fed. Cir. 1993).
905. *Id*.

Similarly, DNA encoding heparin-binding growth factors (HBGFs) was not rendered obvious by partial amino acid sequence for HBGF because "the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequence coding for the protein."[906] Reaffirming the standard set in *In re Bell*,[907] the court held that a known general method for obtaining DNA sequence using the partial amino acid sequence did not render the claims obvious because "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed cDNAs."[908]

The Board has reversed an obviousness rejection because "[n]o reasons have been given . . . which would have motivated the artisan . . . to prepare a 'modified' form of the interferons of the prior art by recombinant DNA technology, the isolated natural proteins of the [prior] references being limited to those structures and properties as found."[910] The Board noted, "variations in the number of amino acids in natural leukocyte interferons clearly cannot be the basis for a holding of obviousness of those at tissue, they being neither taught nor suggested by the references, nor present in their systems."[911]

[C] Indefiniteness

The Federal Circuit acknowledged that a "claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants."[912] The court, however, concluded that with only a partial amino acid sequence "the chemical structure of all nucleic acid molecules that can serve the function of encoding that sequence . . . cannot be determined and the written description requirement is consequently not met."[913]

[D] Enablement

Claims to genetic antisense technology were found not enabled based on the level of skill in the art and on findings "that the claims

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906. *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995).
907. *In re Bell*, 991 F.2d 781.
908. *Deuel*, 51 F.3d at 1559.
909. [Reserved.]
910. *Ex parte* Goeddel, 5 U.S.P.Q.2d (BNA) 1449 (B.P.A.I. 1987).
911. *Id*.
912. *In re* Wallach, 378 F.3d 1330, 1334 (Fed. Cir. 2004).
913. *Id*. at 1335.

at issue were quite broad, that the antisense technology was highly unpredictable, that the quantity of experimentation necessary to practice antisense in cells other than *E. coli* was quite high, . . ." and "that the specification provided virtually no disclosure of the practice of antisense in cells other than *E. coli*."[914] Similarly, a claim to a method of producing HGH by expressing and then "cleaving [a] conjugate protein" was not enabled by the disclosure of the "DNA encoding HGH" and "cleavable fusion expression techniques," because the specification did "not describe in any detail whatsoever how to" practice its claimed method of "mak[ing] HGH using cleavable fusion expression" which was a novel aspect of the invention.[915]

Claims to a yeast DNA sequence encoding for a mature heterologous protein and process for obtaining the mature protein were not enabled by a "single successful demonstration of producing and secreting a mature heterologous protein," where it was "unpredictable that constructs in which the heterologous gene is inserted in positions other than that demonstrated by the working examples of the present specification would, in fact, result in secretion of a mature protein as required by the claims on appeal."[916]

The Board has found a claim to amino acid sequence for interferon enabled despite the patentee's failure to deposit the sequence because "it is clearly not the only way by which [enablement] can be accomplished."[917] However, there was no enablement where the "specification fail[ed] to provide those having ordinary skill . . . assurance, as by adequate representative examples, that vectors and yeast transformants falling within the scope of the appealed claims can be prepared and used."[918]

[E] Best Mode

In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,[919] the Federal Circuit analyzed the best mode requirement for "genetically-engineered biological subject matter."[920] The court concluded that when "the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying

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914. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1377 (Fed. Cir. 1999).
915. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365–66 (Fed. Cir. 1997).
916. *Ex parte* Singh, 17 U.S.P.Q.2d (BNA) 1714, 1715 (B.P.A.I. 1990).
917. *Ex parte* Goeddel, 5 U.S.P.Q.2d (BNA) 1449, 1450 (B.P.A.I. 1987).
918. *Ex parte* Hitzeman, 9 U.S.P.Q.2d (BNA) 1821, 1823 (B.P.A.I. 1988).
919. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991).
920. *Id*. at 1210.

out the invention, not deposit of the cells."[921] According to the court, "when the *best mode* of preparing the cells has been disclosed and the best mode cells have been enabled, *i.e.*, they can be prepared by one skilled in the art from known materials using the description in the specification,"[922] there is no need to deposit biological materials to comply with the best mode requirement.

[F] Inventorship and Conception

The Federal Circuit found that a claim to a particle having a specified sedimentation rate produced from recombinantly transformed yeast cells was not conceived without demonstration that a would-be inventor "had a definite and permanent understanding that the yeast would produce the 22 nm particles."[923] In an interference proceeding involving claims to a DNA coding for human fibroblast beta-interferon, the Federal Circuit rejected an argument that the existence of a workable method for preparing a DNA establishes conception of that material because, "irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility."[924]

In *Amgen, Inc. v. Chugai Pharmaceutical Co.*, the Federal Circuit rejected an argument that conception can be established by knowledge of "its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property."[925] The court held "that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated."[926]

§ 7:6.6 Claim Construction of Nucleic Acid Claims

The following examples serve to illustrate some of the claim construction issues that arise in claims involving nucleic acids.

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921. *Id*. at 1211.
922. *Id*.
923. Hitzeman v. Rutter, 243 F.3d 1345 (Fed. Cir. 2001).
924. Fiers v. Revel, 984 F.3d 1164, 1169 (Fed. Cir. 1993); *see* Sanofi-Aventis v. Pfizer Inc., 733 F.3d 1364, 1366, 1369 (Fed. Cir. 2013) (distinguishing *Fiers* because Pfizer had actual "possession of the isolated DNA segment that was shown to have the desired properties" despite the fact that it had incorrectly sequenced eight out of 1143 nucleotides).
925. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991).
926. *Id*.

Genzyme Corp. v. Transkaryotic Therapies, Inc.[927]

Specification: The word integrated "does not conclusively evince whether one of skill . . . would understand the exogenous sequences to come from outside the host cell, *i.e.*, a vector, or from within the host cell but outside the critical chromosome, *i.e.*, a transposable element. . . . Throughout the '804 patent specification, the applicant consistently uses the term 'integrated' to refer to a foreign gene inserted into a host cell chromosome."[928]

Claim: "A mammalian cell comprising a chromosomally integrated nucleotide sequence encoding human α-galactosidase A"[929]

Construction: "Chromosomally integrated" means combining separate elements, "specifically the 'chromosome of a host cell' and 'an exogenous nucleotide sequence encoding human α-galactosidase A with a promoter and selectable marker.'"[930]

Biogen, Inc. v. Berlex Laboratories, Inc.[931]

Specification: "This application relates to human interferons and their production in Chinese hamster ovary (CHO) cells and therapeutic formulations including the human interferon so produced."[932]

"[A]ny approach may be used to introduce the cloned DNA into CHO cells and to select and grow the transformed cells for expression of the protein."[933]

Nevertheless, the court found that the "specification describes only linked DNA sequences and transformation procedures using single constructs linking human interferon and dihydrofolate reductase marker genes to transfect [CHO] cells."[934]

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927. Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094 (Fed. Cir. 2003).
928. *Id.* at 1098–99.
929. *Id.* at 1096.
930. *Id.* at 1097.
931. Biogen, Inc. v. Berlex Labs., Inc., 318 F.3d 1132 (Fed. Cir. 2003).
932. *Id.* at 1135.
933. *Id.*
934. *Id.* at 1136–37.

Claim: "A method for the production of human interferon in a [CHO] cell, comprising growing" such a cell "having incorporated therein a DNA construction comprising human α- or α-interferon gene . . . ."[935]

Construction: "[T]he specification defines the invention as the use of a single DNA construct to introduce the linked human interferon gene and selectable marker gene into the host [CHO] cell, and that the . . . claims are so limited."[936]

Regents of University of California v. Dako North America, Inc.[937]

Specification: The specification defines "heterogeneous mixture" as a mixture of labeled nucleic acid fragments "compris[ing] many copies each of fragments having different base compositions and/or sizes,"[938] not just unique sequence fragments.

Dependent claims explicitly limit the "heterogeneous mixture" to mixtures that include "repetitive sequences." Dependent claims would be rendered meaningless were the "heterogeneous mixture" construed to exclude repetitive sequences. Such a result is improper.

Claim: "A method of staining target interphase chromosomal DNA to detect an extra or missing portion or portions of a chromosome, or a translocation or an inversion of a portion or portions of a chromosome, the method comprising: (a) providing a heterogeneous mixture of labeled unique sequence nucleic acid fragments which are substantially complementary to nucleic acid segments within the interphase chromosomal DNA for which detection is desired . . . ."[939]

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935. *Id.* at 1134.
936. *Id.* at 1140.
937. Regents of Univ. of Cal. v. Dako N. Am., Inc., 2006 WL 1867618 (N.D. Cal. July 5, 2006).
938. *Id.* at *4.
939. *Id.* at *5.

Construction: The court previously construed "heterogeneous mixture" to include repetitive as well as unique fragments. Based on excerpts from the prosecution history however, the court modified "its construction of the phrase 'heterogeneous mixture of labeled unique sequence nucleic acid fragments' to mean 'a heterogeneous mixture of labeled nucleic acid fragments that includes only unique sequence fragments.'"[940]

§ 7:7 Antibodies*

§ 7:7.1 What Is an Antibody?

[A] Introduction

Antibodies, also known as immunoglobulins, provide the body's immune system with the means to recognize and remove foreign substances.[941] Antibodies bind to portions of the foreign substances, such as bacteria or viruses, that enter the body. A protein or other substance to which an antibody will bind is called an antigen. The specific site on the antigen to which the antibody binds is called an epitope.

Antibodies are Y-shaped proteins encoded by genes expressed in B-cells of the immune system. There are five types of antibodies: IgA, IgD, IgE, IgG, and IgM. The "Ig" stands for immunoglobulin. The IgG antibody is the most common type comprising 70% to 75% of the total immunoglobulin in human serum. IgM, which develops early in the immune response, is about 10%. Each type of antibody also has subtypes.

An antibody's basic structure is a Y-shaped protein formed from two "heavy-chains" and two "light chains." The IgG type antibody consists of a single Y-shaped protein. The IgM type antibody consists of five separate Y-shaped proteins joined by a "J-Chain" protein. Diagnostic and therapeutic products most commonly use IgG-type antibodies.

Near the two arms of the antibody's "Y" shape is a region called the "variable region." It is here that the antibody specifically binds to

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940. *Id.* at *7.

* Written by Richard G. Greco and Sylvia M. Becker.

941. See *infra* Appendices A and B for a glossary of terms and further discussion of antibody technology. This section is drawn from several sources which provide useful scientific overviews of antibodies and the immune system. *See, e.g.*, IVAN M. ROITT, JONATHAN BROSTOFF & DAVID K. MALE, IMMUNOLOGY 5.2–5.3 (2d ed. 1989).

an epitope on an antigen. An IgG antibody, which consists of a single "Y" shape, has two identical binding sites, while an IgM antibody, which contains five conjoined "Y" shapes, has ten identical binding sites. The stem of an antibody's "Y" shape is called the "constant region." The constant region on some antibody types permits the immune system to recognize an antigen bound by the antibody and initiate clearance or destruction of the antigen.

Antibodies play a variety of roles in the immune system. One important role played by some antibodies is binding to a foreign infectious pathogen, like a bacterium or virus, to allow killer cells like phagocytes to attach to the constant region of the antibody, engulf it, and destroy the invading pathogen. Antibodies can also bind to a particular epitope of an antigen to prevent the antigen from interacting with other cells, and thus neutralize the antigen's harmful biological activity.

B-cells make antibodies. Each individual B-cell makes copies of only one specific antibody. Antibodies produced from a particular B-cell have exquisite precision in binding to a particular epitope. The body has billions of B-cells that are capable of making antibodies of different specificity. When an antigen invades the body, an antibody that fits an exposed epitope on the invading antigen will bind to it. This initial antibody binding to a target antigen signals the body to produce many more copies, or clones, of the B-cells that produced the antibody that scored the original hit. At the same time, other B-cells producing other antibodies that bind to different epitopes on the same antigen will rapidly reproduce so that the immune system can have a large number of antibodies attacking different parts of the same antigen.[942] This natural antibody response is called "polyclonal" because the antibodies that bind the infecting antigen are produced by many different B-cells resulting in a polyclonal mixture of many different antibodies.

[B] Monoclonal Antibodies

Georges Kohler and Cesar Milstein pioneered a revolution in antibody technology by publishing their method to make large amounts of the same antibody.[943] The Nobel Prize–winning Kohler-Milstein

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942. If the same bacteria infect the host in the future, a larger number of B-cells producing the required specific antibody will be available resulting in a much faster response to and suppression of the re-infection than was possible before the buildup of the correct types of B-cells. This is the concept behind vaccination.

943. G. Kohler & C. Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495, 495–97 (1975).

method enabled scientists to make an unlimited supply of antibodies, known as monoclonal antibodies, with identical specificity for a particular antigen because they are all made from copies of the same original single B-cell.

The general method involves several steps. The target antigen for the desired antibody is injected into a mouse, rabbit, or other animal. The animal's immune system naturally generates a large antibody response to the injected antigen, if it is foreign, thereby multiplying greatly the number of B-cells making antibodies that bind the antigen. The B-cells are highly concentrated in the spleen. After allowing for sufficient time to develop the response, researchers remove the spleen and harvest the B-cells. Because the immune response was generated in response to the injected antigen, there will be a higher percentage of the desired antibody B-cells in the spleen compared to other B-cells that target the injected antigen.

Although normal B-cells will not survive long in a culture, cancer cell lines are essentially immortal and can be grown in large quantities for extended periods. The Kohler-Milstein method fuses the B-cells from the spleen with cancer cells. The resulting fused cell, called a "hybridoma," combines the immortal features of the cancer cell with the antibody production from the B-cell.

After fusing the spleen B-cells with cancer cells, researchers screen the surviving cells against the target antigen to find hybridomas that produce antibodies to the target. Then they isolate cells producing antibodies that bind to the target antigen and grow them by a variety of methods to produce a culture of hybridoma cells. Each hybridoma cell within a clone secretes exactly the same antibody, referred to as a monoclonal antibody. Further screening isolates antibodies that bind to a particular region or epitope on the antigen, or that bind with desired binding affinities.

The Kohler-Milstein method made it possible for the first time to generate a supply of specific antibodies with uniform binding traits because each antibody is made from a single original B-cell. Antibody-manufacturing technology moved beyond the Kohler-Milstein method by using recombinant DNA to modify cells producing antibodies. As a result, it became possible to make "chimeric" and "humanized" antibodies. Chimeric antibodies join material from two species. A chimeric antibody usually contains the binding region from a mouse or other animal, and the constant region, located on the stem of the "Y" shape, from a human. Humanized antibodies combine only the actual binding sites, located on the tips of the arms of the "Y" shape, from a non-human species into a human antibody.

Chimeric and humanized antibodies, when used in therapeutic applications, have the advantage of reducing the amount of immune response generated when antibodies from a non-human species, like

a mouse, are used in a human. This response is referred to, in the case of a murine antibody, as the Human Anti-Mouse Antibody (HAMA) response. A HAMA response occurs when the human immune system recognizes the mouse antibody as a foreign invader and thus generates its own antibodies against the invading foreign antibody. Avoiding this immune response is desirable for therapeutic applications of antibodies in humans. Human constant regions are also needed in some applications to trigger other parts of the human immune response once the antibody binds to its target.

Techniques have now been developed for producing fully human antibodies made entirely with genetic engineering techniques.[944] One technique is called "phage display." The genes encoding antibodies are inserted into bacterial viruses called "phage." These phage infect a culture of bacteria, which will then express the encoded antibody on their surface. Any antibody on the surface of bacteria that binds to a selected antigen can be isolated. This technique permits the manufacture of fully human antibodies. Transgenic technology has provided another technique for making fully human antibodies. Transgenic mice have been developed that, when challenged with an antigen, produce human antibodies to the antigen. Genetic engineering has also made it possible for the genes encoding any antibody of interest to be placed in an expression system to mass produce that antibody.

[C] Commercial Applications for Antibodies

Antibodies have many medical and scientific uses. They can be labeled with radioactive molecules or other chemicals and then used to detect the presence of the specific antigens to which they bind.

Many diagnostic products are now available that use monoclonal antibodies to detect the presence of a particular antigen. Home pregnancy tests make use of labeled antibodies to a protein that is produced in early pregnancy stages. Other tests exist for detection of infectious diseases, such as hepatitis and HIV, employing labeled monoclonal antibodies specific to the infectious antigen.

Therapeutic uses of antibodies have also been developed, including treatments for cancer and chronic inflammatory diseases, like rheumatoid arthritis, Crohn's disease and ulcerative colitis.

The common feature of virtually all commercial uses of antibodies is that they bind very specifically to a particular target. The binding may be for the purpose of identifying the presence of a target antigen using a labeled antibody as in home pregnancy tests or assays for detecting infectious disease. Or the antigen specific binding may

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944. See *supra* section 7:6.1 and *infra* Appendices A and B for further discussion of genetic engineering techniques.

block the biological activity of a target molecule *in vivo* to down-regulate the effects of that molecule, or initiate an immune system response to destroy it.

Particular features of the antibody, such as the nature of the constant region or the particular affinity the antibody has for binding the target, may be engineered using recombinant technology to achieve specific goals. Antibody fragments can also sometimes be used to exploit the properties of the antibody's binding site without its much larger constant region. For example, the truncated antibody may be used to block particular receptor sites *in vivo* that occupy a confined spatial area too small for an entire antibody to penetrate. Additionally, antibodies can be complexed with other molecules to improve their detection, imaging, half-life, toxicity, or delivery.

§ 7:7.2 Obviousness

[A] Monoclonal Antibodies

The Patent Office, in *Ex parte Erlich*,[945] rejected an application claiming monoclonal antibodies to fibroblast interferon and the hybridoma cell lines that produced the antibodies. The antigen, fibroblast interferon, had been known and characterized in the prior art. The Patent Office Board of Appeals held the antibody claims were obvious because "the basic method of Kohler and Milstein to form monoclonal antibodies specific for human fibroblast interferon" was known and the "human fibroblast interferon was a known antigen (Ganfield, Stewart) of unquestioned research interest as an antiviral or antitumor agent."[946]

The Board also extended its obviousness holding to the claims directed to the hybridoma cell line because:

> the selection of human fibroblast interferon as the starting antigen will lead to the formation of hybrid cell lines that produce monoclonal antibodies specific for human fibroblast interferon. The specifically identified hybrid cell lines of claim 5 are also included in this finding since they are identified only by the process from which they were made (*i.e.*, fusion of primed antibody producing cells and cancer cells) and by the product they produce (*i.e.*, monoclonal antibodies specific for human fibroblast interferon). The present record does not contain any evidence that these specific cell lines differ in any significant manner or produce monoclonal antibodies that differ in any aspect or degree from the hybrid cell lines that would be expected to be formed in using

945. *Ex parte* Erlich, 3 U.S.P.Q.2d (BNA) 1011 (B.P.A.I. 1986).
946. *Id*. at 1015.

> human fibroblast interferon as the starting antigen in the basic method of Kohler and Milstein.[947]

Thus, the Board left open the possibility that an applicant could show that specific cell lines produce monoclonal antibodies that differ from what one would normally expect based on using the known method of Kohler and Milstein.

[B] Sandwich Assay

A monoclonal sandwich assay is a test that uses a complex of two monoclonal antibodies and an antigen to detect the presence of the antigen in a sample. The Federal Circuit, in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*,[948] held that claims to a monoclonal sandwich assay were not obvious over prior art disclosing the Kohler and Milstein method for making monoclonal antibodies, art disclosing polyclonal sandwich assays, and methods for identifying monoclonal antibodies with sufficient affinity to use in the claimed sandwich assay.

[C] 35 U.S.C. § 103(b)

In 1999, section 103 of title 35, the statutory provision governing the obviousness of an invention, was amended to add a provision aimed specifically at "a biotechnological process," which includes "cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody."[949] The provision precludes an obviousness rejection of such claims if:

(a) the procedure and resulting cell line are contained in the same application or in separate applications having the same effective filing date;

(b) both the procedure and the resulting cell line are owned by or subject to assignment to the same person at the time the procedure was invented;

(c) a patent issued on the procedure also contains the claims to the resulting cell lines, or if in different patents, the claims expire on the same date; and

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947. *Id.*

948. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1370–71 (Fed. Cir. 1986) (patent involving claim to a general method for determining the presence of an antigen in a fluid using a technique known as a reverse sandwich assay).

949. 35 U.S.C. § 103(b)(3)(B).

(d) a timely election is made to proceed under the provisions of subsection 103(b).[950]

§ 7:7.3 Written Description

[A] Describing Antibodies by Describing Their Target

[A][1] Overview of Written Description Requirement

Generally, a claim to a previously unknown biological molecule, like a claim to a chemical molecule, requires more than a recitation of its function and disclosure of a plan that could be used to obtain the molecule.[951] The Federal Circuit has repeatedly required that a claim to a biological molecule must be supported by a description of what the molecule is, not merely a description of what the molecule does and a plan to obtain it. For example, in *Regents of the University of California v. Eli Lilly & Co.*,[952] the Federal Circuit held that "[a]n adequate written description of a DNA . . . 'requires a precise definition such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed invention."[953] The court deemed the purely functional definition of the unknown DNA encoding human insulin insufficient, even though the patent specification disclosed a method by which one might acquire the DNA.[954]

Chemical compounds, however, can be described by the process that produced the compound—even if the compound's claimed structure was not known.[955] Similarly, as explained below, the Federal

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950. See *supra* section 5:3.1[B] for a further discussion of 35 U.S.C. § 103(b).
951. See *supra* section 5:4 for a more complete discussion of the written description requirement.
952. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).
953. *Id*. at 1566 (citation omitted).
954. *See also* Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927 (Fed. Cir. 2004) (disclosure of screening assays that could be used to identify a compound that inhibits PGHS-2 gene product was not sufficient to support claim to method requiring administration of such compound); Fiers v. Revel, 984 F.2d 1164, 1169–71 (Fed. Cir. 1993) (strategy or method for obtaining the DNA with other desired properties was not a conception of the DNA, whether or not the desired DNA could be obtained by routine skill following the method described in the patent application); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("It is not sufficient to define [a chemical compound] solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.").
955. *See In re* Edwards, 568 F.2d 1349, 1351–52 (C.C.P.A. 1978) (claim to chemical compound was supported by application disclosing

Circuit has previously remarked that a genus of monoclonal antibodies can be claimed by describing the antigen target to which they bind. However, the Federal Circuit has since rejected this approach in *Amgen Inc. v. Sanofi*.[955.1] Applicants cannot continue to satisfy the written description requirement for antibodies merely by describing the antigens to which they bind. A genus of monoclonal antibodies that bind to a genus of antigens, however, cannot be described by "only describ[ing] the preparation of a single Mab [antibody]."[955.2]

[A][2] Antibodies and DNA

A genus of antibodies, like a genus of nucleic acid sequences, can be described in functional terms if described in relationship to a known structure and method of making. Patentees have claimed as a genus of different monoclonal antibodies all antibodies made using the Kohler-Milstein process that bind to a specified antigen, or that bind with a specified affinity to that antigen.[956] The Federal Circuit has held that, "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."[957] However, the Federal Circuit has since

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chemical reactions and specific reagents that indisputably "will produce" the claimed polyol). *Edwards* is consistent with *Amgen*, which explained that conception, a prerequisite for written description, can occur when an inventor is able to define a chemical "by its method of preparation." *Amgen*, 927 F.2d at 1206.

955.1. Amgen Inc. v. Sanofi, 872 F.3d 1367 (Fed. Cir. 2017).

955.2. *In re* Alonso, 545 F.3d 1015, 1018, 1021 (Fed. Cir. 2008) ("the one compound disclosed by Alonso cannot be said to be representative of a densely populated genus" of "monoclonal antibodies idiotypic to the neurofibrosarcoma"—a class of antibodies that target malignant nerve sheath tumor).

956. An antibody claim can be thought of as implicitly referencing the well-known processes for making an antibody from a known antigen, including the laborious, but routine, screening steps needed to isolate the desired antibody-producing cell lines from cell lines that are either not producing antibodies or producing ones with incorrect specificity. *See In re* Wands, 858 F.2d 731 (Fed. Cir. 1988).

957. Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004). The Federal Circuit Court noted with approval USPTO Guidelines published in 1999, under which:

> [T]he PTO would find compliance with 112, paragraph 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of

rejected this approach in *Amgen Inc. v. Sanofi*. The court criticized it as "flout[ing] [the] basic legal principles of the written description requirement" by "allow[ing] patentees to claim antibodies by describing something that is not the invention, i.e., the antigen."[957.1] In view of this ruling, applicants cannot continue to satisfy the written description requirement for antibodies merely by disclosing the target antigens to which they bind. Similarly, a genus of nucleic acid sequences can be described as all sequences that hybridize (bind) to a specified complementary sequence under specified stringency conditions.[958] Particular DNA sequences, on the other hand, such as naturally occurring genes for particular species, cannot necessarily be described in this manner.[959] Likewise, claiming a particular monoclonal antibody, generally requires a deposit of a cell line that expresses the antibody.[960]

[A][3] Requirement for Describing the Antigen

The court in *Noelle v. Lederman*[961] required that the antigen be fully characterized "either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository."[962] The court upheld the Patent Office Board's decision that a party to an interference could not rely on a parent application that had disclosed an antibody to a mouse T-cell surface antigen to support a claim to antibodies that bind the human T-cell antigen. The human antigen, the court found, was not fully characterized or deposited.[963]

In *Amgen Inc. v. Sanofi*,[963.1] the Federal Circuit rejected the approach announced in *Noelle v. Lederman*. It explained that the "newly characterized antigen test" was announced in prior cases as dicta and is therefore "not based on any binding precedent." "The

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antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.

957.1. *Amgen Inc.*, 872 F.3d at 1378.

958. *See* Enzo Biochem, Inc. v. Gen-Probe, Inc. (*Enzo II*), 323 F.3d 956, 967 (Fed. Cir. 2002). For a discussion of court rulings in this area, see *supra* section 7:6.4[B].

959. *Lilly*, 119 F.2d at 1567–68 (DNA encoding naturally occurring mammalian genes for insulin was not supported by disclosure of rat insulin gene and method for finding other mammalian insulin genes).

960. *See, e.g.*, Evans Med. Ltd. v. Am. Cyanamid Co., 215 F.3d 1347 (Fed. Cir. 1999) (unpublished) (noting the policy reasons behind favoring biological deposits in the case of a particular monoclonal antibody).

961. Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004).

962. *Id*. at 1349.

963. *Id*. at 1349–50.

963.1. Amgen Inc. v. Sanofi, 872 F.3d 1367 (Fed. Cir. 2017).

test was not central to the holding in either *Enzo* or *Noelle* and neither case explored it in much depth."[963.2] It further noted that this approach contravened the "basic legal principles of the written description requirement": "Section 112 requires a 'written description of the invention.' But this test allows patentees to claim antibodies by describing something that is not the invention, i.e., the antigen."[963.3] In view of this ruling, applicants cannot continue to satisfy the written description requirement for antibodies merely by disclosing the target antigen to which they bind.[963.4]

[B] Describing Antibodies in Terms of Their Corresponding DNA or Amino Acid Sequences

[B][1] Describing Antibodies in Terms of Previously Known Sequences

The Federal Circuit held in *Capon v. Eshhar*[964] that a gene encoding a chimeric antibody composed of known subparts can be described by reference to those known subparts without providing the sequence for the complete construct.[965] *Capon* involved an interference between an issued patent and a pending application, both directed to "the production of chimeric genes designed to enhance the immune response by providing cells with specific cell-surface antibodies in a form that can penetrate diseased sites, such as solid tumors."[966] The claimed inventions endowed certain immune system cells with antibody type specificity, "by combining known antigen-binding-domain producing DNA and known lymphocyte-receptor-protein producing DNA into a unitary gene that can express a unitary polypeptide chain."[967] The Federal Circuit addressed the question whether the nucleotide sequence of the complete chimeric gene must be described

963.2. *Id*. at 1376.
963.3. *Id*.
963.4. *See also, e.g.*, Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2021) (finding that a claimed functional genus of antigen binding elements that "specifically interacts with a selected target" and where "[t]he target . . . can be any target of clinical interest to which it would be desirable to induce a T cell response" was invalid for lack of written description, as the patent did not disclose "representative species or common structural features to allow a person of ordinary skill in the art to distinguish between [binding elements] that achieve the claimed function and those that do not").
964. Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005).
965. *Id*. at 1360.
966. *Id*. at 1351.
967. *Id*.

in order to satisfy the written description requirement of section 112, when the nucleotide sequences of the component subparts are already known in the art. The Patent Office's Board of Appeals determined that both the issued patent and the pending application failed to satisfy the written description requirement because the complete nucleotide sequence for the chimeric gene had been described in either specification. The Federal Circuit reversed and remanded, finding that a nucleotide-by-nucleotide "re-analysis" is not required when the structure of the component DNA segments has already been disclosed in the art and determined by known methods. The court explained that "[w]hen the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh."[968] Rather, the court credited the parties' argument that "a person experienced in the field of this invention would know that these DNA segments would retain their DNA sequences when linked by known methods."[969] In particular, the court stated that "[t]he predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention."[970]

[B][2] Describing Antibody Genus in Terms of Amino Acid Sequences

The Federal Circuit affirmed denial of a JMOL, thereby upholding a jury verdict of invalidity for lack of written description of an antibody genus claim supported by disclosure of 300 antibodies.[970.1] Although the disclosed antibodies covered the full range of the claimed binding affinities, they were all structurally similar and therefore did not support the full range of the claimed genus.[970.2] All of the antibodies disclosed by the specification were derived from "Joe-9" based on mutations to its complementary determining regions (CDRs).[970.3] As a result, "they all have VH3 type heavy chains and Lambda type light chains" and "share a 90% or more amino acid sequence similarity in the variable regions," with over 200 of them sharing "a 99.5% sequence similarity in the variable regions."[970.4] In contrast, the accused antibody "differs considerably from the Joe-9 antibodies

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968. *Id*. at 1358.
969. *Id*.
970. *Id*. at 1360.
970.1. AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1290–91 (Fed. Cir. 2014).
970.2. *Id*. at 1299–1302.
970.3. *Id*. at 1291.
970.4. *Id*.

described in AbbVie's patents," sharing only "a 50% sequence similarity with the Joe-9 antibodies" and "could bind to completely different antigens."[970.5]

The patents need not describe the allegedly infringing antibody in exact terms, however, they "must at least describe some species representative of antibodies that are structurally similar" to the accused antibody.[970.6] The court remarked that "[f]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus."[970.7]

[C] Chimeric Antibodies: *Chiron v. Genentech*

In *Chiron Corp. v. Genentech, Inc.*,[971] the Federal Circuit addressed claims to monoclonal antibodies that bind to a human breast cancer antigen. The patent included a claim to "[a] monoclonal antibody that binds to human c-erbB-2 antigen" as well as claims reciting that the antibody binds to a human breast cancer antigen that is also bound by the antibody produced by a specified deposited hybridoma.[972] Chiron's patent issued on a series of continuation-in-part (CIP) patent applications, the first of which was filed in 1984. The specification of the patent, which issued on a CIP application filed in 1995, defined the term "antibody" as "encompass[ing] polyclonal and monoclonal antibody preparations, as well as preparations including hybrid antibodies, altered antibodies, chimeric antibodies and, humanized antibodies."[973] Accordingly, the district court construed the patent claims "to embrace chimeric and humanized antibodies in addition to the murine antibodies that bind to [the antigen]."[974] At issue in the case was whether the issued patent was entitled to priority to the ancestor applications filed in 1984, 1985, and 1986, because the parties had conceded that the issued claims would be anticipated by intervening prior art if not entitled to claim priority to any of those applications.

The Federal Court explained that "[t]he written description requirement prevents applicants from using the amendment process to update their disclosures (claims or specifications) during their

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970.5. *Id*. at 1300.
970.6. *Id*. at 1301.
970.7. *Id*.
971. Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004).
972. *Id*. at 1250.
973. *Id*. at 1258.
974. *Id*. at 1252.

pendency before the Patent Office. Otherwise applicants could add new matter to their disclosures and date them back to their original filing date . . . ."[975] Thus, "[t]he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him."[976] In *Chiron*, the court held:

> [T]he Chiron scientists, by definition, could not have possession of, and disclose, the subject matter of chimeric antibodies that did not even exist at the time of the 1984 application. Thus, axiomatically, Chiron cannot satisfy the written description requirement for the new matter appearing in the [patent in suit].[977]

The court thus refused to grant priority to the 1984 application.

§ 7:7.4 Enablement

[A] Enablement Supported by the Prior Art

[A][1] Evidence of Enablement from the Prior Art

The Federal Circuit held enabled a claim to diagnostic immunoassay methods "for determining the presence or amount of antigen in body fluids such as blood or urine by employing the ability of an antibody to recognize and bind to an antigen."[978] The claimed immunoassays required large amounts of monoclonal antibodies, raising the question of whether the patent enabled "how (1) to make monoclonal antibodies; (2) to screen for proper monoclonal antibodies; and (3) to measure monoclonal antibody affinity."[979] The Federal Circuit found that *in vitro* production of monoclonal antibodies was already known in the art when the patent was filed. Therefore, the court concluded, the statement provided in the specification referring to such prior art sufficiently enabled a person skilled in the art to make the antibodies.[980]

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975. *Id*. at 1255.
976. *Id*. (quoting *In re* Wertheim, 541 F.2d 257, 262 (C.C.P.A. 1976)).
977. *Id*.
978. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1369 (Fed. Cir. 1986).
979. *Id*. at 1384.
980. *Id*.

[A][2] Enablement Based on Level of Skill in the Art: No Undue Experimentation

The Federal Circuit, in *In re Wands*,[981] held enabled a claim to immunoassays methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype.[982] The specification of the patent taught a procedure of "immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg." For the purpose of complying with the best mode requirement under section 112, "a hybridoma cell line that secretes IgM antibodies against HbsAg . . . was deposited at the American Type Culture Collection, a recognized cell depository."[983]

The PTO rejected the claims that were generic to the specified antibodies rather than encompassing solely those secreted by the deposited hybridoma cell line for lack of enablement. The Federal Circuit reversed, stating that no undue experimentation was required to practice the invention. The court found that there was "a high level of skill in the art at the time when the application was filed."[984] It found that although the making of antibodies required numerous steps and extensive screening of "hybridomas to determine which ones secrete antibody with desired characteristics," such screening was routine and within the skill of a person of ordinary skill in the art. The court explained that "in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen."[985]

Consequently, the claims at issue did not have to be narrowed to the specific antibody secreted by the deposited hybridoma cell line.

[B] Failed Attempts Do Not Necessarily Show Lack of Enablement

Consistent with the *Wands* holding that routine experimentation for enablement of an antibody can include a great deal of work, such as screening, the Federal Circuit has also held that occasional failures are not necessarily proof of lack of enablement. In *Johns Hopkins University v. Cellpro, Inc.*,[986] the court addressed a patent claim

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981. *In re* Wands, 858 F.2d 731 (Fed. Cir. 1988).
982. *In re Wands* is also generally cited for enablement law, including the eight so-called *Wands* factors for evaluating enablement. 858 F.2d at 737.
983. *Id*. at 734.
984. *Id*. at 740.
985. *Id*.
986. Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342 (Fed. Cir. 1998).

in which the claimed antibody was defined as one that bound the same antigen as a deposited antibody. With regard to enablement, the Federal Circuit held that evidence of lack of enablement consisting of a failed attempt to make a claimed antibody would not prove lack of enablement unless (i) the attempt was by persons of ordinary skill in the art; and (ii) "the patent's disclosure was followed" in the failed attempt.[987] The fact that a technique for making antibodies "was not foolproof, and that success with this technique commonly required repetition" also did not show that the claimed technique was not enabled, provided that the disclosed technique could be made to work with "routine experimentation."[988] The court further held that a party seeking to demonstrate a lack of enablement "can carry its burden only by showing that all of the disclosed alternative modes are insufficient to enable the claims."[989]

[C] Nascent Technology

The *Chiron v. Genentech*[990] case also addressed whether the priority applications at issue satisfied the enablement requirement for the monoclonal antibody claims at issue. Interestingly, and in contrast to the written description analysis, the court noted that "[t]he law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible."[991] Thus, "[b]ecause the first publication documenting the successful creation of chimeric antibodies occurred after the filing of the 1984 application, this sequence of events shows that this new technology arose after the filing date and thus was, by definition, outside the bounds of the enablement requirement."[992] Notably, the same fact—the nonexistence of chimeric antibodies in 1984—did not preclude Chiron's priority claim to 1984 under the enablement requirement, but did preclude Chiron's priority claim under the written description requirement.

The court in *Chiron* also evaluated compliance with the enablement requirement by the 1985 and 1986 applications to which Chiron claimed priority. The court explained that "[f]or these applications, the jury was entitled to determine as a matter of fact that chimeric

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987. *Id*. at 1360.
988. *Id*.
989. *Id*. at 1361.
990. Chiron v. Genentech, 363 F.3d 1247 (Fed. Cir. 2004). See *supra* section 7:7.3[C] where *Chiron* is discussed in the context of the written description requirement.
991. *Chiron*, 363 F.3d at 1254.
992. *Id*.

antibodies were not future technology, but were nascent technology requiring a 'specific and useful teaching.'"[993] Noting that the record showed chimeric antibodies "required significant experimentation in 1985 and 1986 because those antibodies were unpredictable at that early stage of antibody development," the court upheld the jury's finding of lack of enablement, thereby precluding Chiron's reliance on the 1985 and 1986 application to support its claim.[994] The court rejected Chiron's argument that by 1986, chimeric antibodies were so well-known that they had become routine and thus did not need to be described in detail in the application.

The *Chiron* case illustrates rather dramatically the importance to the enablement analysis of the technological state of the art at the time a patent application is filed to assessing satisfaction of the enablement requirement. Under *Genentech, Inc. v. Novo Nordisk A/S*,[995] technology that is not yet in existence is excused from the enablement requirement, but technology that is "nascent" is subject to a particularly high standard, requiring a "specific and useful teaching," while technology that is routine need not be described in detail in the specification.

[D] Enablement of Functional Genus Claims to Antibodies

In *Amgen Inc. v. Sanofi, Aventisub LLC*, the Federal Circuit affirmed the district court's judgment as a matter of law of lack of enablement of Amgen's claims to genera of monoclonal antibodies defined by their functions of binding to a specified region on the naturally occurring protein PCKS9 and blocking PCSK9 from binding to low density lipoprotein (LDL) receptors.[995.1] The decision marked the second time that the Federal Circuit had considered the patents at issue; the court had remanded the case following an earlier jury

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993. *Id*. at 1255 (quoting Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1368 (Fed. Cir. 1997)).

994. *Chiron*, 363 F.3d at 1256. As with written description, a patent specification need not enable everything that later infringes a claim. The claim is enabled if there is at least one way to practice the invention disclosed in the patent or known in the art. See Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1335 (Fed. Cir. 2003), and cases cited therein. The claim does not become invalid because someone later invents another way to practice the invention, and if the panel in *Chiron v. Genentech* was suggesting otherwise, it is contrary to well established law.

995. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361 (Fed. Cir. 1997).

995.1. Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080 (Fed. Cir. 2021), *petition for reh'g en banc denied*, 850 F. App'x 794 (Fed. Cir. 2021).

determination that the patents were not invalid for lack of enablement and written description.[995.2] On remand, the district court granted Sanofi's motion for judgment as a matter of law for lack of enablement, in part because the claims, which were functionally defined by their ability to bind to one or more of fifteen residues of the PCSK9 protein, encompassed millions of antibody candidates and related to an unpredictable field.

In first discussing precedent on functional claim limitations, the Federal Circuit cautioned that such limitations "pose high hurdles in fulfilling the enablement requirement for claims with broad functional language."[995.3] The Federal Circuit emphasized that "it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim."[995.4]

Then, applying the specific *In re Wands* factors,[995.5] the Federal Circuit agreed with the district court's findings that (1) the scope of the claims was broad; (2) the invention was in an unpredictable field of science; and (3) a person of ordinary skill in the art could obtain undisclosed claimed embodiments only by a trial-and-error process that required a substantial amount of time and effort.[995.6] The Federal Circuit noted that of the disclosed embodiments none bound more than nine residues—despite the claims including antibodies binding up to sixteen—and none bound to three of the claimed residues.[995.7] With respect to unpredictability of the art, the record also lacked "non-conclusory evidence that the full scope of the broad claims can predictably be generated by the described methods."[995.8] Taken together, the Federal Circuit determined that undue experimentation would be required to practice the full scope of Amgen's claims.

On November 4, 2022, the U.S. Supreme Court granted Amgen's petition for writ of certiorari with respect to the following Question Presented:

> Whether enablement is governed by the statutory requirement that the specification teach those skilled in the art to "make and use" the claimed invention, 35 U.S.C. § 112, or whether it must instead enable those skilled in the art "to reach the full scope of claimed embodiments" without undue experimentation—i.e.,

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995.2. *Id*. at 1083–84.
995.3. *Id*. at 1087.
995.4. *Id*. at 1086.
995.5. *In re* Wands, 858 F.2d 731 (Fed. Cir. 1988).
995.6. *Amgen Inc.*, 987 F.3d at 1087–88.
995.7. *Id*. at 1087 n.1.
995.8. *Id*. at 1087–88.

> to cumulatively identify and make all or nearly all embodiments of the invention without substantial "'time and effort,'" Pet. App. 14a.[995.9]

Oral argument at the U.S. Supreme Court was held on March 27, 2023, and the Court issued its decision unanimously affirming the Federal Circuit on May 18, 2023, in an opinion authored by Justice Gorsuch.[995.10] In affirming the invalidity of Amgen's functional genus claims for lack of enablement, the Court reached back to its precedent from the 19th and early 20th centuries holding that claims covering broad classes of subject matter must enable the entire class.

> This Court has addressed the enablement requirement on many prior occasions. See, *e.g.*, *Wood v. Underhill*, 5 How. 1 (1846); *O'Reilly v. Morse*, 15 How. 62 (1854); *The Incandescent Lamp Patent*, 159 U. S. 465 (1895); *Minerals Separation, Ltd. v. Hyde*, 242 U. S. 261 (1916); *Holland Furniture Co. v. Perkins Glue Co.*, 277 U. S. 245 (1928). While the technologies in these older cases may seem a world away from the antibody treatments of today, the decisions are no less instructive for it.
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> Our decisions in *Morse*, *Incandescent Lamp*, and *Holland Furniture* reinforce the simple statutory command. If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.[995.11]

While the Court concluded that its case law established that "a specification may call for a reasonable amount of experimentation to make and use a patented invention," in this case "Amgen has failed to enable all that it has claimed, even allowing for a reasonable degree of experimentation."[995.12] Referring to its prior precedent, the Court concluded that:

> [m]uch as Morse sought to claim all telegraphic forms of communication, Sawyer and Man sought to claim all fibrous and textile materials for incandescence, and Perkins sought to claim all starch glues that work as well as animal glue for wood veneering,

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995.9. Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).
995.10. *Id*.
995.11. *Id*. at 1254.
995.12. *Id*. at 1256.

> Amgen seeks to claim "sovereignty over [an] entire kingdom" of antibodies . . . [I]f our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable. That holds true whether the case involves telegraphs devised in the 19th century, glues invented in the 20th, or antibody treatments developed in the 21st.[995.13]

The Court also rejected Amgen's argument that the methods it disclosed in its patent enabled the making of all the antibodies that it functionally claimed:

> We cannot agree. These two approaches amount to little more than two research assignments. The first merely describes step-by-step Amgen's own trial-and-error method for finding functional antibodies. . . . The second isn't much different. It requires scientists to make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too—an uncertain prospect given the state of the art.
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> Whether [Amgen's] methods . . . might suffice to enable other claims in other patents—perhaps because, as this Court suggested in *Incandescent Lamp*, the inventor identifies a quality common to every functional embodiment, . . . —they do not here. They leave a scientist about where Sawyer and Man left Edison: forced to engage in "painstaking experimentation" to see what works. . . . That is not enablement. More nearly, it is a "hunting license."[995.14]

Finally, the Court rejected Amgen's arguments that the Federal Circuit had "raise[d] the bar for the enablement of claims that encompass an entire genus by its function." Rather, the Court concluded that the Federal Circuit had "recognized only that the more a party claims for itself the more it must enable. As we have seen, that much is entirely consistent with Congress's directive and this Court's precedents."[995.15]

Following the Supreme Court's decision in *Amgen v. Sanofi*, the Federal Circuit in *Baxalta Inc. v. Genentech, Inc.* also held invalid for lack of enablement claims to a genus of antibodies defined by their function.[995.16] In that case, Baxalta had asserted infringement of patent claims to an isolated antibody that binds to Factor IX or Factor IXa

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995.13. *Id*.
995.14. *Id*. at 1256–57 (citing Brenner v. Manson, 383 U.S. 519, 536 (1966)).
995.15. *Id*. at 1257.
995.16. Baxalta Inc. v. Genentech, Inc., 81 F.4th 1362 (Fed. Cir. 2023).

and increases the procoagulant activity of Factor IXa. Genentech's accused product was a bispecific antibody binding to both Factor IXa and Factor X. Federal Circuit Judge Dyk, sitting as a district court judge in Delaware, granted summary judgment that Baxalta's claims were invalid due to lack of enablement.[995.17] The Federal Circuit affirmed this decision based on the precedent set by *Amgen v. Sanofi*, highlighting the insufficiency of disclosed antibodies compared to the expansive claim scope. Despite the millions of potential candidate antibodies, only a few were disclosed, requiring extensive trial and error for others. This inability to predict antibody performance rendered the claims invalid for lack of enablement.[995.18]

In another post–*Amgen v. Sanofi* case, *Teva v. Eli Lilly*,[995.19] the district court held claims to a genus of antibodies defined by their function invalid for lack of enablement and lack of written description. Teva had accused Eli Lilly's Emgality® antibody product of infringing patent claims directed to a method of treating migraine headaches by administering humanized antibodies defined by their ability to bind to the protein CGRP. The district court overturned a jury verdict in Teva's favor, granting Eli Lilly judgment as a matter of law after concluding that Teva's patent claims were invalid for lack of both written description and enablement. The court held that the patent specification did not provide representative species and common structural features sufficient to support written description, citing *Juno* and *Ariad*.[995.20] Citing *Amgen v. Sanofi* and *Baxalta*, the court also found lack of enablement due to the functional claim scope compared to the sole disclosed antibody, necessitating extensive trial and error to enable the full scope of the claim.[995.21]

§ 7:7.5 *Claim Construction*

[A] Chimeric and Humanized Antibodies

The Federal Circuit held that the patentee was "estopped from including chimeric and humanized antibodies within the scope" of its claim to "[a] monoclonal antibody which specifically binds a human

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995.17. Baxalta Inc. v. Genentech, Inc., 579 F. Supp. 3d 595 (D. Del. 2022).
995.18. *Baxalta*, 81 F.4th 1362.
995.19. Teva Pharm. Int'l GmbH v. Eli Lilly & Co., No. 18-cv-12029-ADB, 2023 WL 6282898 (D. Mass. Sept. 26, 2023), *appeal filed*, No. 24-1094 (Fed. Cir. 2023).
995.20. Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021); Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010).
995.21. *Teva*, 2023 WL 6282898.

cytotoxin."[996] The court explained that the examiner had rejected amended claims to "rat, hamster and human antibodies and chimeras thereof" because they "were not supported in the specification" and that in response the patentee cancelled the claims.[997] The court also rejected evidence that scientists in the prior art knew of chimeric antibodies, because that did not support the conclusion that the term "monoclonal antibodies" included chimeric antibodies.[998]

Sanofi and Regeneron initiated an IPR against an Immunex patent claiming "an isolated human antibody" that binds to human IL-4.[999] Immunex proposed that the term should be limited to fully human antibodies, while Sanofi and Regeneron argued that the term should include partially human and humanized antibodies. The Federal Circuit, applying the now-superseded broadest reasonable interpretation standard, affirmed the Board's adoption of Sanofi and Regeneron's construction because the specification stated that "antibodies may be partially human" and that they "include . . . partially human." The court rejected Immunex's extrinsic evidence—"experts' testimony, product catalogs, and a selection of journal articles"—tending to show that "human antibody" had an established meaning in the art apart from the specification because it conflicted with the intrinsic record.[1000]

[B] Bispecific Antibodies

Baxalta, the patentee, sued Genentech and Chugai for infringement of its patent covering "an isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa."[1001] Genentech's product, used to treat hemophilia, is a bispecific antibody, meaning that each branch of the antibody's "Y" shape is different and can therefore bind to a different antigen.

The parties disputed the meaning of "antibody" and "antibody fragment." Baxalta argued that "antibody" should be construed as "[a] molecule having a specific amino acid sequence comprising two heavy chains (H chains) and two light chains (L chains)." Genentech argued that "antibody" should instead be construed as "[a]n immunoglobulin molecule, having a specific amino acid sequence that only

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996. UCB, Inc. v. Yeda Research & Dev. Co., 837 F.3d 1256, 1257, 1261 (Fed. Cir. 2017).
997. *Id*. at 1259.
998. *Id*. at 1260.
999. Immunex Corp. v. Sanofi-Aventis U.S., LLC, 977 F.3d 1212 (Fed. Cir. 2020).
1000. *Id*. at 1221.
1001. Baxalta Inc. v. Genentech, Inc., 972 F.3d 1341 (Fed. Cir. 2020).

binds to the antigen that induced its synthesis or very similar antigens, consisting of two identical heavy chains (H chains) and two identical light chains (L chains)."[1002]

The district court (Judge Dyk, sitting by designation) ruled in favor of Genentech based principally on the specification's statement that "Antibodies are immunoglobulin molecules . . . which only bind to antigens that induce their synthesis . . . ."[1003] Although on appeal the panel found this to be "a plausible reading of the excerpt in isolation," it reversed the construction because "claim construction requires that we consider the specification as a whole."[1004] The Federal Circuit also considered a dependent claim that explicitly covered bispecific antibodies and other portions of the specification that referred to bispecific antibodies.[1005] Accordingly, the court concluded that, "[w]hen considered in the context of the remainder of the written description and the claims, we read the excerpt in column 5 as a generalized introduction to antibodies rather than as a definitional statement."[1006]

[C] Enablement Rejections and Prosecution History Estoppel

When an applicant overcomes enablement rejections by making arguments that do not support the full scope of the claim, it may constitute a prosecution history disclaimer that operates to limit the claim's scope.[1007] This is true even where the applicant did not amend the claim[1008] or where the applicant did not adopt the language used by the examiner in making the rejection.[1009]

1002. *Id*. at 1344.
1003. *Id*. at 1347.
1004. *Id*.
1005. *Id*. at 1346–47.
1006. *Id*. at 1347.
1007. *UCB*, 837 F.3d 1256; Biogen Idec, Inc. v. Glaxosmithkline LLC, 713 F.3d 1090 (Fed. Cir. 2013).
1008. *UCB*, 837 F.3d at 1261.
1009. *Biogen*, 713 F.3d at 1096 (rejecting argument that because the patentee "never explicitly referred to any particular 'epitope'" when responding to the examiner's rejection of claims covering any anti-CD20 antibody "no matter the specificity or affinity for the specific epitope" as not enabled, it did not disavow claim scope to antibodies which bound to epitope's beyond that bound by the disclosed rituxan antibody; disavowing claim scope "does not require the applicant to parrot back language used by the examiner when . . . responding to a particular grounds for rejection. If an applicant chooses, she can challenge an examiner's characterization in order to avoid any chance for disclaimer, but the applicants in this case did not directly challenge the examiner's characterization.").

Chapter 8. The Hatch-Waxman Act

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Chapter 8

The Hatch-Waxman Act

David O. Bickart

§ 8:1 Patent Protection and Litigation

§ 8:1.1 Introduction

[A] Background of the Hatch-Waxman Act

The "Drug Price Competition and Patent Term Restoration Act of 1984," commonly called the "Hatch-Waxman Act,"[1] amended both the patent laws and the Federal Food, Drug and Cosmetic Act (FD&C Act) as part of a comprehensive legislative readjustment of the rights of competing pharmaceutical manufacturers and their customers. Legislative readjustment was needed because, under then-existing law, the arduous pre-marketing regulatory review of "new" pharmaceutical products required by the FD&C Act[2] had a number of untoward consequences.

For innovator drug developers, the FDA's protracted pre-marketing review process not only delayed the introduction of new drugs, but also severely eroded intellectual property rights. The regulatory review period would consume much of the life of a pharmaceutical patent, so that by the time a product was approved for marketing, relatively little time was left for the patentee to obtain the economic benefit of its patent.[3]

Existing law was also unsatisfactory from the standpoint of generic drug companies. Prior to the Hatch-Waxman Act, the FDA had no statutory basis for approving generic copies of currently marketed pharmaceuticals, without requiring the copiers to duplicate the time-consuming and costly clinical studies on human patients that innovators had to

1. Pub. L. No. 98-417, 98 Stat. 1585 (1984). Senator Orrin Hatch (R-UT) and Representative Henry Waxman (D-CA), by whose names the Act is commonly known, were the Act's principal brokers. The Federal Circuit, some of whose members served on Senator Hatch's staff, uniformly puts his name first. *See, e.g.*, DuPont Merck Pharm. Co. v. Bristol-Myers Squibb Co., 894 F. Supp. 804, 808 (D. Del.) ("Waxman-Hatch"), *aff'd*, 62 F.3d 1397, 1399 (Fed. Cir. 1995) ("Hatch-Waxman").
2. Or, in the case of biologics, under the Public Health Service Act (PHSA), 58 Stat. 682 (1944).
3. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669–70 (1990).

perform.[4] Furthermore, a would-be copier who tested its product for purposes of FDA approval prior to patent expiration risked damages for patent infringement. Indeed, the Federal Circuit had ruled that the manufacture, use or sale of a patented invention during the term of the innovator's patent infringed that patent "even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval."[5] Thus, a prudent generic drug company would have to

(a) wait until patent expiration to even begin the studies necessary to obtain FDA approval,

(b) then conduct extensive clinical studies on human patients, and finally,

(c) wait for the FDA to conduct its protracted pre-marketing review.

As a result, the development and introduction of generic drugs was substantially hindered.

[B] Hatch-Waxman Act Overview

The Hatch-Waxman Act was a horse trade. Manufacturers of generic drugs, who were the most vociferous advocates for change, received express statutory authority to market their generic copies upon FDA review and approval of *abbreviated* new drug applications (ANDAs), without having to undertake the costly and time-consuming clinical studies that are required for approval of an innovator drug.[6] While an applicant for approval of a new innovator drug must submit a full new drug application (NDA) demonstrating that the drug is both safe and effective, an applicant for a generic version needs only file an ANDA showing that the generic version and the previously approved innovator drug are "bioequivalent."[7] The Act also creates a separate approval route for a generic drug that is similar, but not identical, to a previously approved drug, allowing the generic applicant in such

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4. *Id*. at 676.
5. *Id*. at 670 (describing Roche Prod., Inc. v. Bolar Pharm. Co., 733 F.2d 858 (Fed. Cir. 1984)).
6. 21 U.S.C. § 355(j).
7. The Hatch-Waxman Act generally defines bioequivalence as the lack of significant difference between the rate and extent of absorption of two drugs when administered at the same molar dose under similar experimental conditions, but allows the FDA to use an alternative measure for drugs that are not intended to be absorbed into the bloodstream. 21 U.S.C. § 355(j)(8)(B) & (C).

cases to rely on published literature and other information in lieu of duplicating the innovator's health and safety studies.[8]

To promote the introduction of generic drugs as soon as possible after an innovator's patents expire, Congress immunized from patent infringement conduct that is reasonably related to drug development or the submission of applications for marketing approval. Specifically, the Act provides that it is not an infringement to make, use, or sell a patented invention "solely for uses reasonably related to the development and submission of information under a federal law which regulates the manufacturer, use, or sale of drugs."[9]

Innovators also received legislative compensation for the delays caused by the pre-market review process. First, Congress amended the Patent Act to extend the term of a patent claiming the innovator's product by a portion of the time that the patent owner had been unable to market that product while it was undergoing regulatory review. Second, Congress granted some innovator drug products marketing exclusivity for defined periods, independent of any patent rights. And third, Congress created a mechanism for innovators to litigate their patent infringement claims *before* FDA approval of the generic products, and barred the FDA from approving the generic products for up to thirty months when such a patent infringement suit is brought.

As the Supreme Court has observed, the Hatch-Waxman Act is not "an elegant piece of statutory draftsmanship" and is full of "legislative imprecision."[10] Some of the 1984 Act's uncertainties have been resolved by subsequent legislation amending the Act.[11] The most comprehensive amendments occurred in December 2003 with the enactment of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA).[12] Nevertheless, many of the new MMA provisions do not apply to ANDAs that were submitted before

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8. 21 U.S.C. § 355(b)(2).
9. 35 U.S.C. § 271(e)(1). Under the Supreme Court's holding in Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990), the exemption from infringement is not limited to information submitted during the new drug approval process of the FD&C Act, but also applies to information submitted during the new medical device approval process of the FD&C Act and the biological approval process of the PHSA.
10. *Eli Lilly*, 496 U.S. at 679.
11. These amendments include, for example, the 1988 Generic Animal Drug and Patent Term Restoration Act of 1988, Pub. L. No. 100-670, 102 Stat. 3971 (1988); the Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 111 Stat. 2296 (1997); and the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823 (2007).
12. Medicare Prescription Drug, Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003).

December 8, 2003, when the MMA was signed into law, and the MMA itself left many interpretive questions open for the FDA, the courts, and the rest of the legal community. In October 2016, more than twelve years after the MMA's enactment, the FDA finally published its regulations implementing the MMA.[12.1]

[C] Requirements for Filing an ANDA

Since 1962, the law has provided that no "new drug" may be introduced into commerce until the FDA finds, on the basis of "adequate and well-controlled" clinical studies in humans, that the drug is both safe and effective for its intended use.[13] Until 1984, the FD&C Act provided no clear statutory avenue for copies of already marketed drugs to receive FDA approval unless the copier replicated, at great cost, the studies that had provided the basis for approval of the "pioneer" drug's application.[14] The Hatch-Waxman Act added a new subsection 505(j) to the FD&C Act to authorize the submission and approval of ANDAs for generic copies of previously approved drugs. The new subsection was codified as 21 U.S.C. § 355(j).

Under 21 U.S.C. § 355(j), an ANDA must contain the same information necessary for approval of any "new drug," with one crucial exception: the ANDA is not required to contain the results of preclinical and clinical safety and efficacy testing. The fundamental premise underlying the Hatch-Waxman Act's ANDA process is that once a pioneer brand-name drug product has been determined to be safe and effective, a generic copy of that product is also considered to be safe and effective if it is therapeutically equivalent to the pioneer product—that is, if it is both "pharmaceutically equivalent" (that is, it has the same active ingredient, the same strength, and the same dosage form)[15] and "bioequivalent."

12.1. 81 Fed. Reg. 69,580 (Oct. 6, 2016).

13. 21 U.S.C. § 355(d).

14. Although generic manufacturers had argued that their copies were not "new" because they used the same active ingredients in the same concentrations that the FDA had already determined to be safe and effective, the Supreme Court confirmed that the phrase "new drug" applies to the entire "drug product," for example, the tablet, as well as to the active ingredient contained in that tablet. *See* United States v. Generix Drug Corp., 460 U.S. 453 (1983).

    Some generic manufacturers had also sought and obtained FDA approval for their products based on data contained in previously published studies, instead of conducting their own clinical studies. However, the lawfulness of such "paper NDAs" was unclear. *See infra* section 8:1.1[E].

15. The FDA considers drug products to be "pharmaceutical equivalents" if they contain "the same salt or ester of the same therapeutic moiety" and appear in "identical dosage forms." However, pharmaceutical equivalence

If the FDA concludes that the ANDA product is therapeutically equivalent, it assigns the ANDA drug an "AB" rating in its publication *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly called the "Orange Book."[16] Under the laws of most states, an AB rating allows (and in some states, requires) pharmacists to substitute the lower-priced generic product for the corresponding pioneer drug, unless the prescription specifically insists otherwise.[17]

To demonstrate that a proposed generic product is therapeutically equivalent to a previously approved pioneer drug, the ANDA applicant must show:

- that it has similar labeling;
- that it has the same active ingredient(s);
- that it has the same route of administration, dosage form, and strength; and
- that it is bioequivalent.[18]

Each of these requirements is discussed below.

[C][1] Labeling

An ANDA applicant must, with certain exceptions, provide the following:

- a copy of the labeling for the "reference listed drug" (that is, the previously approved pioneer drug);[19]
- a copy of the proposed labeling for the ANDA product;[20] and
- a "side-by-side comparison of applicant's proposed labeling . . . with the approved labeling for the reference listed drug with all differences annotated and explained."[21]

Generally, an ANDA applicant must show that the labeling proposed for the ANDA product is the same as for the reference drug,

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does not require the inactive ingredients (for example, binders) to be the same. 21 C.F.R. § 320.1(c) (2006).

16. Originally published with an orange cover in 1980, the Orange Book, now in its thirtieth edition, is accessible online with regularly issued supplements. *See Approved Drug Products with Therapeutic Equivalence Evaluations*, Orange Book (Aug. 2010), www.fda.gov/cder/orange.
17. The National Association of Boards of Pharmacy publishes an annual survey of state substitution laws, which is available at www.nabp.net.
18. *See* 21 C.F.R. § 314.94(a) (2006).
19. 21 C.F.R. § 314.94(a)(8)(i) (2006).
20. 21 C.F.R. § 314.94(a)(8)(ii) (2006).
21. 21 C.F.R. § 314.94(a)(8)(iv) (2006).

except for differences necessitated by the fact that the drug makers are different entities (such as the name of the manufacturer and the place of manufacture).[22] Additional permissible labeling differences include "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act."[23]

As a practical matter, the ANDA filer will ordinarily copy the pioneer's labeling word-for-word, whenever it is feasible to do so. The Second Circuit has held that such copying cannot constitute copyright infringement, because the ANDA applicant has a legal duty to use the "same labeling" as the reference drug.[24]

[C][2] Active Ingredient

An ANDA filer must show that its active ingredient is the same as that of the reference drug.[25] An "active ingredient" is a component of a drug product "that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body . . . ."[26] Thus, for example, the FDA will not approve an ANDA for a different salt form of the active ingredient in the reference drug.[27]

However, although FDA regulations require that the active ingredients be "identical,"[28] the FDA does not always insist that the active ingredient in the ANDA have exactly the same physical characteristics as the ingredient in the pioneer drug. For example, the FDA may approve an ANDA product if the crystal structure of its active ingredient differs from that of the pioneer drug, or if its active ingredient is anhydrous while the pioneer's is hydrated.[29] Similarly, the FDA determined that the active ingredient in a copy of the hormone drug Pergonal® was the "same" as that in Pergonal® even though the

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22. *See* 21 U.S.C. § 355(j)(2)(A)(i); 21 C.F.R. § 314.94(a)(8)(iv) (2006).
23. 21 C.F.R. § 314.94(a)(8)(iv) (2006).
24. SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharm., Inc., 211 F.3d 21 (2d Cir. 2000) (no copyright infringement where the FDA has required the ANDA applicant to use a copyright-protected instruction video for consumers).
25. 21 U.S.C. § 355(j)(2)(A)(ii); 21 C.F.R. § 314.94(a)(5) (2006).
26. 21 C.F.R. § 210.3(b)(7) (2006).
27. *See* 54 Fed. Reg. 28,872, 28,881 (July 10, 1989).
28. 21 C.F.R. § 314.92(a)(5) (2006).
29. *See* Letter from Dennis Baker to Donald O. Beers (Feb. 15, 2002), in Dkt. Nos. 00P-1550 and 01P-0428 (variant crystal form of cefuroxime axetil), www.fda.gov/ohrms/dockets/ac/02/briefing/3860b2_12_CDER%20response.pdf.

side-chains of these complex molecules differed somewhat, because the basic amino acid sequences comprising the backbone were the same and the differences that did exist would not have any clinical significance.[30]

[C][3] Route of Administration, Dosage Form, and Strength

An ANDA filer must provide "[i]nformation to show that the route of administration, dosage form, and strength of the drug product are the same as those of the reference listed drug except for any differences that have been the subject of an approved [suitability] petition."[31]

Neither the FD&C Act nor the FDA's regulations define "dosage form," but the FDA has historically focused on the product's physical appearance and how it is administered.[32] Thus, for example, capsules and tablets are different dosage forms, because they look and feel different even though their mode of action (the patient swallows them, after which their ingredients dissolve) is essentially the same.[33] In contrast, the FDA considers all transdermal patches to be the same dosage form, regardless of how the active ingredient is released into the subject's bloodstream.[34]

[C][4] Bioequivalence

An ANDA filer must provide "[i]nformation that shows that the drug product is bioequivalent to the reference listed drug."[35] Two drugs are "bioequivalent" if they do not differ significantly with respect to

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30. *See* Serono Labs., Inc. v. Shalala, 158 F.3d 1313 (D.C. Cir. 1998) (deferring to the FDA's determination).
31. 21 C.F.R. § 314.94(a)(6)(i) (2006); for a discussion of suitability petitions, see *infra* section 8:1.1[D].
32. The Court of Appeals for the District of Columbia upheld this approach in Warner-Lambert Co. v. Shalala, 202 F.3d 326 (D.C. Cir. 2000). The pioneer manufacturer argued, unsuccessfully, that the FDA had arbitrarily classified a tablet-like product encased in a capsule-like shell as a "capsule" rather than as a "tablet."

    The most recent edition of the Orange Book identifies more than seventy-five different dosage forms, such as "aerosol," "liquid," "capsule," "tablet," and "extended release," and is available at www.fda.gov/cder/orange.
33. Letter from Janet Woodcock to Alan Kaplan et al. (Dec. 1, 2000), in Dkt. No. 95-0262, www.fda.gov/ohrms/dockets/dailys/00/Dec00/120700/pdn001.pdf.
34. Letter from Steven K. Galson to Susan Rinne et al. (Jan. 28, 2005) in Dkt. Nos. 2004P-0506/CP1, 2004P-0472/CP1 & SUP1, 2004P-0540/CP1, & 2004P-0340/CP1, www.fda.gov/ohrms/dockets/dockets/06p0290/06p-0290-cp00001-03-exhibit-02-vol1.pdf.
35. 21 C.F.R. § 314.94(a)(1) (2006).

the rate and extent to which their active ingredients become available at their site of action on or in the body. For most drugs, bioequivalence is determined by conducting studies that measure absorption of the drug into the bloodstream.[36]

Despite the critical role that bioequivalence studies play in the ANDA approval process, the FDA has not issued regulations governing the evaluation of such studies. Instead, it has published "guidance" documents, which are said only to represent the FDA's "current thinking."[37] For drugs that are absorbed into the bloodstream, the standard bioequivalence study consists of separately administering the tested product and the reference product, and then measuring the respective concentrations of the two drugs in the blood over time. The extent and rate of absorption of the two drugs are then compared graphically, usually in terms of the areas under the two curves (AUC) and their peak concentrations ("C_{max}"). If the differences between the two drugs are within the acceptance criteria set forth in the FDA's "guidance" documents, the FDA considers the two products to be "bioequivalent."[38]

[C][5] Drug Master File References

Commonly, an ANDA product contains ingredients, including active ingredients, supplied by companies other than the ANDA applicant. In such circumstances, the supplier may submit a "Drug Master File" (DMF), to the FDA containing information (such as chemistry, manufacturing, and quality control information) about the ingredient, and then authorize the ANDA applicant to refer to that DMF in its ANDA. The ANDA applicant may then simply incorporate the DMF by reference.[39]

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36. 21 U.S.C. § 355(j)(8)(B). The original Hatch-Waxman Act defined "bioequivalence" in terms of absorption, making the test difficult to apply to drugs that work topically. In 2003, Congress explicitly authorized the FDA to use alternative measures for drugs that are not intended to be absorbed into the bloodstream. 21 U.S.C. § 355(j)(8)(C).
37. *See, e.g.*, Center for Drug Evaluation and Research (CDER), "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations" (Mar. 2003), www.fda.gov/cder/guidance/5336fnl.htm.
38. *Id.*; *see also, e.g.*, Letter from Randall W. Lutter to Christopher V. Powala in Dkt. No. 2003P-0315 (May 13, 2005) (stating FDA policy), www.fda.gov/ohrms/dockets/dockets/04p0517/04p-0517-pdn0001-vol1.pdf.
39. 21 C.F.R. § 314.420 allows an "applicant" to incorporate by reference the information in another party's DMF. The contents of a DMF remain confidential, and usually are not known by the applicant who incorporates the DMF reference in its application. The DMF owner is not an "applicant," and notwithstanding its potentially critical role in supplying

[D] "Suitability Petitions" for Variant Dosage Forms and Strengths

Although normally an ANDA must be for the same dosage form and for the same strength as the reference drug, the Hatch-Waxman Act provides a mechanism for an ANDA applicant to seek relief from those requirements. Specifically, section 355(j)(2)(C) allows a would-be ANDA applicant to petition the FDA to permit an ANDA for a drug one of whose active ingredients is different,[40] or whose dosage form, route of administration, or strength is different from that of the reference pioneer drug.

The FDA establishes a public electronically accessible docket for each "suitability" petition, and places the petition and any "public" comments (usually from the pioneer manufacturer or another ANDA submitter) in the docket. Although the statute requires the FDA to approve or disapprove the petition within ninety days, it not infrequently fails to do so.

[E] Paper NDAs: Section 505(b)(2) Applications

Although generic drug makers most commonly seek approval for their generic products by filing ANDAs, the Hatch-Waxman Act also provides an alternative mechanism. This mechanism is often referred to as a "505(b)(2) application" or a "paper NDA."[41]

Under section 505(b)(2) an NDA applicant may establish the safety and effectiveness of a new drug by relying on clinical data that it did not develop and to which it has no contractual rights. For example, the applicant may rely on public literature or data submitted by a pioneer drug company that the FDA had previously found sufficient for approval of a similar but not identical product. Where such prior approvals are not themselves sufficient to demonstrate safety or efficacy, the 505(b)(2) applicant may "bridge" its proposed product to a previously approved product with new bioavailability or other

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ingredient to the ANDA applicant it cannot be held liable for infringement under 35 U.S.C. § 271(e)(2). *See* Shire LLC v. Amneal Pharm., Inc., 802 F.3d 1301, 1310 (Fed. Cir. 2015).

40. The FDA has interpreted the somewhat ambiguous statutory text to allow a change in an active ingredient only when the ingredient is one of several active ingredients in a combination drug, but not to allow a change in the active ingredient of a single entity product. 21 C.F.R. § 314.93(e)(1)(ii) (2006) states that the FDA will disapprove a suitability petition that seeks to change an active ingredient if the listed drug is not a combination drug.

41. Set forth in section 505(b)(2) of the FD&C Act, 21 U.S.C. § 355(b)(2).

studies.[42] Because the statutory text does not limit itself to published studies, the FDA has taken the position that it may approve a 505(b)(2) application based on the agency's findings of safety and efficacy for a previously approved drug. The degree to which the FDA is entitled to rely on previous safety and efficacy findings is controversial. The U.S. District Court for the District of Columbia has concluded that the FDA may rely on any data in its files from any source, including a previously approved NDA or 505(b)(2), but that ruling was subsequently vacated on mootness grounds.[43]

Under FDA regulations, a 505(b)(2) application may not be used for a "duplicate" of a pioneer drug that could properly have been the subject of an ANDA.[45] Nonetheless, there are some products for which approval may be sought, at the option of the filer, either by 505(b)(2) application or by ANDA. A product that differs from a reference drug in dosage form or strength may be considered for approval under section 505(b)(2) even if approval may also have been sought by means of an ANDA and a suitability petition.[46]

Between 2010 and 2012 FDA approved more than one hundred 505(b)(2) applications for a broad variety of products, in many cases without requiring any additional clinical data to support safety or efficacy.[47] Significantly, the FDA has approved section 505(b)(2) applications for over-the-counter (OTC) versions of prescription drugs. For

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42. In *Eli Lilly*, 496 U.S. at 676, the Supreme Court described section 505(b)(2) as permitting an applicant to rely "on published literature to satisfy the requirement of animal and human studies demonstrating safety and effectiveness." However, this description is narrower than the statutory language, which authorizes an applicant to rely on studies that it did not itself conduct and for which it has received no "right of reference or use." Because the statutory text does not limit itself to published studies, the FDA has taken the position that it may approve a "paper NDA" under section 505(b)(2) based upon its knowledge of non-public studies conducted by the innovator. Letter from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER) to William H. Carson, et al. (Oct. 5, 2015), Docket No. FDA-2015-P 2482, http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2482-0015.
43. Takeda Pharm., U.S.A., Inc. v. Burwell, 78 F. Supp. 3d 65, 71 (D.D.C. 2015), *vacated in pertinent part as moot*, No. 15-5021, 2016 WL 4098633 (D.C. Cir., July 15, 2016).
44. [Reserved.]
45. 21 C.F.R. § 314.101(d)(9) (2006).
46. FDA Draft Guidance, "Applications Covered by Section 505(b)(2)" (Oct. 1999) at 4 (citing 57 Fed. Reg. 17,956 (Apr. 28, 1992)), www.fda.gov/cder/guidance/2853dft.pdf.
47. S. Agarwal, W. Qiu & C. Sahajwalla, *Overview of Recently Approved 505(b)(2) New Drug Applications (2010–2012): Rule of Clinical Pharmacology*, 54 J. CLIN. PHARMACOLOGY 1330, 1330 (Dec. 2014).

example, the FDA approved 505(b)(2) applications to market non-prescription versions of the popular antihistamine Claritin®.[48] The FDA has also asserted the authority to approve some peptide or protein products, which may be classifiable as "biologics," under section 505(b)(2).[49] For example, FDA recently approved a section 505(b)(2) application for the recombinant growth hormone Omnitrope® (somatropin [rDNA origin]). In a lengthy justification of its action the FDA pointed out that it had regulated naturally derived growth hormones as "drugs" for thirty years, long before the Hatch-Waxman Act, and it asserted that "every protein product approved under section 505 of the [FDC] Act is an appropriate candidate for reference by an applicant seeking approval of a follow-on protein product though an abbreviated pathway."[50]

§ 8:1.2 Orange Book Listing

The FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly called the "Orange Book" (because of its original hard-copy orange cover), plays a central role in identifying and assembling pharmaceutical patent disputes for judicial resolution. The FDA first published the Orange Book in 1979 to help state pharmacy boards decide when generic drugs could safely be substituted for the "branded" drug specified in a prescription. When the Hatch-Waxman Amendments were enacted five years later, the Orange Book took on a new role as the statutorily required "list" of FDA-approved drug products, and it began to include, as the Hatch-Waxman Amendments also required, the "patent information" that each new drug applicant was required to submit in connection with its NDA.[51] The Orange Book is published annually with quarterly supplements and is accessible electronically on the FDA's website in a version that is updated daily to show newly listed patents and newly approved generic drugs.[52]

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48. Letter from Steven Galson to Charles Raubicheck regarding P03P-0160/CPI & RCI (June 24, 2004) (rejecting challenge to approval of loratidine tablet marketed by L. Perrigo), www.fda.gov/ohrms/dockets/dailys/04-June04-063004-03p-0160-pdn00001/vol1.pdf.
49. The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary, 108th Cong. (June 23, 2004) (statement of Lester M. Crawford, Acting Commissioner, FDA), www.fda.gov/ola/2004/fob0623.html.
50. Letter from Steven K. Galson to Kathleen M. Sanzo et al. (May 30, 2006), in Dkt. No. 2004P-0231, at 52; www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf.
51. 21 U.S.C. § 355(j)(7)(A)(i)–(iii).
52. *See supra* note 16.

[A] What Patent Information Must Be Submitted

A new drug applicant must include in its NDA, for listing in the Orange Book, the patent number and the expiration date of any patent that "claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[53]

On August 18, 2003, the FDA substantially revised and expanded its regulations governing the submission of patent information. In particular, FDA regulations state that "[p]rocess patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents . . . must not be submitted to FDA" for listing in the Orange Book.[54] Further, all patent information must now be submitted

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53. 21 U.S.C. § 355(b)(1). NDAs must be supplemented with such information for patents issuing after NDA approval. 21 U.S.C. § 355(c)(2).

    The phrases, "claims the drug" and "claims a method of using such drug," echo the language of section 271(e)(2). *See infra* section 8:1.4[B]. Therefore, with the exception of patents claiming certain antibiotics, patents that are enforceable under section 271(e)(2) may be listed in the Orange Book. Conversely, patents that cannot be enforced under section 271(e)(2)—because they claim neither the "drug" nor a method of using the drug—are ineligible for Orange Book listing.

    Although patents claiming "old" antibiotic drugs (that is, those first submitted for approval before FDAMA's enactment in 1997) are enforceable under section 271(e)(2), such patents are ineligible for the Orange Book. *See* Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339 (Fed. Cir. 2004) (citing FDAMA § 125(d)). In October 2008, a provision was added to 21 U.S.C. § 355, allowing an NDA sponsor to qualify for three-year exclusivity for a newly approved condition of use for one of these "old" antibiotics. Further, for any antibiotic drug for which an application for approval was submitted before November 21, 1997, but has not yet been approved, a sponsor may qualify for five-year exclusivity provided that the antibiotic's active moiety had not been the subject of another approved NDA. 21 U.S.C. § 355(v)(2). Whether a product is classified as an "antibiotic" therefore may have significant consequences. The statute is not completely clear whether a compound is an "antibiotic" if it has antimicrobial effect at any concentration, or only if it has antimicrobial effect in the concentration in which it appears in the drug product. *See* Collagenex Pharm., Inc. v. Thompson, 2005 U.S. Dist. LEXIS 5543 (D.D.C. Jan. 19, 2005) (concentration not controlling), *appeal dismissed*, 2005 U.S. App. LEXIS 15619 (D.C. Cir. July 27, 2005).

54. 21 U.S.C. § 355(j)(2)(B)(iii).

on FDA-approved forms, which are designed to assure that only the proper patents are submitted.[55]

[A][1] "Drug Product" (Formulation or Composition) Patents

By statute, only patents that "claim[ ] *the drug* for which the applicant submitted the application or which claim[ ] a method of using such drug" may be submitted for listing in the Orange Book.[56] The FDA has interpreted the statutory term "drug" to include not only the active pharmaceutical ingredient but also the "drug product," that is, the entire dosage form (for example, the tablet, capsule, solution, or spray) in which the drug is administered to the patient.[57]

The FDA has accepted for Orange Book publication a patent claiming a transdermal patch as the transdermal nitroglycerin product "Nitro-Dur,"[58] and a patent claiming a drug delivery system of twenty-four daily dosage units as claiming the contraceptive product "Mircette."[59] The definition of "drug product," however, is not infinitely elastic. The FDA does not regard a bottle or other packaging as constituting a "drug product." Patents claiming such packaging may not be submitted, and do not appear in the Orange Book.[60]

Furthermore, a patent may not be submitted for listing in the Orange Book unless it claims the "drug product" (or a method of using the drug product) that is the subject of the approved or pending NDA. For example, a patent that claims a capsule formulation of a drug may not be submitted in connection with an NDA for a tablet formulation of that drug.[61]

[A][2] "Drug Substance" (Active Ingredient) Patents

The FDA construes the obligation to submit information for patents that claim the "drug" to also include patents that claim the "drug substance," that is, the active ingredient contained in the drug product, which, when released on or in the body, provides the claimed

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55. The forms, FDA 3542 (for already-approved NDAs) and 3542a (for NDAs that have not yet become effective), are available at www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.
56. 21 U.S.C. § 355(j)(2)(B)(iii) (emphasis added).
57. *See* 68 Fed. Reg. 36,676, 36,680 (June 18, 2003) (citing 21 C.F.R. § 314.3).
58. *See* Key Pharm. v. Hercon Labs. Corp., 161 F.3d 709 (Fed. Cir. 1998) (upholding judgment of validity and infringement).
59. *See* Bio-Tech. Gen. Corp. v. Duramed Pharm., Inc., 325 F.3d 1356, 1358 (Fed. Cir. 2003) (reversing summary judgment of non-infringement).
60. 21 C.F.R. § 314.53(b)(1) (2006).
61. Pfizer, Inc. v. FDA, 753 F. Supp. 171, 175 (D. Md. 1990).

therapeutic effect. Because the patent must claim a drug substance for "which the applicant submitted the [new drug] application," a patent that claims a different salt of the approved drug substance may not be submitted for inclusion in the Orange Book; the FDA generally regards different salt forms as constituting different drugs.[62]

The FDA's 2003 regulations specifically state that "patents claiming metabolites and patents claiming intermediates" may not be listed in the Orange Book, and information on these patents may not be submitted to the FDA.[63] A patent claiming a metabolite may not be listed because it "does not claim the approved drug." However, if the patent claims an "approved method of using an approved drug to administer a metabolite," that patent may be submitted for listing on the theory that it claims a method of using the approved drug.[64]

Although FDA regulations bar submission of patents that claim an "intermediate," they do not define that term, and the scope of the ban is not entirely clear. In proposing the rule barring the listing of patents on "intermediates," the FDA distinguished between "in-process materials," which may not be the subject of patent submissions, and "drug components," for which patent information apparently may be submitted.[65] However, there is some support in the case law for the proposition that precursors of approved active ingredients may be considered "components" of the approved drug even if they undergo chemical change during manufacture and appear in a different form in the finished drug product. In *Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corp.*,[66] the court concluded that a patent claiming a hydrated form of pamidromate had been properly submitted for inclusion in the Orange Book as a "component" even though the FDA-approved product contained only anhydrous pamidromate. In adopting its rule against the listing of intermediates, it is not clear if the FDA implicitly repudiated *Ben Venue*'s reasoning.[67]

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62. 54 Fed. Reg. 28,872, 28,881 (July 10, 1989).
63. 21 C.F.R. § 314.53(b)(1) (2006).
64. 68 Fed. Reg. 36,676, 36,680 (June 13, 2003), and FDA Form 3542a, ¶ 3.
65. 68 Fed. Reg. 65,448, 65,452 (Oct. 24, 2002) (citing 21 C.F.R. § 210.3(b)(9)).
66. Ben Venue Labs., Inc. v. Novartis Pharm. Corp., 10 F. Supp. 2d 446, 458 (D.N.J. 1998).
67. The FDA's current rule permits the listing of a patent on a different polymorphic form of the approved active ingredient if it can be shown that the two forms are really versions of the "same" active ingredient, that is, that they are therapeutically equivalent. The result of *Ben Venue* (though not its reasoning) could be supported on the same theory, which is that the hydrated and anhydrous forms of pamidromate were merely versions of the "same" active ingredient.

[A][3] Patents Claiming "Polymorphs"

In 2003, the FDA adopted regulations resolving a controversy about whether patents claiming "polymorphs" (which the FDA defines to include both variant crystal structures and differently hydrated forms) of FDA-approved drug substances may be submitted for listing in the Orange Book.[68] The new rule establishes that patents on polymorphs may (and indeed must) be listed, but *only* if the NDA holder has evidence that the drug substance in the claimed polymorphic form is the "same" as the drug substance that was approved in the NDA, that is, that it is therapeutically equivalent to the drug substance in the form that it actually appears in the approved drug product. Evidence of equivalence does not have to be submitted to the FDA, but the NDA holder must certify that it has test data demonstrating that the claimed polymorph will "perform the same as the drug product described in the [NDA]."[69]

[A][4] Method of Use Patents

Even before the 2003 regulations were adopted, the FDA had required NDA applicants or holders to submit information only on patents claiming indications or conditions of use that were "the subject of the pending or approved application."[70] Thus, patents claiming methods of use that were not the subject of the pending or approved application could not be submitted for listing in the Orange Book.

The 2003 rules enforce this prohibition by requiring the submitter to answer "yes" or "no" as to whether the patent claims a permitted use of the approved drug, and warn that a "no" answer will disqualify the patent from Orange Book listing. To further enforce the prohibition, the FDA's patent listing forms (FDA 3542 and 3542a) require the NDA holder to identify by claim number the patent claim that claims the

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68. For a general discussion of polymorphs, see *supra* section 7:2.5; for a discussion of *in vivo* conversion, see *supra* section 7:2.7.

69. 21 C.F.R. § 314.53(b)(1) (2006). Such test data must include, inter alia, data detailing how the polymorph is made and what controls and specifications are used; records showing preparation of a sample batch under the FDA's "good manufacturing practice" procedures; and data showing that this batch is bioequivalent to the NDA drug. 21 C.F.R. § 314.53(b)(2) (2006). The FDA has explained that the substantiation required to support a polymorph patent listing by an NDA holder is the same as the substantiation that is required of an ANDA filer who wishes to use a polymorphic form of the NDA drug substance. *See* Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676, 36,679 (June 18, 2003).

70. 21 C.F.R. § 314.53(b) (2003). In Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348 (Fed. Cir. 2003), the Federal Circuit cited this language with apparent approval.

FDA-approved use (or the use for which FDA approval is being sought), and to identify where in the approved (or proposed) label that use is specified.[71] A claim to a method of using a combination of drugs does not constitute claiming one of the individual components under the listing statute.[71.1] A claim imposing "a condition of use" does not convert a "system" claim into a listable method-of-treatment.[71.2]

[A][5] Method of Manufacture Patents

Maintaining longstanding FDA policy, the 2003 regulations provide that information on process (method of manufacture) patents may not be submitted for listing in the Orange Book.[72] However, the FDA distinguishes between "process patents," which do not qualify for Orange Book listing, and "product-by-process" patents, which do. To keep this distinction intact, the FDA requires NDA holders to verify on an FDA-supplied form, under penalty of perjury, that the *product* claimed by the patent (that is, not just the recited process) is "novel."[73]

[B] Who Must Submit Patent Information

Submission of a patent for Orange Book listing is the responsibility of the NDA applicant or holder. In most instances, the NDA holder will also be the patent owner, or at least have the same interest as the patent owner in maximizing the patent's enforceability. However,

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71. The forms also require the NDA holder to draft a proposed "use code" for the FDA-approved use, to appear in the Orange Book. Before the new forms were introduced, the use codes were drafted by the FDA based on its understanding of the NDA holder's patent submission. This had led to misunderstandings, or at least purported misunderstandings, about the relationship between the use code and the FDA-approved label. *See* Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191 (D.D.C. 2002) (discussing FDA's belief that the patent claimed an approved use), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004).

71.1. United Food & Commercial Workers Local 1776 v. Takeda Pharm. Co., 11 F.4th 118 (2d Cir. 2021) (holding that "under the 'Listing Requirement' of 21 U.S.C. § 355(b)(1), the" patents containing method of treatment claims to a combination of ACTOS and another drug "do not 'claim the drug' ACTOS.").

71.2. Jazz Pharm., Inc. v. Avadel CNS Pharm., LLC, __ F.4th __ (Fed. Cir. 2023) (claiming a "computer-implemented system" that prevents abuse of a drug for treating narcolepsy not a method of treatment and therefore not listable).

72. 21 C.F.R. § 314.53(b) (2006).

73. A prudent NDA holder should therefore make some independent assessment of novelty, rather than merely relying on the fact of patent issuance, even though issuance of the patent arguably implies that the PTO had found no such product in the prior art. *See* M.P.E.P. § 2113.

that is not always the case. If the patent in question is owned by another party and the NDA holder regards it as invalid or otherwise inappropriate for listing, the patent owner has no right to submit the patent itself, and has no statutory avenue for compelling the NDA holder to submit the patent for listing.[74]

[C] Patent Certification and Duty of Care

The FDA's patent listing forms require a declaration that the patent information being submitted is "accurate" and "complete," as well as a verification "under penalty of perjury" that the application conforms with the regulatory requirements governing listing.

As noted in the preceding section, the NDA applicant may be required to submit patent information about patents that it does not own, and even about patents that it has no authority to enforce.[75] This creates a potential problem: If the NDA applicant is not the patent owner, it may not have sufficient information to make the required declarations, for example, that a product claimed in a patent is "novel." Further, because patents may be submitted only if a claim of infringement "could reasonably be asserted" by the owner, NDA applicants who do not own the patents in question and who may themselves have disputes with the owner about the scope or validity of the patent, may be reluctant to declare under penalty of perjury that the patent was properly submitted. These problems are somewhat ameliorated by the fact that although the "applicant" must *submit* the requisite forms, the FDA allows the patent owner to fill out the form and make the required declarations.[76]

[D] Consequences of False Certification

The intentional submission of false patent information for listing in the Orange Book and subsequent enforcement of the listed patents may have antitrust and patent misuse implications.

[E] Resolution of Orange Book Listing Disputes

FDA regulations allow "any person" to write the agency to "dispute the accuracy or relevance" of an Orange Book patent listing.[78] But FDA disclaims any patent expertise and, as a matter of policy, does not resolve patent disputes. Upon receiving a dispute letter, the FDA

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74. aaiPharma Inc. v. Thompson, 296 F.3d 227 (4th Cir. 2002); *accord* Alphapharm Pty. Ltd. v. Thompson, 330 F. Supp. 2d 1 (D.D.C. 2004).
75. *See* 59 Fed. Reg. 50,338, 50,343 (Oct. 3, 1994); *aaiPharma Inc.*, 296 F.3d 227.
76. 21 C.F.R. § 314.53(c)(4) (2006); FDA Form 3542a, part 6.2, www.fda.gov.
77. [Reserved.]
78. 21 C.F.R. § 314.53(f) (2006).

requests the NDA holder to confirm the Orange Book listing's correctness.[79] Unless the NDA holder withdraws or amends the Orange Book listing, the FDA will retain the patent listing unchanged.

Until the MMA's enactment in 2003, an ANDA applicant had no judicial forum in which to contest whether a patent was properly listed in the Orange Book, and the FDA, claiming a lack of expertise and a lack of resources, did not review the correctness of an Orange Book listing. The Federal Circuit held that the district courts lacked jurisdiction to adjudicate Orange Book listing disputes in the context of a section 271(e)(2) infringement action[80] and it effectively closed the door to an Administrative Procedure Act suit against the FDA for improper Orange Book publication by upholding the FDA's policy of not reviewing Orange Book listings.[81] The MMA now allows an ANDA filer who has been sued under section 271(e)(2) to counterclaim for a declaration that the patent was improperly listed.[82] The Supreme Court has held that the statutory counterclaim to "correct" patent information also provides a basis for an action to correct an incorrect or overly broad "use code."[82.1]

[F] Orange Book Delisting Limitations

Once a patent is removed from the Orange Book, FDA regulations require pending ANDA applications to be amended to change the certification to the delisted patent to "paragraph I" (that is, that information about the patent does not appear in the Orange Book).[83] However, the same regulation requires a patent to remain in the Orange Book during the pendency of any litigation challenge to that patent. The

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79. A "challenge" letter for two patents that had been listed as claiming Zocor® is reproduced as Tab 7 of the Administrative Record in Ranbaxy Labs. Ltd. v. Leavitt, 2006 U.S. Dist. LEXIS 24612 (D.D.C. May 1, 2006). After receiving the letters, the NDA holder Merck "delisted" the patents. Ranbaxy, whose ANDA contained a "paragraph IV" certification as to both patents, sued to challenge the FDA's authority to allow the patents to be delisted. *See infra* note 84 and accompanying text.
80. Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323, 1331 (Fed. Cir. 2001).
81. Apotex, Inc. v. Thompson, 347 F.3d 1335, 1336 (Fed. Cir. 2003).
82. 21 U.S.C. § 355(j)(5)(C)(ii).
82.1. Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670, 1688 (2012); *see also* Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 688 F.3d 766 (Fed. Cir. 2012) (holding on remand from the Supreme Court that, although ANDA applicant prevailed on counterclaim to correct patentee's use code, it was an abuse of discretion for the district court to dictate the precise terms of a use code; the court must allow patentee an opportunity to submit their own modified use code); Jazz Pharm., Inc. v. Avadel CNS Pharm., LLC, ___ F.4th ___ (Fed. Cir. 2023) ("§ 355(c)(3)(D)(ii)(I) provides [accused ANDA filer] with a delisting remedy").
83. 21 C.F.R. § 314.94(a)(12)(viii)(B) (2006). *See infra* section 8:1.3.

U.S. Court of Appeals for the District of Columbia recently ruled, however, that the FDA may not remove a patent from the Orange Book if any ANDA has made a so-called paragraph IV challenge to that patent (that is, that the patent is invalid, unenforceable, or will not be infringed), even if no litigation has ensued.[84] Indeed, a challenged patent may not be removed from the Orange Book even if the patent owner subsequently disclaims the patent, thereby rendering that patent unenforceable.[84.1] In that case the Federal Circuit held that Apotex's declaratory judgment challenge to Daiichi's patent presented a sufficiently "live" controversy to establish jurisdiction, because a judgment in Apotex's favor would begin the clock running on the "first applicant's" 180-day exclusivity, thereby allowing Apotex to enter the market earlier than it would absent a judgment in its favor.[84.2]

[G] Reissue Patents

A patent may be "reissued" under the Patent Act to correct certain errors or defects in the patent's scope or description that would otherwise have rendered the patent invalid. Although such reissued patents are identified by a new patent number preceded by the letters "RE," the reissued patent, as narrowed, continues to have the same exclusionary effect as the original patent and it retains the same expiration date as the original patent.[84.3] In applying its patent listing and certification regulations, FDA has required NDA holders to submit information about reissued patents within thirty days of reissue, and it has required ANDA applicants to amend their certifications to address the patent as reissued. In an unpublished opinion, the U.S. Court of Appeals for the Fourth Circuit has ruled, however, that ANDA applicants must maintain a proper certification to the original patent, as well as amend their certification to address the patent as reissued, so the reissued patent may trigger a new round of litigation, with an associated thirty-month stay, as well as potential 180-day exclusivity for the challenger.[84.4]

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84. Apotex, Inc. v. Daiichi Sankyo, Inc., 781 F.3d 1356 (Fed. Cir. 2015); Ranbaxy Labs. Ltd. v. Leavitt, 469 F.3d 120 (D.C. Cir. 2006); *accord* Teva Pharm. USA, Inc. v. Sebelius, 595 F.3d 1303 (D.C. Cir. 2010) (applying MMA).

84.1. *See Apotex*, 781 F.3d at 1359.

84.2. *Id*. at 1361–62.

84.3. 35 U.S.C. §§ 251, 252.

84.4. Mylan Pharm., Inc. v. FDA, 594 F. App'x 791, 797 (4th Cir. 2014).

§ 8:1.3 Patent Certifications by ANDA or 505(b)(2) Applicant: Paragraphs I, II, III, and IV

[A] Patent Certifications by ANDA Applicant

An ANDA applicant must include in its application one of four certifications regarding the patent status of the Orange Book–listed drug it seeks to copy.[85] Specifically, for each patent that is listed (or that should have been listed) in the Orange Book for the pioneer drug, the applicant must certify that, "in [its] opinion . . . and to the best of [its] knowledge":

- Patent information has not been submitted for listing in the Orange Book (known as a "paragraph I certification");[86]
- The patent has expired (known as a "paragraph II certification");[87]
- The patent will expire on a given date (known as a "paragraph III certification");[88] or
- The patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted" (known as a "paragraph IV certification").[89]

If the applicant makes a paragraph I or II certification, the FDA may approve the ANDA "effective immediately."[90] If the applicant makes a paragraph III certification, then the ANDA approval cannot become effective until the patent expires.[91]

Thus, if the Orange Book lists any unexpired patent for the referenced NDA product and the ANDA filer wishes to obtain FDA marketing approval before patent expiration, it must certify pursuant paragraph IV. A paragraph IV certification triggers the Hatch-Waxman Act's mechanism for resolving patent challenges.

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85. 21 U.S.C. § 355(j)(2)(A)(vii). Under 21 U.S.C. § 355(b)(2)(A), a section 505(b)(2) applicant must make one of the same four certifications regarding the patent status of the Orange Book–listed drug whose safety and efficacy investigations the applicant has "relied" upon in seeking approval of its application.
86. 21 U.S.C. § 355(j)(2)(A)(vii)(I).
87. 21 U.S.C. § 355(j)(2)(A)(vii)(II).
88. 21 U.S.C. § 355(j)(2)(A)(vii)(III).
89. 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Although the statute refers only to invalidity and non-infringement, FDA regulations provide for a paragraph IV certification of unenforceability as well. 21 C.F.R. § 314.94(a)(12)(i)(A)(4) (2006).
90. 21 U.S.C. § 355(j)(5)(B)(i).
91. 21 U.S.C. § 355(j)(5)(B)(ii).

As discussed more fully below, an applicant making a paragraph IV certification must provide notice of its certification to the patent owner and the holder of the NDA for the referenced drug. If the patent owner then fails to bring an action for patent infringement within forty-five days, the approval of the ANDA may be "made effective immediately"[92] after the FDA concludes that all other requirements for the ANDA have been satisfied. But if a patent infringement lawsuit is brought within the forty-five-day window, FDA approval is deferred for thirty months, unless the ANDA applicant prevails in the litigation before the thirty-month period expires.[93]

[B] Patent Certifications by Section 505(b)(2) Applicant

Under 21 U.S.C. § 355(b)(2)(A), a section 505(b)(2) applicant must make one of the same four certifications discussed above regarding patents that claim the listed drug upon whose investigations the applicant has "relied," with the same consequences.

As discussed above in section 8:1.1[E], FDA asserts the authority to review and approve a section 505(b)(2) application based on any information in its files, even if the applicant has not purported to "rely" on some of this information. In *Takeda Pharmaceuticals U.S.A., Inc. v. Burwell*, the district court upheld FDA's interpretation, but the court's ruling was subsequently vacated as moot.[93.1]

[C] Notice of Paragraph IV Certification

[C][1] Contents of Notice

An ANDA applicant who makes a paragraph IV certification that a listed patent is invalid, unenforceable, or not infringed is required to provide notice so that the patentee may decide whether to bring an action for patent infringement.[94] The statutory notice must include a "detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid [or unenforceable] or will not be infringed."[95]

In theory, the "detailed statement" should be sufficient either to provide grounds for an infringement lawsuit or to convince the patent

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92. 21 U.S.C. § 355(j)(5)(B)(iii).
93. *Id. See infra* section 8:1.6.
93.1. Takeda Pharm., U.S.A. Inc. v. Burwell, 78 F. Supp. 3d 65 (D.D.C. 2015), *vacated in pertinent part as moot*, No. 15-5021, 2016 WL 4098633 (D.C. Cir. July 15, 2016).
94. *See* 21 U.S.C. § 355(j)(2)(B)(i).
95. 21 U.S.C. § 355(j)(2)(B)(iv)(II); *see also* 21 C.F.R. § 314.95(c)(6) (2006) (requiring a "full and detailed explanation" of invalidity or non-infringement).

owner that it has no viable infringement claim, obviating a baseless lawsuit and allowing the ANDA applicant to enter the market without delay. In practice, however, patent owners have complained that some of the notices they receive are useless for conducting an infringement analysis. Nonetheless, the statute provides no judicially enforceable means of eliciting a meaningful notice from the ANDA filer before the patent owner has to make its decision whether or not to sue.[96]

[C][2] When Served

The notice of a paragraph IV certification must be mailed within twenty days after the FDA has confirmed that it has accepted the ANDA for filing. A notice mailed before the FDA accepts the ANDA for filing has no legal effect.[96.1] For amendments to ANDAs, the statutory notice must be mailed at the time the amendment is submitted.[97]

[C][3] Who Served

The notice must be sent to the owner of each patent that is the subject of the paragraph IV certification, as well as to the holder of the approved NDA for which the patent was listed in the Orange Book.[98]

§ 8:1.4 ANDA Filing As "Artificial Act of Infringement" Under 35 U.S.C. § 271(e)(2)

[A] Statutory Provisions

The Hatch-Waxman Act was designed to encourage patent owners and prospective generic drug makers to identify and resolve patent disputes before the generic reaches the market. In the pre-market stage, the would-be generic manufacturer is not yet selling the patented invention, and the Hatch-Waxman Act elsewhere immunizes from infringement the use of the invention in studies directed to FDA approval of its product.[99] It was therefore necessary to create a new, statutorily defined "act of infringement" to provide a jurisdictional basis for adjudicating pre-approval patent disputes. To accomplish this, Congress amended the basic infringement section of the Patent Act[100] to add a new subsection (e), which provides in pertinent part:

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96. Minn. Mining & Mfg. Co. v. Barr Labs., Inc., 289 F.3d 775 (Fed. Cir. 2002).
96.1. SB Pharmco P.R., Inc. v. Mut. Pharm. Co., 552 F. Supp. 2d 500 (E.D. Pa. 2008).
97. 21 U.S.C. § 355(j)(2)(B)(ii).
98. 21 U.S.C. § 355(j)(2)(B)(iii).
99. *See infra* section 8:1.8.
100. 35 U.S.C. § 271.

It shall be an act of infringement to submit—

> . . . an application under Section 505(j) of the [FD&C Act] or described in Section 505(b)(2) of such act for a drug claimed in a patent or the use of which is claimed in a patent . . .
>
> if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.[101]

We will now discuss some of the key statutory phrases requiring further elucidation—"submit an application," "under Section 505(j)," and "a drug claimed in a patent or the use of which is claimed in a patent."

[B] Elements of Section 271(e)(2) Infringement Claim

[B][1] "submit an application"

The technical "act of infringement" occurs when the FDA receives the ANDA application (either by hard-copy, or more typically, by electronic submission).[102] However, the submission of an ANDA is not a public act: the FDA is barred from disclosing even the existence of an ANDA until the application is ready for approval.[103] Therefore, the patent owner is not likely to become aware of the ANDA submission—the act of infringement—unless the applicant notifies it of the submission. As discussed above,[104] the ANDA applicant is required to provide such notice if its ANDA contains a so-called paragraph IV certification.[105]

Amendments to an ANDA can also constitute an "act of infringement" under section 271(e)(2). The Federal Circuit has held that the subsequent filing of a Paragraph IV certification directed at a patent

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101. 35 U.S.C. § 271(e)(2)(A)–(B). The statutory cross-references are to 21 U.S.C. § 355(b)(2) and (j), and the provisions governing FDA approval of "paper NDAs" and "ANDAs." *See* 35 U.S.C. § 271(e)(5). Because the patent protection and litigation provisions generally apply in the same fashion to both forms of generic drugs, for the sake of simplicity the text will refer to "ANDAs."
102. FDA, *Guidance for Industry, Providing Regulatory Submissions in Electronic Format—ANDAs* (Oct. 2002), www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163188.pdf.
103. 21 C.F.R. § 314.430(b) (2006).
104. *See supra* section 8:1.3.
105. *See* 21 U.S.C. § 355(j)(2)(B).

that issued after the original ANDA application was filed, but before its FDA approval, constituted an amendment to the ANDA and therefore an "act of infringement."[105.1] The court explained:

> "There is no support for the proposition that the question of infringement be addressed solely based on the initial ANDA filing, given that the statute contemplates that the ANDA will be amended as a matter of course." *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1382, 1390 (Fed. Cir. 2014). Amendments to an ANDA, including a Paragraph IV certification for a later-issued patent, can constitute an act of infringement under § 271(e)(2)(A).[105.2]

There is some authority for the proposition that a section 271(e)(2) claim does not require the existence of a paragraph IV certification.[105.3] In addition, there is authority for bringing suit on patents first listed in the Orange Book after the accused ANDA has been filed.[105.4]

Sometimes a U.S. subsidiary of a foreign parent signs an ANDA, raising the question of whether that subsidiary's actions qualify it as a submitter under section 271(e)(2). The Federal Circuit affirmed a district court's use of the following test addressing this situation:

> [A] wholly-owned subsidiary of a foreign ANDA applicant, which signs an ANDA as the agent of its parent-applicant, and which intends to benefit directly if the ANDA is approved by participating in the manufacture, importation, distribution and/or sale of the generic drug [i]s subject to suit under § 271(e) as the one who has "submitted" the ANDA.[105.5]

105.1. Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1127 (Fed. Cir. 2018) ("[I]t is undisputed that West-Ward amended the ANDA by submitting a Paragraph IV certification regarding the '610 patent after that patent issued. . . . Such an act is a qualifying act of infringement under § 271(e)(2)(A)").

105.2. *Id*.

105.3. Research Found. of the State Univ. of N.Y. v. Mylan Pharm. Inc., No. 1:10-cv-00892-LPS, at *13 (D. Del. May 16, 2012) ("The Court further concludes that a Paragraph IV certification against the Chang Patent was not required for Galderma to bring suit under Section 271(e)(2)."); AstraZeneca Pharm. LP v. Apotex Corp., 669 F.3d 1370, 1380 (Fed. Cir. 2012) (evaluating the merits of a section 271(e)(2) claim despite the absence of a paragraph IV certification and ultimately affirming dismissal because the ANDA did not seek approval for a patented use).

105.4. *Research Found.*, No. 1:10-cv-00892-LPS, 2012 U.S. Dist. LEXIS 80737 (citing Impax Labs., Inc. v. Aventis Pharm. Inc., 468 F.3d 1366, 1372–73 (Fed. Cir. 2006)).

105.5. *In re* Rosuvastatin Calcium Patent Litig., 705 F.3d 511, 528 (Fed. Cir. 2012).

The court affirmed a finding of infringement based on Apotex U.S.'s filing an ANDA for its parent, Apotex Canada, and the fact that Apotex U.S. "actively participated with Apotex Canada in preparation of the ANDA, and that Apotex U.S. intends to directly benefit from the ANDA by selling the drug product in the United States upon approval of the ANDA."[105.6]

[B][2] "under Section 505(j) . . . or described in Section 505(b)(2)"

The act of infringement defined by section 271(e)(2) requires submission of an application under either section 505(j) (21 U.S.C. § 355(j)), or section 505(b)(2) (21 U.S.C. § 355(b)(2)), of the FD&C Act. The statute thus excludes drugs that consist of pharmaceutical proteins, such as interferons, that are approved under the "biologics" licensing provisions of the Public Health Service Act (PHSA) rather than the FD&C Act.[106] Similarly, prior to the enactment of FDAMA in 1999, antibiotic drugs were excluded from the Hatch-Waxman Act's patent enforcement provisions because such drugs, although licensed under the FD&C Act, were not subject to the FD&C Act's "new drug" provisions.[107]

[B][3] "for a drug claimed in a patent or the use of which is claimed in a patent"

Section 271(e)(2) does not provide a pre-approval enforcement mechanism for all patents that may relate to a drug. Only those patents that "claim" the pioneer NDA-approved "drug" or the NDA-approved "use" of that "drug" may be enforced under section 271(e)(2). It is therefore necessary to examine the meaning of those terms.

105.6. *Id*.

106. 42 U.S.C. § 262(j). The PHSA exempts biologics licensed under that statute from the NDA licensing requirements. However, the procedures and standards for approval applicable to "Biologic License Applications" (BLAs) under the PHSA are essentially the same as those applicable to NDAs. *Compare* 21 C.F.R. § 314.50 (2006) (NDAs), *with* 21 C.F.R. § 601.25 (2006) (BLAs). Like NDAs, BLAs are now subject to review by the FDA's Center for Drug Evaluation and Research (CDER), rather than its Center for Biologics Evolution and Research (CBER). As discussed in section 8:4, *infra*, there is no statutory basis, parallel to that for ANDAs, for "generic" biologics.

107. As discussed, the enactment of FDAMA in 1999 brought antibiotics within the ambit of section 271(e)(2). However, copies of "old" antibiotics, that is, those whose active moiety was submitted for approval before FDAMA's enactment date, are not subject to the Hatch-Waxman Act's thirty-month litigation stay. Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1349 (Fed. Cir. 2004).

[B][3][a] "drug claimed in a patent"

Under section 271(e)(2), the "drug claimed in [the] patent" must be either the active ingredient (also known as the "drug substance" or "Active Pharmaceutical Ingredient" (API)), or what the FDA calls the "drug product," that is, the finished, formulated pharmaceutical product (the tablet, capsule, etc.) that is described in the approved NDA.[108] The following subsections discuss the special cases that require further examination.

[B][3][a][i] Patents on Different Formulations

Since the phrase "drug claimed in a patent" in section 271(e)(2) applies only to APIs and drug products described in the approved NDA, section 271(e)(2) does not apply to patents claiming formulations of the active ingredient that are different from the formulation that is approved in the NDA.[109] For example, if the only approved NDA is for a capsule formulation, a patent claiming a tablet formulation is not enforceable under section 271(e)(2).[110]

[B][3][a][ii] Patents on Methods of Manufacture

Patents that claim a method of manufacturing the drug product or the API are not enforceable under section 271(e)(2).[111]

[B][3][a][iii] Product-by-Process Patents

In contrast to patents on methods of manufacture, product-by-process patents are regarded as claiming the "drug" itself (albeit describing that drug in terms of the process used to make it).[112] Therefore, product-by-process patents may be enforced under section 271(e)(2).[113]

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108. *See* 21 C.F.R. § 314.53(b) (2006).
109. See *supra* section 7:3 for a discussion of pharmaceutical formulation patents.
110. Pfizer, Inc. v. FDA, 753 F. Supp. 171, 174 (D. Md. 1990).
111. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1570 (Fed. Cir. 1997). Pre-approval enforcement may nonetheless be available if the patent owner is able to satisfy the "case or controversy" requirements of the Declaratory Judgment Act. *Id*. at 1570–71. See *supra* section 7:5 for a discussion of pharmaceutical manufacturing patents.
112. See *supra* section 7:5.2 for a discussion of product-by-process claims.
113. *See* 68 Fed. Reg. 36,676, 36,679–80 (June 18, 2003) (stating that product-by-process patents "claim" the "drug" and are therefore properly included in the Orange Book). *See also* SmithKlineBeecham Corp. v. Apotex Corp., 2002 U.S. Dist. LEXIS 25275 (E.D. Pa. Dec. 20, 2002) (adjudicating product-by-process patent under section 271(e)(2) and finding patent invalid).

[B][3][a][iv] Patents on Different Polymorphs

There has been some controversy over whether a patent that claims a different polymorph (that is, a different crystalline form) of the API described in the approved NDA may properly be described as claiming the same API.[114] The FDA's position is that a patent on a different polymorph does claim the same API if the polymorph is shown to be functionally the "same," for example, in terms of dissolution, solubility and bioavailability, as the API in the NDA-approved product.[115] There is some judicial support for the FDA's interpretation.[116]

[B][3][a][v] Patents on Metabolites

In *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*,[117] the Federal Circuit held that a patent that claims a metabolite of the active pharmaceutical ingredient does not claim the "drug" itself. Although the Federal Circuit in that case was interpreting the patent extension provisions of the Hatch-Waxman Act rather than section 271(e)(2), the court's holding has been extended to the patent enforcement provisions of the Hatch-Waxman Act as well.[118] Thus, it appears that a patent on a metabolite of the API in the approved NDA is not enforceable under section 271(e)(2).

[B][3][a][vi] Patents on Intermediates

For similar reasons, FDA regulations exclude patents that claim intermediates used in manufacturing a drug or drug product from the class of patents that "claim" the drug or drug product.[119] However, these regulations are in some tension with the case law. In *Ben Venue Laboratories, Inc. v. Novartis Pharmaceutical Corp.*,[120] the court pointed out that another section of the FDA's regulations (relating to "Good Manufacturing Practices") defines "active ingredient" to include "components that undergo chemical change in the

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114. See *supra* section 7:2.5 for a discussion of polymorph patents.
115. 68 Fed. Reg. 36,676, 36,679 (June 18, 2003) (codified at 21 C.F.R. § 314.53(b)(2) (2006)).
116. Ben Venue Labs., Inc. v. Novartis Pharm. Corp., 10 F. Supp. 2d 446 (D.N.J. 1998); Zenith Labs., Inc. v. Abbott Labs., Inc., 1996 WL 33344963 (D.N.J. Aug. 7, 1996).
117. Hoechst-Roussel Pharm., Inc. v. Lehman, 109 F.3d 756 (Fed. Cir. 1997). See *supra* section 7:2.7 for a discussion of *in vivo* conversion including by conversion of a drug in the body into an active metabolite.
118. *In re* Buspirone Patent Litig., 185 F. Supp. 2d 340 (S.D.N.Y. 2002) (patent claiming metabolite not enforceable under section 271(e)).
119. 21 C.F.R. § 314.53(b) (2006). See *supra* section 7:5.1 for a discussion of intermediate patents.
120. Ben Venue Labs., Inc. v. Novartis Pharm. Corp., 10 F. Supp. 2d 446 (D.N.J. 1998).

manufacture of the drug product . . . and [are] present in the drug product in a modified form."[121] Based on this latter definition, the court held that a patent claiming a polymorph of the active ingredient claimed the "drug," in part because the polymorph was used in manufacturing the active ingredient described in the approved NDA, even though that polymorph was not preserved in the final product.

[B][3][b] "or the use of which is claimed in a patent"

"[A] patentee does not need to prove an actual past instance of direct infringement by a physician to establish infringement under 35 U.S.C. § 271(e)(2)(A)." This section "makes it possible for a patent owner to have the court determine whether, if a particular drug *were* put on the market, it *would* infringe the relevant patent."[121.1]

Where "the proposed label instructs users to perform the patented method . . . the proposed label may provide evidence of [the ANDA applicant's] affirmative intent to induce infringement."[121.2] "When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, "'[t]he label must encourage, recommend, or promote infringement.'"[121.3] "The contents of the label itself may permit the inference of specific intent to encourage, recommend, or promote infringement."[121.4] If the label merely "establishes that some users might infringe," without establishing that users are instructed "to perform the patented method," there is no infringement under section 271(e)(2)(A).[121.5]

The Federal Circuit has ruled that where the patent sought to be enforced under section 271(e)(2) claims a method of use, the use must be one that the FDA has approved for the pioneer drug.[122] What is more, the Federal Circuit has held that "a patented method of using a

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121. *Id*. at 457.

121.1. Bristol-Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995).

121.2. AstraZeneca Pharm. LP v. Apotex Corp. (AstraZeneca I), 633 F.3d 1042, 1060 (Fed. Cir. 2010).

121.3. Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd., 877 F.3d 1117, 1129 (Fed. Cir. 2018) (quoting *Takeda*, 785 F.3d at 631).

121.4. *Id*. (citing Sanofi v. Watson Labs. Inc., 875 F.3d 636, 646 (Fed. Cir. 2017)).

121.5. HZNP Medicines LLC v. Actavis Labs. UT, Inc., 940 F.3d 680, 702 (Fed. Cir. 2019) (claim requiring applying inventive formulation, waiting for it to dry, and then applying some other topical medication not infringed by label that merely warns user to wait before applying another substance without instructing the application of any other substance).

122. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348 (Fed. Cir. 2003); *accord* Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322 (Fed. Cir. 2003). See *supra* section 7:4 for a discussion of method of treatment patents.

123. [Reserved.]

drug can only be infringed under § 271(e)(2) by filing an ANDA that seeks approval to market the drug for that use."[124]

The latter limitation is particularly significant. A pioneer drug may be approved for several different uses. However, Congress allowed ANDA applicants to seek approval for fewer than all of the uses for which the pioneer was approved.[125] Thus, if the pioneer drug is approved for unpatented use *A* and patented use *B*, an ANDA applicant may avoid infringement by seeking approval to label its generic copy only for use *A*.[125.1]

However, the fact that the label for an ANDA product omits any mention of a patented use may have little bearing on whether physicians and patients will actually use the product for the patented method of treatment. Although an ANDA product may be *promoted* only for those uses for which it has received FDA approval, nothing in the FD&C Act limits physicians from prescribing or pharmacists from dispensing the ANDA product for other, so-called off-label uses.[126] As one court put it, "[a] physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA."[127]

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124. AstraZeneca Pharm. LP v. Apotex Corp., 669 F.3d 1370, 1379 (Fed. Cir. 2012) (citing *Warner-Lambert*, 316 F.3d at 1358–59); H. Lundbeck A/S v. Lupin Ltd., __ F.4th __ (Fed. Cir. 2023) (seeking approval to treat MDD (covered by an expiring patent) does not constitute an act of infringement with respect to a later patent covering treatment of MDD for a specific subclass of patients).

125. *Warner-Lambert*, 316 F.3d at 1362 (discussing 21 U.S.C. § 355(j)(2)(A)(vii) & (viii) and their legislative history).

125.1. Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316, 1326 (Fed. Cir. 2012) ("As applied to this case, *Warner–Lambert* and *Allergan* make clear that the defendants do not infringe Bayer's '652 patent under section 271(e)(2)(A) and that their sale of the generic form of Yasmin would not induce infringement of that patent. The defendants' ANDAs seek approval to market the generic form of Yasmin solely for contraceptive use, and there is no valid patent on the use of the drug for that purpose alone.").

126. *AstraZeneca*, 669 F.3d at 1380 ("AstraZeneca also argues that Section viii statements and restricted generic labeling ignore market realities because even if a generic drug is formally approved only for unpatented uses, pharmacists and doctors will nonetheless substitute the generic for all indications once it becomes available. We find this argument unpersuasive."); *see also Allergan*, 324 F.3d at 1324 n.1; Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 351 (2001) (recognizing legitimacy of off-label prescribing).

127. Wash. Legal Found. v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000). States that participate in the Medicaid program must reimburse the cost of drugs that are prescribed for "off-label" uses as long as these uses

Because a generic drug is presumed to be therapeutically equivalent to the corresponding pioneer drug, and because state laws generally *require* prescriptions to be filled with a generic drug (unless the prescription forbids it),[128] generic drugs may in practice be expected to be substituted for all of the uses for which the pioneer drug is approved—regardless of what uses are listed in the generic drug's labeling. Thus, while a generic manufacturer may be able to avoid liability under section 271(e)(2) by excluding infringing uses from its label, infringing uses are still likely to occur, to the generic manufacturer's benefit and the pioneer's corresponding harm.

The pioneer is not left entirely without a remedy. If, after approval of its ANDA, the generic manufacturer promotes its product for a patented use, the patentee may be able to bring a conventional action under 35 U.S.C. § 271(b) for inducement of infringement.[129] Moreover, if the patent owner can demonstrate that the ANDA owner is likely to induce infringement, the patent owner may rely on section 271(e)(2) to support an induced infringement claim prior to ANDA approval.[130] To do so, the patent owner must establish the traditional elements of a claim of induced infringement: the patent owner must show (a) that if the ANDA is approved, then the accused infringer will induce third parties (for example, physicians) to directly infringe, and (b) that the accused infringer knows or should know that its actions will induce such infringement.[131]

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are recognized in a statutorily recognized "compendium." Edmonds v. Levine, 417 F. Supp. 2d 1323 (S.D. Fla. 2006).

128. *Warner-Lambert*, 316 F.3d at 1364.

129. *Allergan*, 324 F.3d at 1332 (citing Fina Research, S.A. v. Baroid, Ltd., 141 F.3d 1479 (Fed. Cir. 1998)). It should be noted that the ANDA holder commits a criminal violation if it actively promotes its product for a use for which the FDA has not authorized the product to be marketed. *See* TorPharm, Inc. v. Thompson, 260 F. Supp. 2d 69, 74 n.6 (D.D.C. 2003), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004); 21 U.S.C. § 333 (criminal sanction for misbranding and other FD&C Act violations). Therefore, any inducement of infringement by the ANDA holder is unlikely to be explicit. In addition, it may be argued that some of the ways in which an ANDA holder may influence "off-label" prescribing behavior, for example, by placing information about "off-label" uses in medical journals, may enjoy First Amendment protection. *See generally Henney*, 202 F.3d at 333.

130. *Allergan*, 324 F.3d at 1331. *See also* Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1128 (Fed. Cir. 2018).

131. *Id*. at 1336; *Warner-Lambert*, 316 F.3d at 1363–64. In MGM Studios, Inc. v. Grokster, Ltd., 545 U.S. 913, 940 (2005) (a copyright infringement case), the Supreme Court held that inducement of infringement requires "distribution of a device suitable for infringing use," "actual infringement by recipients of the device," and "intent to bring about infringement." In DSU Med. Corp. v. JMS Co., 471 F.3d 1293 (Fed. Cir. 2006) (en banc),

In short, no action under section 271(e)(2) may be brought on a method of use patent if the use is not approved for the pioneer NDA product. If the patented use is FDA-approved for the pioneer product but the ANDA applicant is not seeking approval for that use, the patentee must satisfy the traditional requirements of an action for inducement of infringement.

[B][4] Enforcement of Non–Orange Book Patents

The Supreme Court explained, in *Eli Lilly & Co. v. Medtronic, Inc.*,[132] that section 271(e)(2) was intended to create "a highly artificial act of infringement" sufficient to give the district court "case or controversy" jurisdiction over patent disputes between patent owners and ANDA filers that could be adjudicated before the ANDA product was marketed.[133] The Court described the statutory infringement act as "submitting an ANDA or paper NDA *containing the fourth type of certification*."[134] The statutory text is not limited, however, to paragraph IV certifications, and the *Eli Lilly* remark was clearly dictum.[135]

Some early lower court decisions nevertheless followed the Supreme Court's dictum and ruled that section 271(e)(2) does not apply unless the patent in suit was listed in the Orange Book and the ANDA filer made (or at least was required to have made) a paragraph IV certification as to that patent.[136]

The Federal Circuit's ruling in *Glaxo Group, Ltd. v. Apotex, Inc.*,[137] strongly suggests that the statute should be read literally, and that an action may be brought under section 271(e)(2) even if the patent in suit does not (and cannot) appear in the Orange Book and no paragraph IV

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the Federal Circuit applied the Supreme Court's *Grokster* test to a claim of induced infringement under the Patent Act. *See also* Aventis Pharm., Inc. v. Barr Labs., Inc., 411 F. Supp. 2d 490 (D.N.J.), *aff'd*, 2006 U.S. App. LEXIS 28524 (Fed. Cir. Nov. 8, 2006) (applying *Grokster* test to a claim for induced patent infringement under section 271(e)(2)); *Vanda Pharm. Inc.*, 887 F.3d at 1128.

132. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990).

133. *Id*. at 678.

134. *Id*. (emphasis added).

135. *Eli Lilly* did not involve an ANDA, or even a drug. Rather, it involved a medical device, as to which section 271(e)(2) does not apply, and the issue was whether section 271(e)(1) insulates the manufacturer of such a device from liability arising out of activities related to obtaining FDA approval.

136. *See, e.g.*, Abbott Labs., Inc. v. Zenith Labs., Inc., 1995 U.S. Dist. LEXIS 3256 (N.D. Ill. Mar. 15, 1995) (patent was "late-listed" in Orange Book and ANDA contained no paragraph IV certification); Marion Merrell Dow v. Hoechst Roussel, 1994 WL 424207 (D.N.J. May 5, 1994) (finding that ANDA should have included paragraph IV certification because patent was properly listable in Orange Book).

137. Glaxo Grp., Ltd. v. Apotex, Inc., 376 F.3d 1339 (Fed. Cir. 2004).

certification is made. The patent in suit in Glaxo claimed the antibiotic "Ceftin®" (cefuroxime hydrochloride). Although antibiotics are "drugs" for which ANDAs may be submitted, Ceftin® does not appear in the Orange Book, and thus Apotex was not required to include any patent certification in its ANDA.[138] After finding the patent to be valid and infringed, the district court issued an injunction pursuant to 35 U.S.C. § 271(e)(4) against marketing the ANDA product before the patent expired, and, after finding the infringement to have been willful, it awarded *Glaxo* attorney fees under section 285. The district court rejected Apotex's argument, based on the *Eli Lilly* dictum, that since it had not made any paragraph IV certification, it could not have committed the "artificial act of infringement" under section 271(e)(2).[139] The Federal Circuit affirmed the infringement finding and the section 271(e)(4) injunction, but reversed the fee award. In so doing, it did not question that Apotex's ANDA filing was itself an infringement under section 271(e)(2), or that fees could be awarded in an action to enforce a non–Orange Book patent based upon litigation misconduct. It held only that, in the absence of any misconduct during the litigation, filing an ANDA itself did not make the case "exceptional."[140] In light of *Glaxo*, it appears that an action may be brought under section 271(e)(2) on a patent not listed in the Orange Book and as to which no paragraph IV certification was made, as long as the patent "claims" the FDA-approved product or an FDA-approved method of using that product, and the ANDA applicant is seeking approval for the claimed product or its use prior to the expiration of the patent. One district court, however, has read *Glaxo* narrowly to apply only where the lack of Orange Book listing resulted from the pre-FDAMA exclusion of antibiotic patents.[140.1]

[C] The Section 271(e)(2) Infringement Analysis

[C][1] Similarities to Standard Infringement Actions

Although the statutory language describes the "act of infringement" as the act of ANDA submission, the ultimate issue in a section 271(e)(2) action "is the same as it is in any other infringement suit,"

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138. As discussed in *supra* section 8:1.4[B][2], ANDAs for antibiotics were not allowed until the enactment of FDAMA in 1997, and a transition provision in FDAMA, Pub. L. No. 105-115, § 125(d)(2), 111 Stat. 2327 (1997), excluded from Orange Book listing patents that claimed pioneer antibiotics that had been approved under the old regime.
139. Glaxo Grp., Ltd. v. Apotex, Inc., 272 F. Supp. 2d 772, 777–79 (N.D. Ill. 2003).
140. *Glaxo*, 376 F.3d at 1350–51.
140.1. Eisai Co. v. Mut. Pharmacal Co., U.S. Dist. LEXIS 93585 (D.N.J. Dec. 20, 2007).

that is, whether the patent in suit is "invalid or will not be infringed by the manufacture, use or sale of the drug for which the [ANDA] is submitted."[141] With regard to the patent's validity or enforceability, the facts in a section 271(e)(2) action are the same as in a conventional infringement action under section 271(a). However, where the issue is infringement, the factual inquiry takes on a "hypothetical" cast: "whether, *if* the drug were approved based upon the ANDA, the manufacture, use or sale of that drug *would* infringe the patent in the conventional sense."[142] It is this "hypothetical" nature of the infringement analysis which introduces some differences from standard infringement cases. These are addressed in the next section.

[C][2] Differences from Standard Infringement Actions

[C][2][a] Overview

The ultimate infringement inquiry under section 271(e)(2) "is focused on a comparison of the asserted patent claims against the product that is likely to be sold following ANDA approval and determined by traditional patent law principles."[143] Although all relevant evidence must be considered, "'[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug,' the ANDA itself dominates the analysis."[144] Thus, in cases where the ANDA "defines a proposed generic product in a manner that either meets the limitations of an asserted patent claim or is outside the scope of such a claim," consideration of the ANDA itself resolves the infringement determination.[145] This remains true even if the ANDA applicant offers to certify that it will not manufacture products within

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141. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997).
142. *Id*. (emphasis added).
143. Ferring B.V. v. Watson Labs., Inc.-Fla., 764 F.3d 1401, 1408 (Fed. Cir. 2014); *accord* Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1365 (Fed. Cir. 2003); Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002); Bristol-Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995).
144. *Ferring*, 764 F.3d at 1408 (quoting *Abbott Labs.*, 300 F.3d at 1373).
145. *Id*.; *see also* Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc., 731 F.3d 1271, 1279–80 (Fed. Cir. 2013) (finding infringement because the ANDA specified an amount of stereoisomer falling within the asserted claim); Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1248–50 (Fed. Cir. 2000) (finding noninfringement because the ANDA specified a surface area falling outside of the claimed range).

the claim scope despite seeking approval from the FDA to do so.[146] In other cases, patentees must resort to evidence such as "biobatch data and actual samples of the proposed generic composition that [the ANDA filer] had submitted to the FDA."[147]

Prior to bringing suit, as discussed in section 8:1.4[C][2][b], the patentee may not have access to either. Once suit is commenced, the patent owner can use the discovery process to gain access to the ANDA and obtain samples of the proposed ANDA drug. However, neither necessarily reflects the product that will actually be marketed upon FDA approval. The ANDA itself is a work in progress, subject to significant change before final approval as discussed in section 8:1.4[C][2][c] below; and the only available product samples at this stage are the samples on which bioequivalence testing was performed, since commercial batches do not yet exist.[148] Accordingly, determining the characteristics of the product that will likely be sold under the approved ANDA may raise difficult issues of proof.

[C][2][b] Pre-Suit Investigation

Because the patent owner will ordinarily commence a section 271(e)(2) action very soon after the ANDA is submitted, it will have no samples of the putative infringing product and it will typically have little or no factual information about the proposed ANDA drug's composition. The patentee may ask the ANDA applicant for samples and documentation prior to bringing suit.[149] While the ANDA applicant is not required to provide such discovery prior to suit, a pre-suit request for information and samples—even if declined—may in some cases

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146. *Sunovion*, 731 F.3d at 1279–80 (reversing judgment of noninfringement of claim requiring less than 0.25% levorotary isomer because the ANDA sought approval of less than 0.6% levorotary isomer despite Reddy's willingness to certify to the court that it would only manufacture product with greater than 0.3% levorotary isomer).

147. *Id.*; *Ferring*, 764 F.3d at 1387 ("[T]he 2010 ANDA is silent with respect to the claim limitations of the patents-in-suit, which do not specify dissolved dissolution rate at 60 minutes.").

148. *See* Biovail Corp. Int'l v. Andrx Pharm., Inc., 239 F.3d 1297, 1304 (Fed. Cir. 2001); Ben Venue Labs., Inc. v. Novartis Pharm. Corp., 146 F. Supp. 2d 572 (D.N.J. 2001) (analyzing amended ANDA).

149. Under 21 U.S.C. § 355(j)(5)(C)(i)(III), an ANDA applicant may offer the patent owner "confidential access" to its ANDA, but there is little incentive for it to do so. The MMA made an offer of confidential access a precondition to the ANDA applicant's ability to sue for a declaratory judgment of noninfringement if the patent owner declines to bring suit. 21 U.S.C. § 355(j)(5)(C)(i)(I)(cc).

be useful to satisfy the patentee's pre-suit investigation obligations under Rule 11 of the Federal Rules of Civil Procedure.[150]

[C][2][c] Determining Infringement Based on ANDA

As discussed above in section 8:1.4[C][2][a], infringement under section 271(e)(2) can be proven based on the ANDA where it provides sufficient specificity with respect to the relevant claim limitations or based on other evidence such as biobatch data and actual samples. The Federal Circuit will "not assume that [an ANDA filer] will not act in full compliance with its representations to the FDA."[150.1] Nevertheless, the Federal Circuit has made clear that infringement under section 271(e)(2) is determined by ascertaining the characteristics of the product that will ultimately be approved and marketed, not the characteristics of the product described in the originally filed ANDA or the characteristics of the biobatch. Accordingly, the filed ANDA "application" which triggers the infringement inquiry under section 271(e)(2) "means the ANDA as filed and all amendments to that application that have been allowed by the FDA."[151] Applicants may amend or resubmit their ANDA for a variety of reasons.[152]

Thus, a section 271(e)(2) case may proceed based on an amended ANDA even after a finding of infringement.[152.1] It is not, however, required to reconsider an infringement finding in view of a subsequent amendment. "Allowing an amendment is within the discretion of the district court, guided by principles of fairness and prejudice to the patent-holder."[152.2]

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150. *See* Hoffman-La Roche Inc. v. Invamed Inc., 213 F.3d 1359, 1365 (Fed. Cir. 2000).

150.1. *In re* Brimonidine Patent Litig., 643 F.3d 1366 (Fed. Cir. 2011); *see also* Par Pharm., Inc. v. Eagle Pharm., Inc., ___ F.4th ___ (Fed. Cir. 2022).

151. *Ferring*, 764 F.3d at 1390.

152. Reasons to amend or resubmit include:

- 21 C.F.R. § 314.101(a)(3) (FDA refusal to file ANDA because the reference drug is entitled to a five-year exclusivity period);
- 21 U.S.C. § 355(j)(D)(ii) ("[N]othing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.");
- 21 C.F.R. § 314.102(b) (permitting corrections by amendment during the review process);
- 21 C.F.R. § 314.100 (providing for different review timelines if applicant submits a major amendment);
- 21 C.F.R. § 314.160 (authorizing approval based on newly submitted data of a previously refused, suspended, or withdrawn application).

152.1. *Ferring*, 764 F.3d at 1391 ("A district court may reconsider its own finding of infringement in light of an amended ANDA or other information.").

152.2. *Id*.

Bayer AG v. Elan Pharmaceutical Research Corp. provides an example of applying section 271(e)(2) to an amended ANDA.[152.3] In *Bayer*, the starting material for the active ingredient used in Elan's "biobatch" appeared to fall within the patented range, but the ANDA was later amended to specify that only material outside the patented range would be used.[152.4] In affirming summary judgment for Elan, the Federal Circuit ruled that the latest available information about the proposed product—that provided by the product specification in the amended ANDA—required a finding of noninfringement. When the latest version of the ANDA obligates the applicant to market a product that does not satisfy a claim element, that is generally dispositive of noninfringement, because the FD&C Act requires the ANDA applicant to conform its product to the ANDA specification. The applicant in *Bayer* specified it would not use an ingredient within the claimed range; therefore, there was no basis for concluding that the ultimate commercial product would infringe.[152.5]

Conversely, "[i]f an ANDA specification defines a property of a compound such that it must meet a limitation of an asserted claim, then there will almost never be a genuine dispute of material fact that the claim is infringed with respect to that limitation."[152.6]

[C][2][d] Determining Infringement Based on Evidence Beyond the ANDA

If the ANDA specification does not clearly require satisfaction or nonsatisfaction of a claim element, it will not be determinative of infringement. The patent owner cannot carry its burden of showing that the proposed product is "likely" to infringe merely because the ANDA fails to forbid the ANDA holder from making an infringing product. In *Glaxo, Inc. v. Novopharm, Ltd.*,[152.7] the ANDA permitted some amount of the crystal form claimed by the patent to appear in the proposed product, but the "biobatch" contained none of the infringing form. The court ruled that the test is not what the ANDA applicant "can" sell, but rather what it is "likely" to sell.[152.8]

152.3. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241 (Fed. Cir. 2000).
152.4. *Id*. at 1246.
152.5. *Id*. at 1250; *see also In re* Brimonidine Patent Litig., 643 F.3d 1366, 1378 (Fed. Cir. 2011) ("[N]either party disputes that if Exela complies with its ANDA, it will never manufacture or sell a product at a pH above 6.7," which does not infringe; therefore the court "reverse[s] the district court's judgment" of infringement.).
152.6. Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002).
152.7. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562 (Fed. Cir. 1997).
152.8. *Id*. at 1569. The appellate court ascribed some significance to Glaxo's failure to test the biobatch samples.

For the same reason, testing anything but what will be the finished product may be insufficient to prove infringement.[152.9]

[C][2][e] Determining Infringement for Method Claims

An analysis similar to the above applies to establishing infringement of a patent claiming the use of the drug to treat a medical condition. In most method cases, infringement is determined based on the proposed labeling set forth in the ANDA.[152.10]

§ 8:1.5 *Procedural Considerations in ANDA Litigation*

[A] Parties, Jurisdiction, and Venue

[A][1] Proper Plaintiff

The necessary plaintiff in a section 271(e)(2) infringement action is the same as in any other patent infringement case—the owner of the patent.[153] If the pioneer NDA holder does not own the patent or hold all substantial rights under the patent, it lacks standing to sue for infringement.[154] Therefore, if the NDA holder merely possesses a license—without holding all substantial rights under the patent—it must persuade or compel the patent owner to join in the action.[155]

[A][2] Proper Defendants

Because the statutory text makes it an act of infringement to "submit" an ANDA, the "submitter" is a proper defendant. The identity of the "submitter" is usually evident. FDA regulations require that the name of the "applicant"—defined as "any person who submits" an ANDA—to appear on the application.[156] And because the Hatch-Waxman Act requires the ANDA "applicant" to provide notice to the patent owner and NDA holder that it is seeking approval to market

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152.9. *Ferring*, 764 F.3d at 1409 ("The infringement evaluation is concerned only with the final, coated commercial tranexamic acid tablets for which Watson sought and was granted FDA approval to market as a generic version of a treatment of menorrhagia.").

152.10. *See supra* section 8:1.4[B][3][b].

153. For purposes of standing to sue, the "owner" of a patent includes an exclusive licensee who holds all substantial rights under the patent. Sicom Sys. Ltd. v. Agilent Tech., Inc., 427 F.3d 971 (Fed. Cir. 2005).

154. *E.g.*, Pfizer, Inc. v. Elan Pharm. Research Corp., 812 F. Supp. 1352 (D. Del. 1993); *see* Vaupel Textilmaschinen KG v. Meccanica Euro Italia S.P.A., 944 F.2d 870, 875 (Fed. Cir. 1991).

155. Abbott Labs. v. Diamedix Corp., 47 F.3d 1128, 1130–33 (Fed. Cir. 1995).

156. 21 C.F.R. §§ 314.3(b) & 314.94(a)(1) (2006).

its product prior to the expiration of all relevant patents,[157] a plaintiff can generally identify at least one appropriate defendant from the notice it has received. Where the "applicant" is a foreign corporation, FDA's regulations require that the application be countersigned by the applicant's U.S. agent, which has led one court to conclude that where the "agent" is the foreign applicant's subsidiary, the subsidiary may also be subject to suit under section 271(e)(2), perhaps on the theory that by "countersigning" the application the agent also becomes a "submitter."[158]

The patentee may also wish to sue the entity that is actually making the allegedly infringing product (or its active ingredient), and who is supplying that product to the ANDA applicant. It is common for an ANDA applicant to incorporate by reference a DMF submitted to the FDA by the supplier.[159] The district courts have disagreed as to whether such DMF holders are proper defendants under section 271(e)(2). In *SmithKline Beecham Corp. v. Geneva Pharmaceutical, Inc.*,[160] the court allowed a section 271(e)(2) claim to be asserted against the DMF holder based on an inducement of infringement theory. However, the court in *Astrazeneca AB v. Mylan Laboratories, Inc.*[161] disagreed, and held that a section 271(e)(2) complaint could not properly be asserted against a manufacturer who would be participating in the manufacture of the commercial ANDA product and whose manufacturing records were referred to in the ANDA. Thus, it remains unclear whether any person other than the ANDA applicant is a proper defendant in a section 271(e)(2) case.[162]

[A][3] Jurisdiction and Venue

Subject matter jurisdiction and venue in section 271(e)(2) cases are governed by the regular patent jurisdiction and venue statutes:

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157. 21 U.S.C. § 355(j)(2)(B)(i). The notification obligation applies only to an applicant who has made (or at least is required to have made) a so-called paragraph IV certification to patents that have been listed in the "Orange Book." *See supra* section 8:1.3.
158. Aventis Pharma Deutschland GmbH v. Lupin Ltd., 403 F. Supp. 2d 484, 488 (E.D. Va. 2005) (citing 21 C.F.R. § 314.50(a)(5) (2005)); *but see* Pfizer, Inc. v. Ranbaxy Labs. Ltd., 321 F. Supp. 2d 612 (D. Del. 2004) (dismissing claim against U.S. subsidiary).
159. *See supra* section 8:1.1[C][5].
160. SmithKline Beecham Corp. v. Geneva Pharm., Inc., 287 F. Supp. 2d 576 (E.D. Pa. 2002).
161. Astrazeneca AB v. Mylan Labs., Inc., 265 F. Supp. 2d 213 (S.D.N.Y. 2003).
162. *See also Pfizer*, 321 F. Supp. 2d 612 (holding that a claim for inducement of infringement cannot be based solely on allegations that a defendant aided and abetted the applicant's filing of the ANDA).

28 U.S.C. § 1338(a), which establishes exclusive federal jurisdiction; section 1400(b), which provides that an action may be brought where the defendant "resides" or where the act of infringement is committed; and section 1391(c), which in the case of a corporation, defines "resides" to mean "is subject to service of process." "[T]he requirements for [subject matter] jurisdiction in the district courts are met once a patent owner alleges that another's filing of an ANDA infringes its patent under § 271(e)(2), and this threshold jurisdictional determination does not depend on the ultimate merits of the claims."[162.1] This is true even if no paragraph IV certification has been filed, although the claim may still be subject to a motion to dismiss on the merits.[162.2] Additionally, this is true even if the asserted patent is issued after the ANDA application has been filed and before FDA approval.[162.3]

Recent Supreme Court rulings in *Daimler AG v. Bauman*[162.4] and *Goodyear Dunlop Tires Operations, S.A. v. Brown*[162.5] have taken a narrow view of when a defendant is "at home" in the potential forum state. In the wake of these rulings district courts have taken a close look at whether an ANDA filer is subject to the district court's "general" jurisdiction, *e.g.*, by having registered to do business in the forum state, or the court's "specific" jurisdiction, *e.g.*, by having directed a paragraph IV "notice letter" to the plaintiff in the district.[162.6] The

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162.1. AstraZeneca Pharm. LP v. Apotex Corp., 669 F.3d 1370, 1377 (Fed. Cir. 2012); Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1330 (Fed. Cir. 2003) ("Section 271(e)(2) is not a jurisdictional statute in the strict sense of the word. . . . We explained in *Glaxo* that section 271(e)(2) 'provide[s] patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity.' Once Congress creates an act of infringement, jurisdiction in the district court is proper under 28 U.S.C. § 1338(a).") (citations omitted). *See also* Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1124 (Fed. Cir. 2018) ("Here, Vanda's complaint alleged that West-Ward infringed the '610 patent under 35 U.S.C. § 271(e)(2)(A) by filing the ANDA. . . Nothing more was required to establish the district court's subject matter jurisdiction pursuant to 28 U.S.C. § 1338(a).").

162.2. *See* AstraZeneca, 669 F.3d at 1377 (rejecting argument that no subject matter jurisdiction existed to evaluate section 271(e)(2) claim in the absence of a paragraph IV certification).

162.3. *Vanda Pharm. Inc.*, 887 F.3d at 1124 (rejecting argument that "a claim for § 271(e)(2) infringement can only be based on patents that have issued before an ANDA is filed").

162.4. Daimler AG v. Bauman, 134 S. Ct. 746 (2014).

162.5. Goodyear Dunlop Tires Ops., S.A. v. Brown, 131 S. Ct. 2846 (2011).

162.6. *See, e.g.*, AstraZeneca AB v. Mylan Pharm., Inc., 72 F. Supp. 3d 549 (D. Del. 2014); Acorda Therapeutics, Inc. v. Mylan Pharm., Inc., 78 F. Supp. 3d 572 (D. Del. 2015).

Court of Appeals for the Federal Circuit heard interlocutory appeals in two of these cases,[162.7] and ruled that "the minimum-contacts standard is satisfied by the particular actions Mylan has already taken—its ANDA filings—for the purpose of engaging in that injury-causing and allegedly wrongful marketing conduct in Delaware."[162.8] Personal jurisdiction may be disputed if the ANDA applicant can demonstrate it has no plans to market the accused drug in the jurisdiction upon approval.[162.9]

Technically, the "act of infringement" in a section 271(e)(2) case is the submission of an ANDA, which takes place at the FDA's principal office in Maryland. The mere act of filing the ANDA with the NIH, without taking into account the actual sales that will occur upon approval, does not confer personal jurisdiction in Maryland.[163] The Federal Circuit, however, as explained above, subsequently held that a Court may consider "the real-world actions for which approval is sought" in determining infringement under section 271(e)(2) and assessing whether that future infringing conduct will take place in the forum so as to confer personal jurisdiction.[163.1]

The consequences of filing in the wrong forum, where personal jurisdiction is ultimately found lacking, may be severe. The forty-five-day window for triggering the thirty-month stay may have closed by the time a jurisdictional challenge is resolved. Patent owners therefore commonly hedge their bets by filing duplicate actions, hoping to establish jurisdiction somewhere other than the defendant's home court.[164] Even for foreign ANDA applicants there will always be at least one forum in which the patent owner can establish jurisdiction, because FDA regulations require foreign applicants to designate an agent in the United States authorized to accept service of process.[165]

162.7. Acorda Therapeutics, Inc. v. Mylan Pharm., Inc., No. 15-1456 (Fed. Cir. 2015); AstraZeneca AB v. Aurobindo Pharm. Ltd., No. 15-1460 (Fed. Cir. 2015).

162.8. Acorda Therapeutics, Inc. v. Mylan Pharm., Inc., 817 F.3d 755, 759–60 (Fed. Cir. 2016).

162.9. *Id*. at 760 ("Delaware is undisputedly a State where Mylan will engage in that marketing if the ANDAs are approved.").

163. Zeneca, Ltd. v. Mylan Pharm., Inc., 173 F.3d 829 (Fed. Cir. 1999).

163.1. *Acorda*, 817 F.3d at 762–63 (holding that *Zeneca* does not mandate a different result because it was "decided without any majority opinion" and did not "address[ ] whether the location of the ANDA filer's future sales could support specific personal jurisdiction over the filer in the § 271(e)(2) suit.").

164. *See* Abbott Labs. v. Mylan Pharm., Inc., 2006 U.S. Dist. LEXIS 13782 (N.D. Ill. Mar. 28, 2006).

165. 21 C.F.R. § 314.95(c)(7) (2006).

[B] Pretrial Proceedings

Pretrial proceedings in a section 271(e)(2) case resemble those of a conventional patent infringement action, although there is no need for discovery or expert testimony on damages.

[C] No Jury Trial

Unless the defendant has already commercialized its ANDA product, the only relief available in an action under section 271(e) is an order delaying the effective approval date for the defendant's ANDA and an injunction against commercialization of the ANDA product until after the patent expires.[166] Because, in the ordinary case, the plaintiff is entitled only to injunctive relief, no jury trial is available in the ordinary section 271(e) infringement action.[167]

Until 2005, district courts disagreed about whether a defendant charged with infringement under section 271(e) is entitled to a jury trial on its counterclaim.[168] However, in *In re Technology Licensing Corp.*,[169] the Federal Circuit made clear that an accused infringer-counterclaimant is entitled to a jury trial only if the infringement claim, as asserted by the patentee, would give rise to a jury trial. Thus, it appears that in the absence of commercialization and a claim for damages, neither the plaintiff nor the defendant in a section 271(e) case is entitled to a jury.

§ 8:1.6 *Thirty-Month Litigation Stay Preventing Launch of Generic*

In return for providing generic manufacturers an earlier entry than had existed under prior law, the Hatch-Waxman Act provides pioneer patent owners an opportunity to vindicate their patent rights before generic entry occurs. This opportunity is provided by requiring pioneer NDA-holders to submit patent information regarding their drug products for listing in the Orange Book. As discussed earlier,[170] for each of the listed patents, an ANDA applicant must "certify" whether it will respect that patent. The FDA is then barred from approving the ANDA prior to patent expiration unless the applicant has challenged the patent by certifying that in its opinion, the patent is invalid,

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166. *See infra* section 8:1.7. In an "exceptional case," the plaintiff may also recover attorney fees under 35 U.S.C. § 285.
167. *See* Tegal Corp. v. Tokyo Electron Am., Inc., 257 F.3d 1331, 1341 (Fed. Cir. 2001).
168. The conflicting authorities were considered and evaluated in Sanofi-Synthelabo v. Apotex Inc., 64 U.S.P.Q.2d (BNA) 1684 (S.D.N.Y. 2002).
169. *In re* Tech. Licensing Corp., 423 F.3d 1286 (Fed. Cir. 2005).
170. *See supra* section 8:1.2.

unenforceable or not infringed.[171] Such a certification is called a "paragraph IV certification."[172]

A paragraph IV certification is a statutory gauntlet. If the patent owner does not respond to the challenge, the FDA may approve the ANDA "immediately," that is, without regard to any unresolved patent or exclusivity issues. If, however, the patent owner picks up the gauntlet and sues, the FDA generally may not approve the ANDA for thirty months, or (if earlier) until the court enters a judgment finding the patent to be invalid, unenforceable, or not infringed.[173]

[A] Orange Book Listing Is Prerequisite to Thirty-Month Stay

The thirty-month stay is invoked only if "an action is brought for infringement of the patent that is the subject of the [paragraph IV] certification and for which information was submitted" to the FDA in an NDA or an NDA amendment or supplement.[174] Therefore, patents that are not listed in the Orange Book cannot benefit from the thirty-month stay.[175]

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171. 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Although the statutory text refers only to invalidity or non-infringement, FDA regulations treat a certification of unenforceability as equivalent to a certification of invalidity, and the courts have followed the regulations. *See* Teva Pharm., USA, Inc. v. FDA, 182 F.3d 1003, 1009 (D.C. Cir. 1999) (citing 21 C.F.R. § 314.94(a)(12)(i)(A)(4)); Merck & Co. v. Danbury Pharmacal, Inc., 694 F. Supp. 1 (D. Del. 1988), *aff'd*, 873 F.2d 1418 (Fed. Cir. 1989).

172. *See supra* section 8:1.3.

173. Where the pioneer drug is entitled to non-patent data-based exclusivity as a "new chemical entity" (NCE), the statutory litigation stay ends 7½ years from the date the pioneer's NDA was originally approved. The stay period for NCE drugs is designed to be at least as long as the normal thirty-month period, and may last longer. *See In re* Ciprofloxacin Hydrochloride Antitrust Litig., 261 F. Supp. 2d 188, 195 n.8 (S.D.N.Y. 2003) (recognizing that longer period resulted for NCE); *see also infra* section 8:3.2. The trial court may also expand or shorten the stay period if it finds that a party has unduly delayed the litigation. *See infra* section 8:1.6[B].

174. 21 U.S.C. § 355(j)(5)(B)(iii).

175. The criteria for listing a patent in the Orange Book is discussed *supra* section 8:1.2[A]. As explained in that section, patents that neither claim the drug nor claim a method of using the drug, and patents on certain antibiotics, are ineligible for listing in the Orange Book. These patents cannot give rise to a thirty-month stay.

Prior to enactment of the MMA, an ANDA applicant had no right to challenge the propriety of an Orange Book listing in a section 271(e)(2) action. Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001). The MMA now allows an ANDA filer who has been sued under

Moreover, for ANDAs filed after August 18, 2003, the patent must have issued *before* the ANDA was filed.[176] An infringement suit on a patent that issued after the ANDA was filed does not give rise to a thirty-month stay. However, because FDA considers the original and reissued patent to possess "a single bundle of patent rights," the thirty-month stay will remain in effect even though the original patent has been cancelled and replaced by a reissue patent within the thirty-month period.[176.1]

[B] Beginning of the Thirty-Month Stay

[B][1] Calculated from Receipt of Notice

FDA rules provide that the thirty-month statutory stay period starts to run when the patent owner receives notice from the ANDA filer that it has made a paragraph IV certification.[177]

[B][2] The Forty-Five-Day Window

After receiving the statutory notice of a paragraph IV certification, the patent owner must sue within forty-five days to benefit from the statutory stay.[178] The FDA counts the forty-five-day period from the receipt of the notice by the patent owner and NDA holder's mailroom, rather than its corporate or legal offices, and it has insisted on strict compliance with the forty-five-day period.[179] If the patent owner fails to sue within forty-five days, there is no thirty-month stay.[180]

[C] Adjustment of Thirty-Month Stay

The Hatch-Waxman Act authorizes the presiding judge in a section 271(e)(2) action to make the thirty-month stay shorter or longer if the judge finds that a party has failed to "reasonably cooperate

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section 271(e)(2) to counterclaim for a declaration that the patent was improperly listed. 21 U.S.C. § 355(j)(5)(C)(ii). *See supra* section 8:1.2[E].

176. 21 U.S.C. § 355(j)(5)(B)(iii), as amended by the MMA, Pub. L. No. 108-173, § 1101(c) (2003).

176.1. *See* Mylan Pharm., Inc. v. FDA, 2014 U.S. Dist. LEXIS 73448 (N.D. W. Va. May 29, 2014).

177. 21 C.F.R. § 314.107(b)(3) (2006).

178. 21 U.S.C. § 355(j)(5)(B)(iii). If the forty-fifth day falls on a weekend or legal holiday, the next non-holiday weekday counts as the forty-fifth day. 21 C.F.R. § 314.107(f) (2006).

179. *See* Mylan Labs., Inc. v. Thompson, 332 F. Supp. 2d 106, 113 n.9 (D.D.C.), *aff'd*, 389 F.3d 1272 (D.C. Cir. 2004).

180. Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1284 (D.C. Cir. 2004) ("if the patent holder fails to [sue] within forty-five days, it will lose the benefit of the 30-month stay period").

in expediting the action."[181] Statutory stay adjustments have not been frequent, however, perhaps because courts have been unwilling to blame one party exclusively for failure to cooperate. However, the stay has been extended where the defendant has violated a court's case management order, and shortened where the plaintiff unjustifiably delayed disclosing the patent's inventors.[182] The statutory adjustment has also been used when the litigation has been delayed, with court approval, at a party's request.[183] In *Eli Lilly & Co. v. Teva Pharmaceuticals USA, Inc.*,[183.1] the Federal Circuit held that the district court did not abuse its discretion by extending the thirty-month stay by four months based on Teva's amendment of its ANDA to change the particle size manufacturing specification of its API and the method of measuring the particle size for its proposed generic product—where Teva's ANDA amendment occurred late in the litigation, which in turn led to the production of product samples and thousands of pages of related documents past the discovery deadline.[183.2]

In light of the statutory language "expediting the action," courts have held that the stay period may be adjusted only for a party's conduct occurring after the lawsuit has begun. Thus, one court concluded that it lacked the power to extend the thirty-month stay based upon an ANDA filer's inadequate pre-litigation notice.[184]

[D] Termination of Thirty-Month Stay

[D][1] Judgment of Non-Infringement, Invalidity, or Unenforceability

Under 21 U.S.C. § 355(j)(5)(B)(iii)(I), as amended by the MMA, the statutory stay terminates before the thirty-month period has elapsed if "the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of

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181. 21 U.S.C. § 355(j)(5)(B)(iii).

182. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 58 U.S.P.Q.2d (BNA) 1543 (S.D. Ind. 2001) (late expert report); Dey, L.P. v. Eon Labs, Inc., 2005 U.S. Dist. LEXIS 39475 (C.D. Cal. Dec. 22, 2005).

183. Novartis Corp. v. Dr. Reddy's Labs., Ltd., 2004 U.S. Dist. LEXIS 21094 (S.D.N.Y. 2004) (extending thirty-month period as requested by defendant).

183.1. Eli Lilly & Co. v. Teva Pharm. USA, Inc., 557 F.3d 1346 (Fed. Cir. 2009).

183.2. *Id*. at 1350. Judge Prost dissented on the ground that Teva's conduct did not meet the statutory standard for an extension of the thirty-month stay, that is, a failure "'to reasonably cooperate in expediting the action.'" *Id*. at 1352 (Prost, J., dissenting) (quoting 21 U.S.C. § 355(j)(5)(B)(iii)).

184. AstraZeneca AB v. Mut. Pharm. Co., 221 F. Supp. 2d 528 (E.D. Pa. 2002).

action for patent infringement or invalidity)."[185] The FDA has ruled that a district court judgment of non-infringement or invalidity terminates the thirty-month stay, even though that judgment is later vacated or stayed.[185.1]

The statute thus provides that a judgment of non-infringement or invalidity terminates the stay, and once the stay is terminated, the later vacation of the district court judgment does not revive the stay.[185.2] The statutory phrase "substantive determination that there is no cause of action for patent infringement or invalidity" appears to endorse the D.C. Circuit's suggestion in *Teva Pharmaceutical USA, Inc. v. FDA*,[186] that dismissal of a declaratory judgment action for lack of subject matter jurisdiction might be regarded as a court decision that the patent was unenforceable, where the "controversy" needed to establish jurisdiction was eliminated by the patent owner's stipulation of non-infringement. However, the FDA, with D.C. Circuit approval, has subsequently rejected the "estoppel-based" approach suggested by the 1999 D.C. Circuit opinion.[187]

[D][2] Effect of Settlement

Settlement of a litigation may also have the effect of terminating the statutory stay, because a settlement eliminates the stay's rationale, giving the parties an opportunity to resolve the patent challenge in court prior to FDA approval.

In 1999, the FDA proposed regulations that would have terminated the statutory stay upon any dismissal of the underlying litigation, including (presumably) a dismissal "without prejudice."[188] Although this proposal was never enacted, it would have had little practical effect in any event. A settlement agreement can, and should, stipulate when the defendant may enter the market. For example, if the defendant agrees to defer market entry until after patent expiration, the agreement may

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185. The MMA did not amend the statutory language to conform to the FDA's regulatory practice of terminating the stay on a judgment of unenforceability. Nevertheless, the FDA continues to approve ANDAs upon a judgment of unenforceability.

185.1. Sanofi-Aventis v. FDA, 643 F. Supp. 2d 82, 87 (D.D.C. 2009) (denying plaintiffs' motion seeking a temporary restraining order and preliminary injunction ordering the FDA to rescind the approval it gave to third-party drug manufacturers to manufacture and market generic versions of plaintiffs' drug after the district court entered judgment of non-infringement of plaintiffs' patent).

185.2. Sanofi-Aventis v. FDA, 725 F. Supp. 2d 92, 99–101 (D.D.C. 2010).

186. Teva Pharm. USA, Inc. v. FDA, 182 F.3d 1003 (D.C. Cir. 1999).

187. Apotex, Inc. v. FDA, 449 F.3d 1249 (D.C. Cir. 2006).

188. 64 Fed. Reg. 42,873, 42,881 (Aug. 6, 1999). Under FED. R. CIV. P. 41(a)(1), a dismissal without prejudice may be effected without any court order.

require the defendant to amend its ANDA to include a so-called paragraph III certification that it does not seek marketing approval until the patent expires.[189]

[E] Multiple Thirty-Month Stays

There are various scenarios where NDA holders have attempted to obtain multiple thirty-month stays with respect to the same ANDA. One such situation, arising from adding (usually later-issuing) patents to the Orange Book after the ANDA was filed, has been eliminated by statute.[189.1]

Another scenario arises when an ANDA applicant initially challenges some listed patents with a paragraph IV certification and then subsequently changes paragraph III certifications against previously listed patents into paragraph IV certifications. An amendment to the ANDA application must "contain an appropriate patent certification or statement described in § 314.94(a)(12)."[189.2] The ANDA applicant must notify the NDA holder at the time of any amendment that includes a paragraph IV certification.[189.3] If the NDA holder files suit within the forty-five-day window upon receipt of that notice, it may be entitled to a thirty-month stay in addition to any previous stays that it obtained from prior paragraph IV certifications.[189.4]

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189. *See* Mylan Pharm., Inc. v. Henney, 94 F. Supp. 2d 36 (D.D.C. 2000), *vacated as moot sub nom.* Pharmachemie B.V. v. Barr Labs., Inc., 284 F.3d 125 (D.C. Cir. 2002).

189.1. *See* section 8:1.6[A] on Orange Book listing.

189.2. 21 C.F.R. § 314.96(d)(1).

189.3. An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph— . . . (II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

21 U.S.C. § 355(j)(2)(B)(ii)(II).

189.4. 21 U.S.C. § 355(j)(2)(B); 81 Fed. Reg. 69,580, 69,616 (Oct. 6, 2016) ("We recognize that a 30-month stay of approval may result from initiation of a patent infringement action in response to a second notice of paragraph IV certification that is provided with an amendment to a 505(b)(2) application or ANDA. This scenario may occur if the patent at issue in the infringement action was listed before the date of submission of the original 505(b)(2) application or ANDA and, for example, the infringement action was warranted by the change proposed in the amendment."); Letter from FDA to John B. Dubeck, FDA-2003-P-0519, n.6 (Feb. 6, 2015) ("We note that a 30-month stay of approval may result from initiation of a patent infringement action in response to a second notice of paragraph IV

§ 8:1.7 Remedies

[A] Order Precluding FDA Approval of ANDA Until Patent Expiration

Upon determining that an ANDA filing infringes, the court can enter an order preventing approval of the ANDA prior to patent expiration. The statute states: "the effective date of any approval of the . . . drug involved in the infringement [shall] be on a date which is not earlier than the date of the expiration of the patent which has been infringed."[190]

The Federal Circuit has explained that "[i]f the court determines that the patent is not invalid and that infringement would occur, and that therefore the ANDA applicant's paragraph IV certification is incorrect, the patent owner is entitled to an order that FDA approval of the ANDA containing the paragraph IV certification not be effective until the patent expires."[191] However, despite the statutory command that the court "shall" order that the effective date of FDA approval be no earlier than the date the patent expires, there is some authority to support judicial discretion.[192]

The ANDA's effective date may be set at patent expiration even if the FDA has already granted final marketing approval for the ANDA.[193]

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certification provided at the time of submission of an amendment to a 505(b)(2) application or ANDA if the patent at issue in the infringement action was listed prior to the date of submission of the original 505(b)(2) application or ANDA and, for example, the infringement action was warranted by the change proposed in the amendment or supplement.").

190. 35 U.S.C. § 271(e)(4)(A).

191. Bristol-Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995) (finding the patentee entitled to an order that the effective date of any approval of the ANDA would not be earlier than the expiration date of the patent as extended by the Uruguay Round Agreements Act (URAA) because URAA's safe harbor provision did not render the ANDA filing non-infringing for purposes of the Hatch-Waxman Act). *Accord In re* Omeprazole Patent Litig., 536 F.3d 1361, 1367–68 (Fed. Cir. 2008) (FDA approval effective date deferred until six months after patent expiry to account for pediatric exclusivity under 21 U.S.C. § 355a).

192. SmithKline Beecham Corp. v. Apotex Corp., 247 F. Supp. 2d 1011, 1048–52 (N.D. Ill. 2003) (Posner, J.) (declining to issue an order delaying ANDA approval based on "hypertechnical infringement" because such a delay order "is subject to equitable principles"), *aff'd on other grounds*, 365 F.3d 1306 (Fed. Cir. 2004).

193. Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004).

[B] Injunctive Relief

Upon determining that an ANDA filing infringes, a court may also enjoin the infringer from making, using, or selling the product. The statute provides that "injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biologic product."[194] The four-factor test that the Supreme Court has required for permanent injunctions under section 283 of the Patent Act governs injunctions under section 271(e)(4)(B) as well.[194.1]

[C] Damages Only upon Commercial Sales of Infringing Product

The Hatch-Waxman Act allows damages or other monetary relief (other than attorney fees) only "if there has been commercial manufacture, use, offer to sell, or sale within the United States . . . of an approved drug."[195]

[D] Attorney Fees

[D][1] Statutory Provisions: Sections 271(e)(4) and 285

In the American legal system, each party to a litigation generally pays its own costs regardless of who wins.[196] Section 285 of the patent statute, however, states that the "court in exceptional cases may award reasonable attorney fees to the prevailing party."[197] Furthermore, section 271(e)(4) states that the attorney fees provision of section 285 fully applies when the act of infringement is the filing of an ANDA.[198]

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194. 35 U.S.C. § 271(e)(4)(B); *see also* Glaxo Grp., Ltd. v. Apotex, Inc., 268 F. Supp. 2d 1013, 1035 (N.D. Ill. 2003) (issuing "a permanent injunction enjoining Apotex from manufacturing its [infringing ANDA] product for the life of those patents").

194.1. Pozen, Inc. v. Par Pharm., Inc., 800 F. Supp. 2d 789, 824–25 (E.D. Tex. 2011) (citing eBay, Inc. v. MercExchange, LLC, 547 U.S. 388, 391 (2006)), *aff'd*, 696 F.3d 1151 (Fed. Cir. 2012).

195. 35 U.S.C. § 271(e)(4)(C).

196. Alyeska Pipeline Serv. Co. v. Wilderness Soc'y, 421 U.S. 240, 247 (1975).

197. 35 U.S.C. § 285.

198. 35 U.S.C. § 271(e)(4) states that "[f]or an act of infringement described in [section 271(e)(2)] . . . a court may award attorney fees under section 285." As explained in section 8:1.4[B][1], *supra*, section 271(e)(2) provides that submitting an ANDA to the FDA is "an act of infringement . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a

Thus, in a Hatch-Waxman Act case, an award of attorney fees may be appropriate even when there have been no commercial sales of the infringing product.

[D][2] Factors for Determining Exceptional Case

Section 271(e)(4) authorizes attorney fee awards in ANDA cases "in accordance with the standards for section 285 exceptional cases."[199] In *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*,[200] the Supreme Court held that under section 285 "an 'exceptional' case is simply one that stands out from others with respect to the substantive strength of a party's litigating position . . . or the unreasonable manner in which the case was litigated." The Court rejected as "overly rigid" a more restrictive formulation that the Federal Circuit had adopted in *Brooks Furniture Manufacturing, Inc. v. Dutailer International, Inc.*[201] But, while rejecting *Brooks Furniture*, the Supreme Court approved the reasoning and language of *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*,[202] discussed below, which had upheld a fee award under section 271(e)(4). What effect *Octane Fitness* will have on other Federal Circuit precedents construing section 271(e)(4) remains to be seen.

[D][3] Hatch-Waxman Act Exceptional Case Litigation

[D][3][a] Baseless Certification

Whether or not there is willful infringement, courts may award fees in ANDA cases if the ANDA filer makes a "baseless certification" under paragraph IV of the Hatch-Waxman Act's ANDA-filing provision.[207] As explained above,[208] an ANDA filer seeking approval

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drug . . . claimed in a patent . . . before the expiration of such patent." *See* Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1346 (Fed. Cir. 2000).

199. 35 U.S.C. § 271(e)(4).

200. Octane Fitness, LLC v. ICON Health & Fitness, Inc., 134 S. Ct. 1749, 1756 (2014).

201. Brooks Furniture Mfg., Inc. v. Dutailer Int'l, Inc., 393 F.3d 1378 (Fed. Cir. 2005).

202. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000).

203.–206. [Reserved.]

207. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1347 (Fed. Cir. 2000); Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 459 F. Supp. 2d 227, 232 (S.D.N.Y. 2006) ("A baseless certification includes the failure 'to present even a prima facie case of invalidity in filing [the] paragraph IV certification.'"), *aff'd*, 549 F.3d 1381 (Fed. Cir. 2008).

208. *See supra* section 8:1.3[A].

to market a drug prior to patent expiration must certify pursuant to paragraph IV that "in the opinion of the applicant and to the best of his knowledge, each patent . . . for which the applicant is seeking approval . . . is invalid or will not be infringed."[209] The certification "shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed."[210] The certification requirement "imposes a duty of care on an ANDA certifier."[211] The ANDA paragraph IV certifier must "display care and regard for the strict standards of the Hatch-Waxman Act when challenging patent validity" and presumably also when asserting non-infringement.[212] An infringement case based on an ANDA filing may therefore "become exceptional if the ANDA filer makes baseless certifications."[213]

In *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*,[214] the Federal Circuit affirmed an award of attorney fees based at least in part on the ANDA filer's baseless paragraph IV certification.[215] The following facts supported the court's finding that the paragraph IV certification was baseless:

- The obviousness case "contained glaring weaknesses, precipitating a JMOL."
- The ANDA "notice [did] not present a prima facie case of invalidity, and ma[de] no reference to [the drug's] potency, safety, and lack of side effects, among other distinguishing properties accompanying its unusually high activity."

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209. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).
210. 21 U.S.C. § 355(j)(2)(B)(ii) (2006); *see also* 21 C.F.R. § 314.95(c)(6) (2006) (requiring a "full and detailed explanation" of invalidity or non-infringement).
211. *Yamanouchi*, 231 F.3d at 1347. The Federal Circuit has "abandon[ed] the affirmative duty of due care" that previously applied to all infringers but this decision does not address the duty of care that arises from the certification requirement. *See In re* Seagate Tech., LLC, 497 F.3d 1360, 1371 (Fed. Cir. 2007) (en banc); Halo Elec., Inc. v. Pulse Elec., Inc., 136 S. Ct. 1923 (2016) (rejecting *Seagate*'s test for willfulness but not explicitly rejecting *Seagate*'s abandonment of the affirmative duty of care).
212. *Id*.
213. *Id*.
214. *Yamanouchi*, 231 F.3d 1339.
215. *Id*. at 1347; *see also* Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1350 (Fed. Cir. 2004) (stating that the *Yamanouchi* court "determined that a baseless and 'wholly unjustified' paragraph IV certification in an ANDA filing, when combined with litigation misconduct, warranted an exceptional case finding").

The ANDA filer's expert admitted that he could not tell from the claimed compound's "chemical structure whether it would be toxic nor predict its lack of side effects . . . [and] could not predict the effects on potency that would be caused by the structural manipulations he claimed to be obvious."[216]

After determining that the certification was baseless, the court considered the "totality of the circumstances" to decide if the case qualified as "exceptional." The court found that the case was indeed exceptional in view of the ANDA filer's admission that the opinion of counsel on which the paragraph IV certification was based contained "an acknowledged error in chemistry . . . critical to its conclusion of obviousness," and the ANDA filer's litigation misconduct.[217]

More recently, in *Takeda Chemical Industries, Ltd. v. Mylan Laboratories, Inc.*,[217.1] the Federal Circuit upheld a district court's determination that the case was "exceptional," based on its findings that both ANDA filers had filed baseless certification letters and then engaged in bad faith litigation misconduct. Specifically, the Federal Circuit cited (1) the abandonment by both ANDA filers of the invalidity arguments made in their respective certifications, and (2) litigation misconduct consisting of one filer's pursuit of "constantly shifting, but always baseless, obviousness arguments," and the other filer's continuous pursuit of a frivolous inequitable conduct claim.[217.2] Such conduct was, according to the Federal Circuit, sufficient to justify an award of $16.8 million for attorney fees, expenses, and expert fees plus interest."[217.3]

In light of *Takeda* and *Yamanouchi*, it now appears settled that abandoning arguments made in an ANDA certification can be evidence supporting an award of attorney fees.[218]

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216. *Yamanouchi*, 231 F.3d at 1347.

217. *Id.*; *Takeda*, 459 F. Supp. 2d at 232 ("Filing a baseless Paragraph IV certification and proceeding to challenge a patent's validity despite glaring weaknesses in the theory of invalidity constitute litigation misconduct."); Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 2007 WL 840368 (S.D.N.Y. Mar. 21, 2007) (awarding $14 million in attorney fees and costs).

217.1. Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 549 F.3d 1381 (Fed. Cir. 2008), *cert. denied*, No. 08-1461, 2009 U.S. LEXIS 6785 (Oct. 5, 2009).

217.2. *Id.* at 1385–91.

217.3. *Id.* at 1391. The court noted that while a district court may not award expert fees under section 285, it may use its "inherent powers" to do so. *Id.*

218. *See Takeda*, 459 F. Supp. 2d at 235, 236 ("[d]espite the centrality of compound (b) to Alphapharm's trial strategy, and the Herculean efforts that its trial expert made to explain despite all the evidence to the contrary why" one would be lead to compound (b) as a starting point, "the

[D][3][b] Willfulness

Yamanouchi was the first decision to consider willfulness in an ANDA case. The district court found that the ANDA filer's conduct amounted to willful infringement.[219] The Federal Circuit, however, stated that "the trial court need not have elevated the ANDA certification into a finding of willful infringement" because an ANDA filing is a "highly artificial act of infringement."[220] The court of appeals did not reach the question of whether the act of filing an ANDA may constitute willful infringement because it found the ANDA filer's "misconduct in filing a wholly unjustified ANDA certification and misconduct during the litigation . . . warranted the district court's finding that this case was exceptional."[221]

Subsequently, in *Glaxo Group Ltd. v. Apotex, Inc.*,[222] the Federal Circuit had an opportunity to squarely address the issue.[223] Reversing the district court's award of attorney fees based on a finding of willful infringement, the Court of Appeals held "that the mere fact that a company has filed an ANDA application or certification cannot support a finding of willful infringement for purposes of awarding attorney fees."[224] The court distinguished *Yamanouchi*, noting that the ANDA filer in *Glaxo* did not engage "in any litigation misconduct," and "did not file a paragraph IV certification."[225]

Since *Glaxo* did not involve a paragraph IV certification, the question arises whether the filing of an ANDA with a baseless certification may constitute willful infringement. Prior to *Glaxo*, a district court awarded attorney fees based on its finding that the ANDA filer, who had made a paragraph IV certification, committed willful

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[certification] did not even make that argument"); Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 21 F. Supp. 2d 366, 376 (S.D.N.Y. 1998) (certification "did not mention ICI's tiotidine patent, an element of prior art freely relied upon by [defendant] at trial"), *aff'd*, 231 F.3d 1339 (Fed. Cir. 2000).

219. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 21 F. Supp. 2d 366 (S.D.N.Y. 1998).

220. *Id.*; *see also Glaxo Grp.*, 376 F.3d at 1350 (stating that "in *Yamanouchi*, we did not agree that the generic company had engaged in willful infringement"); *but see* Eli Lilly & Co. v. Zenith Goldline Pharm., 2001 WL 1397304 (S.D. Ind. Oct. 29, 2001) (describing *Yamanouchi* as "affirming finding of willfulness and fee award").

221. *Yamanouchi*, 231 F.3d at 1347.

222. Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339 (Fed. Cir. 2004).

223. *Id*. at 1349.

224. *Id*. at 1349–52.

225. *Id*. at 1352.

infringement.[226] Another district court, subsequent to *Glaxo*, dismissed a claim of willful infringement in an ANDA case. It interpreted *Glaxo* as precluding willfulness in section 271(e)(2) ANDA infringement cases even where the ANDA filer makes a baseless paragraph IV certification.[227] The relevance of an ANDA applicant's certification to the question of willfulness was further diminished, if not eliminated, by the Federal Circuit's decision to "abandon the affirmative duty of care."[228]

[D][3][c] Opinions by Patent Counsel

When evaluating allegations of baseless certifications or willful infringement by ANDA filers, courts have considered opinions by the ANDA filer's patent counsel. The *Yamanouchi* court, in finding that a paragraph IV certification was baseless and that attorney fees were therefore appropriate, relied on the fact that the legal opinion underlying the certification contained "an acknowledged error in chemistry . . . critical to its conclusion."[229] Another court found a willful infringement because the ANDA filer relied on faulty patent opinions.[230]

However, the significance of these decisions must be reevaluated in light of the Federal Circuit's en banc decisions in *Knorr-Bremse Systeme für Nutzfahrzeuge GmbH v. Dana Corp.*[231] and *In re Seagate*,[232] which substantially modified the law governing patent

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226. See *Eli Lilly*, 2001 WL 1397304, and entry on fee petition, May 15, 2003, docket entry #215 (awarding attorney fees of about $1.5 million and costs of $102,000).

227. Aventis Pharma Deutschland GmbH v. Cobalt Pharm., Inc., 355 F. Supp. 2d 586, 590–93 (D. Mass. 2005). Although the *Aventis* court dismissed the willfulness claim it did state that the patentees "may seek to prove additional facts that would support their claim for an award of attorney's fees," including evidence of litigation misconduct as in *Yamanouchi*. 355 F. Supp. 2d at 593.

228. *See In re* Seagate Tech., LLC, 497 F.3d 1360, 1371 (Fed. Cir. 2007) (en banc); *Halo*, 136 S. Ct. at 1926 (rejecting *Seagate*'s test for willfulness but not explicitly rejecting *Seagate*'s abandonment of the affirmative duty of care).

229. *Yamanouchi*, 231 F.3d at 1347.

230. *Eli Lilly*, 2001 WL 1397304; *but see* Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1345 (Fed. Cir. 2004) (reversing district court's willfulness finding, which was "based on the fact that [the ANDA filer] did not receive an opinion from competent patent counsel"); *Seagate*, 497 F.3d 1360.

231. Knorr-Bremse Systeme für Nutzfahrzeuge GmbH v. Dana Corp., 383 F.3d 1337 (Fed. Cir. 2004) (en banc).

232. *Seagate*, 497 F.3d 1360; *Halo*, 136 S. Ct. at 1926 (rejecting *Seagate*'s test for willfulness but not explicitly rejecting *Seagate*'s abandonment of the affirmative duty of care).

opinions. Prior to *Knorr*, the failure of a defendant to produce an opinion of counsel created an adverse inference that no such opinion was obtained or that if it was obtained, the opinion was unfavorable.[233] Therefore, to avoid a finding of willful infringement, defendants often waived the attorney-client privilege and relied on an opinion of counsel.

In *Knorr*, the court held that there is no "legal duty upon a potential infringer to consult with counsel, such that failure to do so will provide an inference or evidentiary presumption that such opinion would have been negative," nor is there an adverse inference "flowing from the infringer's failure to obtain or produce an exculpatory opinion of counsel."[234] In *Seagate*, the court, building on *Knorr*, "abandon[ed] the affirmative duty of due care" and held that the "state of mind of the accused infringer is not relevant" to the newly adopted "objective inquiry."[235]

In view of *Knorr* and *Seagate*, ANDA filers may have less incentive to obtain an opinion of patent counsel prior to filing an ANDA, and if they do obtain such an opinion, less incentive to rely on the opinion in litigation.

[D][3][d] Attorney Fees Sought by ANDA Filer Based on Allegation of Baseless Suit by Patentee

The Federal Circuit has observed that it has "not . . . held any party liable for attorney fees for either vigorously prosecuting its patent application or enforcing a presumptively valid patent, even where that patent was later invalidated, in the absence of [ ] evidence of inequitable conduct or misconduct during litigation."[236] "An award of attorneys fees," however, "might be justified if [the patentee] considered its claims to be frivolous and filed suit solely to initiate the thirty-month stay."[237]

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233. Fromson v. W. Litho Plate & Supply Co., 853 F.2d 1568, 1572–73 (Fed. Cir. 1988).
234. *Knorr*, 383 F.3d at 1344–45.
235. *Seagate*, 497 F.3d at 1371.
236. McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1372 (Fed. Cir. 2003). The quoted text substitutes brackets for the deleted phrase "clear and convincing," which is no longer appropriate in light of *Octane Fitness*, which held that a preponderance of the evidence is sufficient to support an award of attorney fees. Octane Fitness, LLC v. ICON Health & Fitness, Inc., 134 S. Ct. 1749, 1758 (2014).
237. Warner-Lambert Co. v. Apotex Corp., 2003 U.S. Dist. LEXIS 23784, at *11 (N.D. Ill. Dec. 3, 2003).

In several cases, ANDA filers have sought attorney fees based on the allegation that the patentees brought baseless infringement suits, maintained those suits after they became frivolous, and needlessly prolonged the suits to obtain the benefits of the thirty-month stay provided by the Hatch-Waxman Act. Generally, ANDA filers making such allegations have not been successful.[238]

§ 8:1.8 *Exemption from Infringement for Activities Related to FDA Submission**

[A] Statutory Provision: 35 U.S.C. § 271(e)(1)

Section 271(e)(1) states:

> It shall not be an act of infringement to make, use, offer to sell or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs or veterinary biological products.

The statute establishes a safe harbor that protects otherwise infringing conduct that is directed to developing information for submission pursuant to federal laws regulating the manufacture, use,

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238. *McNeil-PPC*, 337 F.3d at 1373 (reversing attorney fee award based in part on allegation that the asserted patents amounted to "a scheme for extending the life of a drug about to go off patent," explaining that the patentee "was entitled to file patent applications on what it considered to be patentable inventions," and that the patent laws do not make "value judgments concerning the motives for making and attempting to patent new inventions of less medical value"); Hoffmann-La Roche, Inc. v. Invamed, Inc., 213 F.3d 1359 (Fed. Cir. 2000) (affirming refusal to award attorney fees based on allegation of inadequate pre-suit investigation where ANDA filer refused to provide information about its manufacturing process); *Warner-Lambert*, 2003 U.S. Dist. LEXIS 23784, at *19 (finding no compelling evidence that patentee filed and maintained suit merely to get the benefit of the thirty-month stay because patentee "had the right to investigate" ANDA filer's representations of noninfringement "by engaging in discovery"); Merck & Co. v. Mylan Pharm., Inc., 79 F. Supp. 2d 552 (E.D. Pa. 2000) (finding "it far from unreasonable" that the patentee "explor[ed] multiple theories . . . and engag[ed] in the discovery necessary to support these theories" against ANDA filer in "such a financially significant lawsuit" even though patentee did not rely on any of this information in the subsequent summary judgment briefing).

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or sale of drugs. The safe harbor, however, does not immunize an accused infringer from declaratory judgment suits based on the likelihood of infringement upon FDA approval.[239]

[B] Affirmative Defense?

The Federal Circuit has referred to section 271(e)(1) as an "exception" to infringement or an "exemption."[240] However, calling section 271(e)(1) an "exception" or "exemption" does not resolve the question of whether it is an affirmative defense. The Federal Circuit has not decided the issue, although some district courts have addressed it.[241]

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239. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1571 (Fed. Cir. 1997) ("the protected status of Novopharm's activities leading to its submissions to the FDA does not by itself prevent the district court from considering Glaxo's request for declaratory relief because such relief is directed to the time after the ANDA is approved, when section 271(e)(1) no longer provides a shelter against infringement liability"); *cf.* Benitec Austl. Ltd. v. Nucleonics, Inc., 2005 WL 2415959 (D. Del. Sept. 29, 2005) (no actual controversy to declaratory judgment plaintiff's action because it "was several years away from obtaining FDA approval . . . , there is no certainty that any product approved by the FDA would be the same product that was in clinical trials at the time this lawsuit was filed . . . [there is] no evidence that it has undertaken sales or marketing activity with regard to any product").

240. Eli Lilly & Co. v. Medtronic, Inc., 915 F.2d 670, 674–75 (Fed. Cir. 1990) ("In the case of a permanent injunction, that necessary predicate is a judgment of infringement, which as previously stated, requires consideration of, and an adverse ruling on, the section 271(e)(1) issue in this case. . . . The statute makes clear that no injunction may issue until the § 271 exception has been adjudicated and ruled out."); Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 866 n.3 (Fed. Cir. 2003) (section 271(e)(1) "has been coined an 'exemption' in the case law"), *rev'd on other grounds*, 545 U.S. 193 (2005) (citing Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1325–26 (Fed. Cir. 2003) ("The exemption to infringement under section 271(e)(1) . . . .")).

241. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104, 109 n.4 (D. Mass. 1998) ("It is not clear whether the exemption is an affirmative defense, rather than a part of the statutory definition of infringement that Amgen must establish."); *but see* Ventrassist Pty. Ltd. v. Heartware, Inc., 377 F. Supp. 2d 1278, 1281 (S.D. Fla. 2005) (finding that "the Section 271(e)(1) safe harbor is an affirmative defense," and therefore denying motion to dismiss because plaintiffs "are not required to negate an affirmative defense").

[C] Policy Behind Enactment of the Exemption

The Hatch-Waxman Act was designed in part to respond to two "unintended distortions of the . . . patent term" resulting from "the requirement that certain products must receive pre-market regulatory approval."[242] The first distortion was that, given the extensive testing and regulatory review process required for new drugs, inventors often could not commercialize and profit from their invention until well after their patents issued.[243] Thus, a substantial portion of the patent term would be used up without providing any commercial benefit to the patentee while the regulatory approval process ran its course.

The second distortion was the result of a Federal Circuit decision holding that the manufacture, use, or sale of a patented invention would constitute an act of infringement even if the infringer had no commercial product and was merely developing information necessary to obtain regulatory approval.[244] "Since that activity could not be commenced by those who planned to compete with the patentee until expiration of the entire patent term, the patentee's de facto monopoly would continue for an often substantial period until regulatory approval was obtained. In other words, the combined effect of the patent law and the premarket regulatory approval requirement was to create an effective extension of the patent term."[245]

Figure 8-1 shows how the Hatch-Waxman Act addressed both of these distortions.

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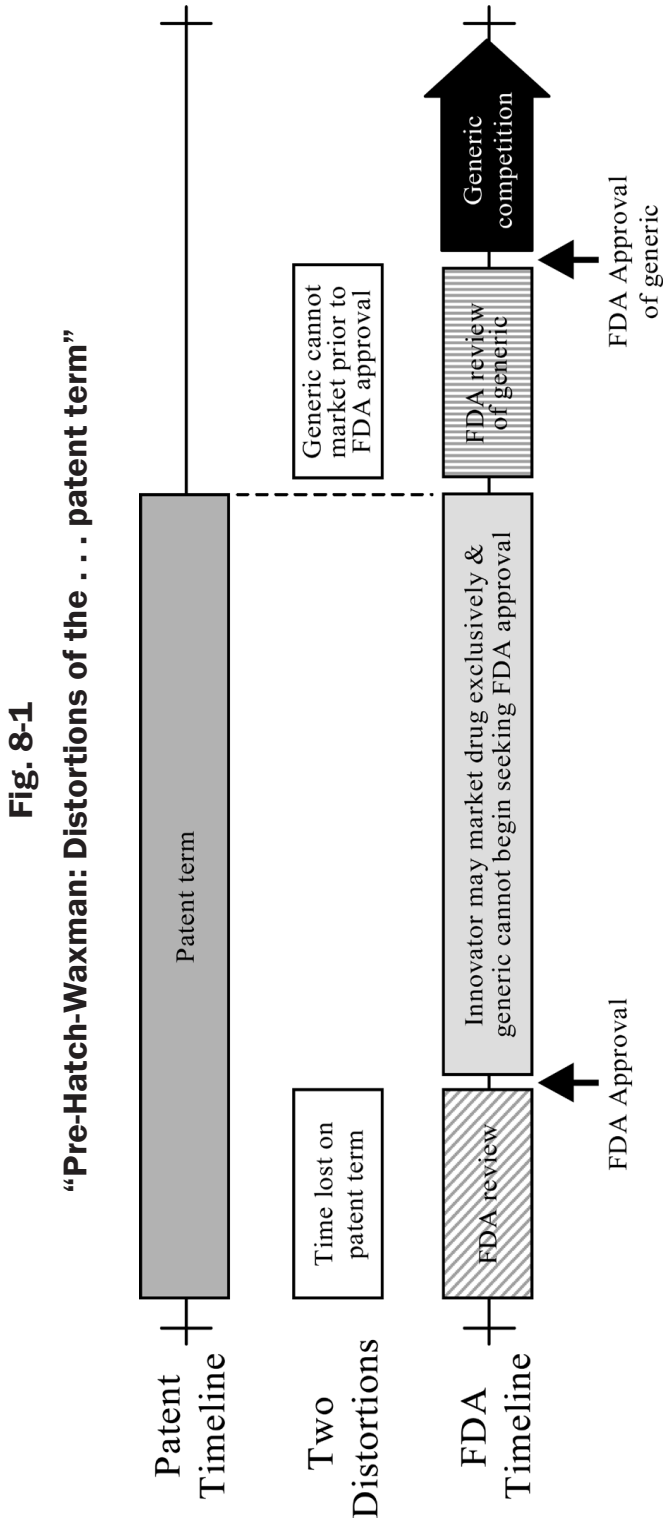
242. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669 (1990); Proveris Sci. Corp. v. Innovasystems, Inc., 536 F.3d 1256, 1260–64 (Fed. Cir. 2008).
243. *Id*. at 669–70.
244. *Id*. at 670 (citing Roche Prods., Inc. v. Bolar Pharm. Co., 733 F.2d 858 (Fed. Cir. 1984)).
245. *Id*.

Fig. 8-1

"Pre-Hatch-Waxman: Distortions of the . . . patent term"



The Hatch-Waxman Act reduced the distortion created by the regulatory approval process at the beginning of the patent term by providing for a patent term extension of up to five years for patents that relate to products that are "subject to a regulatory review period before . . . commercial marketing or use."[246] The Act remedied the distortion created by the regulatory approval process at the end of the patent term by enacting 35 U.S.C. § 271(e)(1), which allows drug companies to develop information for FDA review prior to patent expiration without fear of patent infringement.

The Hatch-Waxman Act "emerged from Congress' efforts to balance two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market."[247] Indeed, "[t]he legislative history speaks almost exclusively in terms of a generic drug manufacturer using a patented drug product, during the life of the patent, so that it may establish the bio equivalency of a generic drug substitute as part of the FDA approval process."[248]

The Federal Circuit, in *Proveris*, relied on the policy behind the Hatch-Waxman Act, as explained by the Supreme Court in *Eli Lilly*, to preclude application of the § 271(e)(1) safe harbor to a patent which did not suffer the two distortions identified in *Eli Lilly*.[248.1]

[D] Situations in Which the Exemption Is Adjudicated

The protection afforded by section 271(e)(1) is invoked typically by companies developing bioavailability information needed to obtain FDA approval of a generic version of a patented drug. However, by its terms, section 271(e)(1) is not confined to generic drug development and the statute's application has not been so limited by the courts.[249]

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246. 35 U.S.C. § 156.

247. Abbott Labs. v. Young, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting). *See supra* section 8:1.1[B].

248. Intermedics, Inc. v. Ventritex, Inc., 775 F. Supp. 1269, 1273 n.2 (N.D. Cal. 1991).

248.1. *Proveris*, 536 F.3d at 1265–66 ("Because Proveris's patented product is not subject to a required FDCA approval process, it is not eligible for the benefit of the patent term extension afforded by 35 U.S.C. § 156(f). At the same time, because Innova's OSA device also is not subject to a required FDCA approval process, it does not need the safe harbor protection afforded by 35 U.S.C. § 271(e)(1).").

249. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 207–08 (2005) (Congress did not "create an exemption [§ 271(e)(1)] applicable only to the research relevant to filing an ANDA for approval of a generic drug").

Furthermore, in *Amgen, Inc. v. International Trade Commission*,[249.1] the Federal Circuit confirmed that section 271(e)(1) applies to administrative proceedings under section 337 of the Tariff Act, as well as to civil actions in the courts.

[E] Statutory Ambiguities

As the Supreme Court has observed, section 271(e)(1) is not "an elegant piece of statutory draftsmanship."[250] The Federal Circuit has described the statutory language as "fraught with ambiguity."[251] Litigation, however, has tested and helped define the contours of the statutory exemption. Courts have addressed:

(1) whether the exemption is limited to the development of information for drugs, or also covers development of information for medical devices;

(2) how the phrase "solely for uses reasonably related" limits the statute's exemption;

(3) whether the statute protects the use of patented research tools in aid of regulatory approval for products not covered by the research tools patent; and

(4) whether the statute protects post-product-approval activity.

[F] Scope of the Statutory Exemption: "Under a Federal Law . . . "

[F][1] Exemption Covers Class III Medical Devices

The Supreme Court, in *Eli Lilly & Co. v. Medtronic, Inc.*,[252] held that the section 271(e)(1) exemption is not limited to activities related to regulatory submissions for drug products. Rather, section 271(e)(1) also covers developing information needed to obtain FDA approval of Class III medical devices.[253]

The Court interpreted the statutory phrase "under a Federal law which regulates the manufacture, use or sale of drugs" as referring

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249.1. Amgen, Inc. v. Int'l Trade Comm'n, 519 F.3d 1343, 1345 (Fed. Cir. 2008) ("We affirm the Commission's ruling that the safe harbor provided by § 271(e)(1) applies in proceedings under the Tariff Act relating to process patents as well as product patents, for imported product that is used for exempt purposes.").

250. *Eli Lilly*, 496 U.S. at 679.

251. Eli Lilly & Co. v. Medtronic, Inc., 872 F.2d 402, 405 (Fed. Cir. 1989).

252. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669 (1990).

253. Class III devices require pre-market approval, pursuant to section 515(a) of the Food, Drug and Cosmetic Act, 52 Stat. 1040 (1938) (21 U.S.C. § 360(e)(a)), based on a showing of safety and efficacy.

to the entirety of such a "Federal law," and not only to those particular provisions of the statute that concern drugs.[254] According to the Court, this reading of the statute is "confirmed" by "the structure of the 1984 Act taken as a whole."[255] The Court explained that the patent term extension enacted by the Hatch-Waxman Act to address the effect that pre-market approval requirements have on the front end of the patent term expressly applies, per the terms of the statute,[256] not only to regulatory submissions relating to drug products, but also to regulatory submissions relating to FDA-regulated medical devices.[257] The Court observed that sections 156 and 271(e)(1) were enacted together to respond to "the dual distorting effects of regulatory approval requirements in this entire area—dual distorting effects that were roughly offsetting, the disadvantage at the beginning of the term producing a more or less corresponding advantage at the end of the term." Congress must, therefore, have intended that both sections apply to the development and submission of information with respect to both drugs and medical devices.[258] In the Supreme Court's view, Congress would not have remedied the effects of pre-marketing regulatory requirements as to drug products at both ends of the patent term while addressing the effect of pre-marketing regulatory requirements as to medical devices only at the front end of the patent term, thereby benefiting patentees of such devices without affording a corresponding benefit to potential competitors.[259]

[F][2] Exemption Covers Class II Medical Devices

Subsequently, the Federal Circuit interpreted the Supreme Court's decision in *Eli Lilly* to include, within the section 271(e)(1) exemption, the development of information needed for approval of Class II medical devices.[260] The Federal Circuit applied the exemption to Class II medical devices even though they are subject only to an "abbreviated approval process" and are not eligible for the patent term extensions made available by the Hatch-Waxman Act for drugs. The court observed that the Supreme Court in *Eli Lilly* had recognized that there may be situations "'in which a patentee will obtain the advantage of the [patent–term] extension but not suffer the disadvantage of the [section 271(e)(1)] noninfringement provision, and others in which

254. *Eli Lilly*, 496 U.S. at 666–67.
255. *Id*. at 669.
256. 35 U.S.C. § 156(f).
257. *Eli Lilly*, 496 U.S. at 672.
258. *Id*.
259. *Id*. at 672–73.
260. Abtox, Inc. v. Exitron Corp., 122 F.3d 1019, 1029–30 (Fed. Cir. 1997).

he will suffer the disadvantage without the benefit.'"[261] Therefore, the Federal Circuit understood the Supreme Court to "command[ ] that statutory symmetry is preferable but not required," and concluded that section 271(e)(1) applies to Class II devices just as it does to Class III devices.[262]

[G] The "Solely for Uses Reasonably Related to" Requirement

Much of the litigation over the scope of section 271(e)(1) concerns the meaning of the statutory phrase "reasonably related" and whether the term "solely" excludes from the statutory exemption activities that have additional purposes beyond developing information for the FDA.

[G][1] "reasonably related"

[G][1][a] Supreme Court Weighs In: *Merck v. Integra*

The Supreme Court addressed the "reasonably related" requirement in *Merck KGaA v. Integra Lifesciences I, Ltd.*[263] Integra owned patents relating to a tripeptide—known as the RGD peptide—which promotes cell adhesion by attaching to receptors commonly located on the outside surface of certain cells. Merck funded cancer research that found that "it was possible to halt angiogenesis"—"the process by which new blood vessels sprout from existing vessels"—by blocking the same receptors to which the patented RGD peptide adheres.[264] Merck then funded the testing of various RGD peptides as potential drug candidates. Thereafter, Merck "initiated a formal project to guide one of its RGD peptides through the regulatory approval process in the United States and Europe" and the National Cancer Institute agreed to sponsor clinical trials.[265]

At trial, the jury found Merck liable for infringing Integra's patents and the district court decided that the section 271(e)(1) exemption did not apply. In affirming the district court, the Federal Circuit held that the Merck-funded research was not protected by section 271(e)(1)'s safe harbor because the research "was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds."[266] The Federal Circuit stated

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261. *Id*. at 1029 (quoting *Eli Lilly*, 496 U.S. at 671–72).
262. *Id*.
263. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005).
264. *Id*. at 197.
265. *Id*. at 199.
266. Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 866 (Fed. Cir. 2003).

that section 271(e)(1) does not embrace "all experimental activity that at some point, however attenuated, may lead to an FDA approval process."[267]

The Supreme Court reversed, stating:

> Though the contours of this provision [section 271(e)(1)] are not exact in every respect, the statutory text makes clear that it provides a wide berth for the use of patented drugs in activities related to the federal regulatory process.[268]

Thus, "[section] 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the [FD&C Act]."[269] The Court held that section 271(e)(1) protects "preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process"; information is not excluded from the exemption "on the basis of the phase of research in which it is developed."[270] On the other hand, the Supreme Court stated that "[b]asic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiology effect is surely not 'reasonably related to the development and submission of information' to the FDA."[271]

The *Merck* Court made clear that section 271(e)(1) is not limited to work related to an ANDA seeking approval of a generic version of an already approved drug. According to the Court, "[section] 271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval."[272] As a result, even if no FDA application is ever filed, as long as the "drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is 'reasonably related' to the 'development and submission of information under . . . Federal law."[273] Section 271(e)(1) applies "as long as there is a reasonable basis for believing that the experiments will produce 'the types of information that are relevant to an IND or NDA.'"[274]

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267. *Id*. at 867.
268. *Merck KGaA*, 545 U.S. at 201–02.
269. *Id*. at 202.
270. *Id*.
271. *Id*. at 205–06.
272. *Id*. at 207.
273. *Id*. (alteration in original).
274. *Id*. at 208.

[G][1][b] Post–*Merck v. Integra*

The Federal Circuit, on remand from the Supreme Court, reversed the judgment of infringement.[275] The court explained, in its own words, that the Supreme Court ruled "that the FDA Exemption includes experimentation on products that are not ultimately the subject of an FDA submission, provided that the particular biological process and physiological effect had been identified and the work was reasonably related to that appropriate for inclusion in an IND application."[276] The court found that all of the accused experiments "were conducted for the purpose of determining the optimum candidate angiogenesis inhibitor and proceeding with commercial development of the selected candidate in compliance with regulatory procedures . . . ."[277] It also found that all of these experiments "were conducted after it had been discovered that a RGD peptide shrank tumors in an animal model."[278]

In addition, relying on the Supreme Court's decision in *Merck*, one district court has since held that vaccine makers were protected by section 271(e)(1) from infringing a patent involving a mechanism for evaluating the safety of vaccine administration schedules when, after FDA approval and commercial launch of a vaccine, they evaluated the risks of using the vaccine. The Court relied on the fact that the FDA "collects vaccine data from vaccine manufacturers after their vaccines have been approved."[279] On the other hand, a district court in another post-*Merck* decision stated that to apply section 271(e)(1) when there is only "a remote desire to obtain FDA approval" would "read the term 'reasonably' out of the ['reasonably related'] provision."[280]

[G][1][c] Pre–*Merck v. Integra*

Several pre-*Merck* decisions of the Federal Circuit and district courts interpreting the "reasonably related" language of section 271(e)(1) appear to be consistent with the Supreme Court's *Merck* decision and therefore remain important precedents. The Federal Circuit held that

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275. Integra Lifesciences, Ltd. v. Merck KGaA, 496 F.3d 1334 (Fed. Cir. 2007).
276. *Id*. at 1340.
277. *Id*.
278. *Id*. at 1345.
279. Classen Immunotherapies, Inc. v. Biogen IDEC, 381 F. Supp. 2d 452, 455 (D. Md. 2005).
280. Third Wave Techs., Inc. v. Stratagene Corp., 381 F. Supp. 2d 891, 912–13 (W.D. Wis. 2005) (exemption did not apply to defendant's testing of its probe-based nucleic acid detection products where the "defendant ha[d] not actually said that its testing was related to obtaining FDA approval in any way" but only that it could not market diagnostic assays without FDA approval).

"reasonably related" imposes an objective standard that does not take into account the intent of the assumed infringer.[281] A district court, in a frequently cited opinion, set forth the test for the "reasonably related" requirement:

> We infer that the phrase "reasonably related" (to development of information for the FDA) as used in § 271(e)(1) reflects Congress' acknowledgment that it will not always be clear to parties setting out to seek FDA approval for their new product exactly what kinds of information, and in what quantities it will take to win that agency's approval. . . . [W]e do not believe that Congress intended a party to lose the exemption simply because it turns out, after the fact, that some of that party's otherwise infringing "uses" either failed to generate information in which the FDA was interested or generated more information than turned out to be necessary to secure FDA approval. Instead, with respect to this aspect of the test, we should ask: would it have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the "use" in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the process by which the FDA would decide whether to approve the product.[282]

In *Telectronics Pacing Systems, Inc. v. Ventritex, Inc.*,[283] the Federal Circuit held that activities that do not themselves generate data for the FDA may nonetheless satisfy the "reasonably related" requirement. The court ruled that demonstrating the accused implantable defibrillator at medical conferences, so as to recruit clinical investigators who would in turn conduct clinical testing, constituted "an exempt use reasonably related to FDA approval, because device sponsors [such as the defendant] are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing."[284]

The Federal Circuit, subsequent to *Merck*, rejected an accused infringer's argument that it used its accused device "in a way which is 'reasonably related' to the 'development and submission of information' pertinent to the FDA premarket approval" because it held

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281. Abtox, Inc. v. Exitron Corp., 122 F.3d 1019, 1030 (Fed. Cir. 1997) (section 271(e)(1) "does not look to the underlying purposes"; if activity is reasonably related to obtaining FDA approval, "intent . . . [is] irrelevant").

282. Intermedics, Inc. v. Ventritex, Inc., 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

283. Telectronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520 (Fed. Cir. 1992).

284. *Id*. at 1523.

the device is not a "patented invention" within the meaning of section 271(e)(1).[284.1] It is not a "patented invention" because the patent was not eligible for patent term extension and the device was not subject to the FDCA approval process. Effectively, the Federal Circuit held that the "reasonably related" and "patented invention" requirements could not be satisfied, at least on the facts present in *Proveris*, when the patent is not subject to the two distortions which the statute was designed to remedy.

[G][2] "solely"

A party's non-infringing activities are not relevant to whether the party's otherwise infringing activities are exempt under section 271(e)(1).[284.2] Thus, the *Telectronics* court held that data generated for purposes of seeking FDA approval could be used in a non-infringing manner for other purposes without forfeiting the protection of section 271(e)(1). The Federal Circuit ruled that disseminating clinical trial data developed for FDA approval at medical conferences or reporting such data to investors, analysts and journalists does not revoke the exemption bestowed by section 271(e)(1). The court explained:

> By permitting the testing and regulatory approval process to begin well before a controlling patent had run its course, Congress must have intended to allow competitors to be in a position to market their products as soon as it was legally permissible. . . . If Congress intended to make that more difficult, if not impossible, by preventing competitors from using, in an admittedly non-infringing manner, the derived test data for fund raising and other business purposes, it would have made that intent clear.[285]

Similarly, in *Intermedics*, the district court made clear that "[w]hen trying to determine whether a party is protected by this exemption, the *target of a court's inquiry is on those acts of manufacture, use or sale* of a patented invention that would constitute acts of infringement but for [the section 271(e)(1)] exemption. . . . In other words, by enacting this exemption, Congress had said to the public: . . . If you engage in infringing activities for other uses, the exemption will not protect

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284.1. *Proveris*, 536 F.3d at 1267.

284.2. Edwards Lifesciences Corp. v. Meril Life Scis. Pvt. Ltd., __ F.4th __ (Fed. Cir. 2024) ("the relevant inquiry is not *why* Meril imported the two transcatherer heart valve systems, but whether the act of importation was for a use reasonably related to submitting information to the FDA").

285. *Id*. at 1525; *see also* Bristol-Myers Squibb Co. v. Rhône-Poulenc Roher, Inc., 2001 WL 1512597, at *8 (S.D.N.Y. Nov. 28, 2001) (fact that "data developed for FDA approval" were also used "for preparing and filing patent applications . . . would not violate the Section 271(e)(1) safe harbor").

you. But if you engage in non-*infringing* acts for other uses you do not lose the benefits of this statutory amendment."[286] Consequently, "the exemption Congress provided is not lost simply as a result of a showing that the defendant has engaged in non-infringing acts whose 'uses' fall outside those permitted by statute."[287]

On the other hand, another court denied defendants the benefit of section 271(e)(1) where it appeared that the activity fell within the scope of the claims, and that at least some of the uses were not related to obtaining FDA approval.[288] The defendants marketed knee and hip implant products that could be used with or without bone cement. They argued that use of their implants with bone cement did not fall within the claims and that use of the implants without bone cement was only for investigative purposes and was therefore exempt under section 271(e)(1). The court first ruled that the accused products were within the scope of the claims regardless of whether they were made with or without cement. The court then held that the products "were not used *solely* for investigative purposes to submit information to the FDA for approval of the products without the use of bone cement" because there was "no difference in the products designed for 'investigational' use and those designed for sale with bone cement only."[289] Accordingly, the court appeared to hold that sale of products that are used for both research and non-research uses forecloses reliance on section 271(e)(1) for all sales of the product.[290] Similarly, the Federal Circuit vacated a district court's judgment of non-infringement based on its misapplication of the section 271(e)(1) safe harbor because, "unlike in *Telectronics*, [the patentee] alleges that Elan's post-submission *activities* using the clinical data for non-regulatory purposes *infringed* the claims" of the asserted patent.[290.1]

In addition to distinguishing between non-infringing and infringing activities, the Federal Circuit has distinguished between activities

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286. *Intermedics*, 775 F. Supp. at 1277–78.
287. *Id*. at 1278.
288. Am. Standard, Inc. v. Pfizer Inc., 722 F. Supp. 86 (D. Del. 1989).
289. *Id*. at 103.
290. *But see* NeoRx Corp. v. Immunomedics, Inc., 877 F. Supp. 202, 202–04 (D.N.J. 1994) (separately analyzing various allegedly infringing activities involving the same products and finding some protected under section 271(e)(1)). This approach is consistent with the language of section 271(e)(1) ("It shall not be an act of infringement to make, use, offer to sell or sell a patented invention . . . *solely for uses reasonably related to the development and submission of information*" to the FDA) (emphasis added).
290.1. Classen Immunotherapies, Inc. v. Elan Pharm., Inc., 786 F.3d 892, 898 (Fed. Cir. 2015).

that are related to gathering information "solely for submission to the FDA" and those that are "primarily for non-FDA purposes."[290.2] The court also rejected the argument that "solely" "means that the patented invention must be the 'sole' means of providing the information for the safe harbor to apply."[290.3]

The Federal Circuit held that the mere fact that an accused infringer's intent is that the accused activity is both for the purpose of submitting data to the FDA and for commercial purposes does not preclude protection of the safe harbor. The Federal Circuit, in *Amgen Inc. v. Hospira, Inc.*, upheld the following jury instruction:

> You must evaluate each of the accused activities separately to determine whether the Safe Harbor applies. If you find that an accused activity was reasonably related to the development and submission of information to the FDA for the purpose of obtaining FDA approval, then Hospira has proved its Safe Harbor defense as to that activity. If Hospira has proved that the manufacture of a particular batch was reasonably related to developing and submitting information to the FDA in order to obtain FDA approval, Hospira's additional underlying purposes for the manufacture and use of that batch do not remove that batch from the Safe Harbor defense.[290.4]

Substantial evidence existed, however, that fourteen batches "were not manufactured 'solely for uses reasonably related to the development and submission of information' to the FDA."[290.5] "Hospira's regulatory witness, Ms. Dianis, admitted that CPV [process verification] is an ongoing process that applies to batches made for commercial use" and that "CPV is not required before FDA approval."[290.6] In addition, evidence showed that "Hospira changed the designation of certain batches from 'commercial inventory' to 'CPV.'"[290.7]

290.2. Momenta Pharm., Inc. v. Amphastar Pharm., Inc., 686 F.3d 1348, 1358 (Fed. Cir. 2012) (distinguishing between *mandated* post-approval testing of enoxaparin required to maintain approval as within the safe harbor and *optional* post-approval studying of adverse reactions to immunization which, if conducted, must be reported as not within the safe harbor).

290.3. *Id.* at 1359–60 ("Momenta is therefore incorrect that the possibility that the FDA would accept the use of other, non-patented, testing methods for the development and submission of information precludes Amphastar from relying on the safe harbor . . . .").

290.4. Amgen Inc. v. Hospira, Inc., 944 F.3d 1327, 1338–39 (Fed. Cir. 2019).

290.5. *Id.* at 1340.

290.6. *Id.*

290.7. *Id.*

[G][3] Post-Product-Approval Activity

Section 271(e)(1) "does not categorically exclude post-approval activities from the ambit of the safe harbor."[290.8] Post-approval clinical trials "to characterize the effect of food on the absorption of Skelaxin" on bioavailability submitted "to the FDA to revise the Skelaxin product label and to propose changes to the approval requirements for generic versions of Skelaxin" "were anything but 'routine' post-approval reporting," and therefore fall within the safe-harbor provision.[290.9] On the other hand, the use of patented immunization schedules to determine whether the timing of immunization using an FDA-licensed vaccine increased a patient's immune-mediated disorders were not exempt from infringement merely because adverse post-approval events had to be reported to the FDA because the studies were "not a 'phase of research' possibly leading to marketing approval."[290.10]

[G][4] Examples

[G][4][a] Exempt Activities

In applying section 271(e)(1) prior to *Merck*, district courts held various activities protected by the statute. For example:

- Manufacture of defibrillators, most of which were used to generate data for the FDA.[291]
- Continued sales of defibrillators to clinical investigators even after submission of an application to the FDA seeking premarket approval, given the possibility that additional clinical data might be required by the FDA.[292]

290.8. *Classen*, 786 F.3d at 897; *Momenta*, 686 F.3d at 1358–59 ("the plain language of the statute is not restricted to pre-approval activities").

290.9. *Classen*, 786 F.3d at 897; Momenta Pharm., Inc. v. Teva Pharm. USA, Inc., 809 F.3d 610, 620 (Fed. Cir. 2015) ("The routine record retention requirements associated with testing and other aspects of the commercial production process contrast with non-routine submissions that may occur both pre- and post-approval, such as the submission of investigational new drug applications ('INDs'), new drug applications ('NDAs'), supplemental NDAs, or other post-approval research results. . . . The routine quality control testing of each batch of generic enoxaparin as part of the post-approval, commercial production process is therefore not 'reasonably related to the development and submission of information' to the FDA, and it was clearly erroneous to conclude otherwise.").

290.10. Classen Immunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1072 (Fed. Cir. 2011) (quoting Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 202 (2005)).

291. *Intermedics*, 775 F. Supp. at 1282.

292. *Id*.

- Scale-up production of accused product, beyond that necessary to demonstrate manufacturing capability, given the uncertainty of the FDA's needs and the FDA's knowledge of the scale-up plans.[293]
- Submission to foreign regulatory authorities of foreign clinical trial data already submitted to the FDA.[294]
- Shipment of vials of accused product to foreign clinical investigator, identified to the FDA, whose test data was to be submitted to the FDA.[295]
- Shipment of accused product to non-profit research center, where not all of the research center's data was submitted to the FDA, because the use for non-FDA purposes was de minimis.[296]
- Shipment of accused product to potential commercial partner that conducted trials to generate data for the FDA and also to facilitate approval in the European market, even though the defendant elected not to submit data from one of the clinical trials to the FDA.[297]
- Export of product to Japan for use in developing alternative manufacturing process different from the process then being considered by the FDA, given that alternative process would require separate FDA approval.[298]
- Rabbit pyrogen testing of pharmaceutical product, given that test results, though not submitted to the FDA, were obtained to confirm the purity and safety of the drug for use in clinical trials that would produce data to be submitted to the FDA.[299]
- Manufacture of commercial scale batches of product, for purposes of demonstrating consistency to the FDA, even though the results were later discarded for reasons unrelated to FDA approval.[300]

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293. *NeoRx*, 877 F. Supp. at 206–07.
294. *Id*. at 208.
295. *Id*. at 208–09.
296. *Id*. at 211.
297. *Id*. at 211–12.
298. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104, 109 (D. Mass. 1998).
299. *Id*. at 110.
300. *Id*.

- Characterization of product's carbohydrate structure as required by the FDA, though findings may also have been used to assess defendant's patent position.[301]
- Use of "data developed for FDA approval" for preparing and filing patent applications.[302]

[G][4][b] Non-Exempt Activities

District courts held various activities outside the scope of section 271(e)(1). For example:

- Manufacturing products in the United States for shipment to regulatory agencies abroad.[303]
- Shipment of vials of the accused product to a foreign clinical investigator, where there was no clear indication that the investigator's data was or would be submitted to the FDA.[304]
- Expenditure of $24 million "to stockpile and prepare to market [the product] immediately upon the anticipated, imminent FDA approval."[305]

[H] Third-Party Support of Section 271(e)(1) Activity

The safe harbor of section 271(e)(1) protects not only the party who would potentially be submitting data to the FDA, but also an outside firm engaged by that party to perform clinical or other testing, or to supply material. The mere fact that an outside firm is the party performing the testing does not affect any defense available under the statute to either the hiring or the hired party.[306] Likewise, supplying

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301. *Id*. at 110–11.
302. Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 2001 WL 1512597, at *8 (S.D.N.Y. Nov. 28, 2001).
303. *NeoRx*, 877 F. Supp. at 207.
304. *Id*. at 209.
305. Biogen, Inc. v. Schering AG, 954 F. Supp. 391, 396 (D. Mass. 1996).
306. *See* Amgen, Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104, 107 (D. Mass. 1998) ("The Federal Circuit has approved of uses such as . . . hiring an outside firm to conduct testing on the invention, even though the decision to do so was motivated by the hope that the testing firm would purchase the rights to the device.") (citing *Abtox*, 122 F.3d at 1029–30 (holding that tests of a medical device by Exitron and by MDT, which was hired by Exitron "to conduct tests . . . consistent with the collection of data necessary for filing an application with the" FDA, were exempt)); Elan Transdermal Ltd. v. Cygnus Therapeutic Sys., 24 U.S.P.Q.2d (BNA) 1926 (N.D. Cal. 1992) ("even assuming that Elan may attribute any infringing activity by Pharmacia to Cygnus [through an

the active ingredient pursuant to a drug master file submitted to the FDA in support of an ANDA filer doing testing to obtain approval for a drug incorporating that active ingredient, is covered by the safe harbor.[306.1] On the other hand, once an ANDA is approved by the FDA, any further third-party activity in support of the ANDA filer may not be protected under section 271(e)(1).[306.2]

[I] Abuse of Regulatory Review Process

Elimination of the bright-line distinction between "pre-approval" activities, which may qualify for safe harbor protection, and "post-approval" activities, which do not, places additional stress on the statutory requirements that the otherwise infringing act must be performed "solely" for uses that are "reasonably related" to FDA review. Sponsors may seek to use the regulatory process as a fig leaf to clothe activities that produce marketing material for their currently marketed products.

The problem has long existed for medical devices that perform diagnostic or medical procedures. Medical devices, classified by the FDA as class I, II, or III, are covered by a separate set of regulations[307] that permit sponsors under certain circumstances to charge for the use of their devices even prior to FDA approval.[308] Depending on how the FDA interprets and enforces these regulations, sponsors may have an incentive to delay obtaining approval so that they can earn a profit by charging for the devices while relying on section 271(e)(1) to shield them against claims of patent infringement.

This issue was confronted in two decisions of the district court in *Nexell Therapeutics, Inc. v. AmCell Corp.*[309] The patentee argued that "the real purpose of [AmCell's] activities is to market its device to

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alleged partnership], the Sachs study conducted by Pharmacia was not an infringement" because it was exempt under section 271(e)(1)).

306.1. Shire LLC v. Amneal Pharm., LLC, Nos. 2014-1736, 2014-1737, 2014-1738, 2014-1739, 2014-1740, 2014-1741, 2015 WL 5603864, at *7–8 (Fed. Cir. Sept. 24, 2015).

306.2. Forest Labs., Inc. v. Ivax Pharm., Inc., 501 F.3d 1263, 1272 (Fed. Cir. 2007) ("just as Ivax will be liable for, and hence is being enjoined from, the commercial exploitation of escitalopram when it is approved by the FDA and during the life of the patent, so should Cipla be enjoined").

307. *See* 21 U.S.C. § 360c(a)(1)(A)–(C); *see also* Medtronic, Inc. v. Lohr, 518 U.S. 470, 476–77 (1996).

308. A sponsor of a regulated medical device may charge investigators and subjects a price not "larger than that necessary to recover costs of manufacture, research, development and handling." 21 C.F.R. § 812.7 (2006).

309. Nexell Therapeutics, Inc. v. AmCell Corp., 143 F. Supp. 2d 407 (D. Del. 2001); Nexell Therapeutics, Inc. v. AmCell Corp., 199 F. Supp. 2d 197 (D. Del. 2002).

physicians, and in doing so, has exceeded the scope of the exemption in § 271(e)(1)."[310] In its initial decision, the court stated that it would defer to the FDA to "define for AmCell what activities are reasonably related to the development and submission of information necessary to obtaining pre-market approval."[311] In a subsequent decision, the court stated that, unless it was "confronted with the extreme case in which either it is clear that certain activities are outside the FDA approval process or the FDA itself affirmatively indicates that a party's activities are not reasonably related to obtaining approval, the court will not find that accused activities that a defendant objectively believes could generate information that is likely to be relevant to the FDA approval process" fail to fall within the exemption.[312]

[J] The Use of Research Tools Under Section 271(e)(1)[313]

In the classic section 271(e)(1) situation, a pharmaceutical company uses a patented drug in developing data to support an application for FDA approval to market a generic version of the patented drug. As explained below, prior to *Proveris Scientific Corp. v. Innovasystems, Inc.*, it was unclear whether the statutory safe harbor exempts the infringing use of patented research tools to develop data to be submitted in seeking FDA approval of a drug or device *other* than the research tool.[313.1] The Federal Circuit, however, held in *Proveris* that the safe harbor did not apply to an optical spray analyzer because it was "not subject to FDA premarket approval, and therefore faces no regulatory barriers to market entry upon patent expiration, Innova is not a party who, prior to enactment of the Hatch-Waxman Act, could be said to have been adversely affected" by the "*de facto* extension of effective patent life at the end of the patent term [resulting] from FDA premarket approval requirements."[313.2]

Prior to *Proveris*, in the *Merck* case (prior to the Supreme Court's decision in *Merck*), the Federal Circuit warned that a broad reading of section 271(e)(1) would "effectively vitiate the exclusive rights of patentees owning biotechnology tool patents."[314] Because patented tools

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310. *Nexell*, 143 F. Supp. 2d at 420.
311. *Id*. at 423.
312. *Nexell*, 199 F. Supp. 2d at 203.
313. See *supra* section 7:1 for a more complete discussion of research tool patents in general and the applicability of the section 271(e)(1) safe harbor.
313.1. Proveris Sci. Corp. v. Innovasystems, Inc., 536 F.3d 1256 (Fed. Cir. 2008).
313.2. *Id*.
314. Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 867 (Fed. Cir. 2003).

often facilitate both "general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs" and because the "downstream clinical testing for FDA approval" would be exempt under section 271(e)(1), the Federal Circuit expressed concern that "these patented tools would only supply some commercial benefit to the inventor when applied to general research."[315] The court's view was that an expansive reading of section 271(e)(1) to encompass general research activities "would swallow the whole benefit of the Patent Act for some categories of biotechnology inventions."[316] However, the Supreme Court in *Merck* specifically declared that the Court did not "express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of 'research tools' in the development of information for the regulatory process."[317] Subsequently, the Federal Circuit expressed the view that the use of research tools, at least on the facts present in *Proveris*, was not exempt from infringement under section 271(e)(1).[317.1]

§ 8:2 The First Paragraph IV Applicant's 180-Day Exclusivity

§ 8:2.1 Introduction

To accelerate the marketing of generic drugs, the Hatch-Waxman Act provides an incentive to the first generic applicant to challenge the pioneer's patent claims. In particular, the first ANDA applicant to make a paragraph IV certification is rewarded with a 180-day head-start over competing generic versions of the same product.

In its original form, the 180-day exclusivity provision[318] was "far from a model of legislative draftsmanship."[319] Legislative imprecision, coupled with shifting FDA interpretations of the statutory text, created fertile ground for disputes among competing generic applicants and between generic applicants and pioneers. In 2003, as part of the MMA, Congress substantially revised the 180-day exclusivity provision to resolve, on a prospective basis, many of the issues that had been disputed under the original statute.

The MMA's revised 180-day exclusivity provision is contained in section 1102 of the MMA.[320] The first provision sets forth the revised

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315. *Id*.
316. *Id*.
317. *Merck*, 545 U.S. 193 n.7.
317.1. *Proveris*, 536 F.3d at 1265–67.
318. Codified at 21 U.S.C. § 355(j)(5)(B)(iv).
319. Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1069 (D.C. Cir. 1998).
320. Codified primarily at 21 U.S.C. § 355(j)(5)(B)(iv) and (5)(D).

eligibility criteria for 180-day exclusivity. The latter provision sets forth circumstances under which the 180-day exclusivity is forfeited.

These new MMA provisions apply only to ANDAs for drugs for which no ANDA containing a paragraph IV patent certification had been submitted as of December 8, 2003.[321] If any such ANDA was filed for the drug prior to December 8, 2003, then all ANDAs for the drug in question, even ANDAs submitted after December 8, 2003, are governed by (and are subject to the uncertainties and ambiguities of) prior law.

We will first describe 180-day exclusivity under current law, applicable to all drugs for which no ANDA was filed prior to December 8, 2003. We will then describe the prior law, which remains applicable to drugs for which at least one ANDA was filed prior to that date.

§ 8:2.2 Basic Statutory Provision: Section 355(j)(5)(B)(iv)

Title 21 U.S.C. § 355(j)(5)(B)(iv), sets forth the general rule for 180-day exclusivity under the MMA:

> [I]f the [ANDA] application contains a [paragraph IV certification] and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

§ 8:2.3 Only the "First Applicant" Is Entitled to Exclusivity

The original Hatch-Waxman Act was not clear about which generic drug applicant was entitled to exclusivity. The MMA specifies that only a "first applicant" for a particular drug is entitled to exclusivity, and it defines "first applicant" as an ANDA filer who, "on the first day" that a "substantially complete" ANDA with a paragraph IV certification is submitted for that drug, submits a "substantially complete" ANDA that "contains and lawfully maintains a [paragraph IV] certification."[322] For reissued patents, FDA has taken the position that only the first applicant to make a paragraph IV certification to both the original and reissue patent qualifies for 180-day exclusivity, and a district court has upheld FDA.[322.1]

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321. Pub. L. No. 108-173, § 1102(b)(1) (2003).
322. 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb).
322.1. Mylan Pharm., Inc. v. FDA, 2014 U.S. Dist. LEXIS 73448, at *12 (N.D. W. Va. May 29, 2014).

[A] First ANDA with a Paragraph IV Certification for Any Patent

The statutory text makes it clear that an ANDA filer becomes eligible for 180-day exclusivity if it is the first to make a paragraph IV certification for *any* Orange Book–listed patent claiming the pioneer drug. Therefore, for ANDAs covered by the MMA, there will ordinarily be a single "first applicant" who alone has exclusivity as against all other ANDAs for the same drug. However, if several ANDAs are submitted on the same day, each of them will be "first," qualifying them for exclusivity as against ANDAs submitted on subsequent days.

[B] "Substantially Complete" ANDA

Under the MMA, an ANDA is "substantially complete" if on its face it is "sufficiently complete to permit a substantive review and contains all the information required" of an ANDA applicant under 21 U.S.C. § 355(j)(2)(A). The new statutory definition of "substantially complete" appears to be broader than the definition that the FDA adopted by regulation prior to 2003, which focused on whether the ANDA included finished bioequivalence studies.[323]

Even under prior law, there were disputes as to which ANDA was first to be "substantially complete" and thus eligible for 180-day exclusivity.[324] Such disputes are likely to recur under the MMA.

[C] "Contains and Lawfully Maintains" a Paragraph IV Certification

As discussed below,[325] the "first applicant" forfeits its eligibility for exclusivity if it amends or withdraws all of its paragraph IV certifications. It is therefore not clear what Congress had in mind when it imposed a separate eligibility requirement that the ANDA filer must "lawfully maintain[ ]" its certification. However, FDA regulations require an applicant to amend its patent certification if, at any time prior to final approval, it learns that its certification "is no longer accurate."[326] The statutory requirement would therefore appear

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323. 21 C.F.R. § 314.107(c)(2) (2003). *See also* 57 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992) (explaining that the previous policy of allowing applicants to provide only study protocols required the FDA to waste time on ANDAs that "had little potential for approval").

324. *E.g.*, Citizen Petition No. 02P-0256 (May 31, 2002) (withdrawn June 19, 2003) (claiming that ANDA was not substantially complete because the Drug Master File (DMF) referenced in the ANDA had not yet been filed with the FDA).

325. *See infra* section 8:2.6[E].

326. 21 C.F.R. § 314.94(a)(12)(viii)(C) (2006).

to apply where the ANDA applicant fails to amend its certification when changed circumstances require an amendment. In such circumstances, the paragraph IV certification would not be "lawfully maintained," and the applicant therefore would not be eligible for 180-day exclusivity.

This raises the issue of when changed circumstances make a paragraph IV certification "no longer accurate." There are several possibilities:

- Under pre-MMA law, if the relevant patent expired before the ANDA was finally approved, the FDA would deem the certification to have been amended to a paragraph II certification (the "patent has expired") even if the ANDA applicant did not make the amendment itself.[327] However, new section 355(j)(5)(D)(i)(VI) deals with this case explicitly by making expiration of all patents an occasion for forfeiture of exclusivity.
- Under prior law, the FDA once took the position that an ANDA applicant could no longer maintain a paragraph IV certification once it settled its patent challenge in return for a license. However, the FDA appears to have abandoned that position after a district court rejected it.[328] Conceivably, a litigant could contend that the FDA's original stance was correct, and argue that a settling "first applicant" has not "lawfully maintained" its paragraph IV certification. However, for ANDAs governed by the MMA, the FDA has ruled that settlement will not forfeit exclusivity unless the settlement has been finally adjudicated to violate the antitrust laws.[328.1]
- It could perhaps be argued that a paragraph IV certification is no longer "lawful" after a district court has ruled that the first applicant's ANDA infringes a valid and enforceable Orange Book–listed patent. In *Mylan Laboratories, Inc. v. Thompson*,[329] the court observed that the FDA "might well" read its regulations as requiring an ANDA applicant to drop its paragraph IV certification immediately upon entry of a district court judgment of infringement. However, such a reading has not as yet been adopted by the FDA.

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327. Ranbaxy Labs. Ltd. v. FDA, 307 F. Supp. 2d 15 (D.D.C.), *aff'd*, 96 F. App'x 1 (D.C. Cir. 2004).
328. Mylan Pharm., Inc. v. Thompson, 207 F. Supp. 2d 476 (N.D. W. Va. 2001).
328.1. Letter from Gary H. Buehler in Dkt. No. 2007N-0382 (Jan. 23, 2008).
329. Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1283 n.10 (D.C. Cir. 2004).

§ 8:2.4 Exclusivity Is Against Subsequent Paragraph IV ANDAs for Same Drug

Under the MMA, as under the prior version of the Hatch-Waxman Act, 180-day exclusivity delays FDA approval only of subsequent ANDAs. A "first applicant" has no exclusivity as against subsequent NDAs or 505(b)(2) applications. Nor is a "first applicant" entitled to exclusivity as against an ANDA for a different dosage strength of the same listed drug, because the FDA regards each dosage strength as representing a "different" drug.[330] Therefore, for example, if the FDA grants a "suitability petition" for an ANDA with a different dosage strength from that of the listed drug, that ANDA will not be blocked by the exclusivity of a previous ANDA that was submitted for the same dosage strength as that of the pioneer.[331]

[A] No Exclusivity Against Authorized Generics

Because 180-day exclusivity prevents FDA approval only of ANDA products, and not NDA products, 180-day exclusivity does not prevent a pioneer drug company from launching its own "authorized generic," that is, an unbranded version of its own pioneer drug, which it markets under the authority of its NDA. Generic manufacturers have argued that such "authorized generics" frustrate congressional intent because they are able to compete immediately with the first applicant, thereby depriving the first applicant of the exclusivity reward it had hoped for when it challenged the pioneer's patent. Nevertheless, the D.C. Circuit has ruled that Hatch-Waxman Act does not prohibit the holder of an approved NDA from marketing, during the 180-day exclusivity period, its own "brand generic" version of its drug.[332]

[B] No Exclusivity Unless Subsequent ANDA Contains Paragraph IV Certification

A "first applicant" enjoys exclusivity only over subsequent ANDAs that contain a paragraph IV certification as to at least one of the patents for which the first applicant has made a paragraph IV certification. If, for example, the first applicant's ANDA contains a single paragraph IV certification to a patent claiming a method of using

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330. The FDA's position was upheld by the D.C. Circuit in Apotex, Inc. v. Shalala, 1999 WL 956686 (D.C. Cir. Oct. 8, 1999), *aff'g* 53 F. Supp. 2d 454 (D.D.C.).

331. Thus, the FDA approved a 7.5 mg tablet version of Bristol-Myers Squibb's BuSpar® although the ANDA applicant's request for approval of other strengths was blocked by 180-day exclusivity, see www.fda.gov/cder/foi/appletter/2001/75467ltr&TA.pdf.

332. Teva Pharm. Indus. Ltd. v. Crawford, 410 F.3d 51 (D.C. Cir. 2005); *accord* Mylan Pharm., Inc. v. FDA, 454 F.3d 270 (4th Cir. 2006).

the pioneer drug, but the subsequent applicant has "carved out" that use from its ANDA, then the "first applicant" is not entitled to exclusivity.[333]

§ 8:2.5 Exclusivity Period Begins Only upon First Applicant's "Commercial Marketing"

In its original form, the Hatch-Waxman Act contained two alternative "triggers" for the commencement of the 180-day exclusivity period: (a) first commercial marketing, or (b) a court decision of invalidity or non-infringement. This scheme—and particularly the "court decision" trigger—engendered considerable controversy.[334]

The MMA contains a single "trigger": the "first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant."[335] Although the statute does not define "commercial marketing," FDA regulations have long defined that term to mean the first introduction of the product into interstate commerce "outside the control" of the manufacturer.[336]

The ANDA applicant's marketing of the pioneer's "listed drug"—like the applicant's marketing of its own ANDA drug—is considered a "commercial marketing" that triggers the commencement of the 180-day exclusivity period. Thus, if the first ANDA applicant settles its infringement litigation in return for a license to market the pioneer's NDA drug as an "authorized generic," then the 180-day exclusivity period will begin when the ANDA applicant introduces that authorized generic into commerce.[337]

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333. *See* TorPharm, Inc. v. Thompson, 260 F. Supp. 2d 69, 85 n.18 (D.D.C. 2003) (citing 21 C.F.R. § 314.107(c)(1) (2006)), *aff'd sub nom.* Purepac Pharm. Corp. v. Thompson, 354 F.3d 877 (D.C. Cir. 2004).

334. *See infra* section 8:2.7[C].

335. 21 U.S.C. § 355(j)(5)(B)(iv)(I).

336. "Commercial marketing commences with the first date of introduction or delivery for introduction into interstate commerce outside the control of the manufacturer of a drug product, except for investigational use under part 312 of this chapter, but does not include transfer of the drug product for reasons other than sale within the control of the manufacturer or application holder." 21 C.F.R. § 314.107(c)(4) (2006).

337. The MMA's express statement that commercial marketing of an authorized generic by the first ANDA filer triggers the commencement of the 180-day exclusivity period codifies the FDA's interpretation of pre-2003 law. *See* Mylan Pharm., Inc. v. Thompson, 207 F. Supp. 2d 476 (N.D. W. Va. 2001) (upholding ruling that Mylan's exclusivity period commenced when it began to market nifedipine hydrochloride produced by Pfizer, the pioneer, in lieu of Mylan's ANDA version).

§ 8:2.6 "Forfeiture" of 180-Day Exclusivity

Although 180-day exclusivity is intended to encourage early generic entry by providing an incentive to challenge pioneer patents, the exclusivity granted to the first filer postpones market entry by other generics. In an effort to assure that subsequent generic entry is not unduly or unfairly deferred, the MMA identifies several circumstances that cause a first filer's exclusivity to be forfeited. In the event of a forfeiture, new section 355(j)(5)(D)(iii) provides that no subsequent ANDA enjoys any exclusivity.[338]

The following forfeiture events are specified in the statute:

[A] "Failure to Market"

To keep "first applicants" from indefinitely "parking" their exclusivity, new section 355(j)(5)(D)(i)(I) deprives the first applicant of its exclusivity if it fails to market its ANDA product within a specified time. Specifically, the first applicant forfeits its exclusivity if it fails to market its product by the later of *two* statutorily defined dates: One date is seventy-five days after final approval or thirty months after ANDA submission, whichever comes first.[339] The other date is seventy-five days after one of the following events:

(1) a non-appealable court decision in favor of *any* ANDA finding that all of the patents for which the first applicant made paragraph IV certifications are invalid or not infringed;

(2) a settlement that includes a judicial finding that all such patents are invalid or not infringed; or

(3) the pioneer's removal of all such patents from the Orange Book.

If the first applicant allows both of these dates to pass without launching its product, it forfeits its right to 180-day exclusivity.

The MMA does not address the effect on a first applicant's exclusivity of an *adverse* judgment, that is, a judgment that one or more of the challenged patents is valid and infringed. But under FDA

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338. Of course, if there were multiple "first applicants" and only one of them forfeits its exclusivity, the remaining "first applicants" retain their exclusivity rights.

339. 21 U.S.C. § 355(j)(5)(D)(i)(I)(aa). Because (absent an earlier court decision) the statutory litigation stay is measured from the date the pioneer receives the paragraph IV certification notice, rather than the ANDA submission, this first trigger may occur before the first applicant's ANDA is approved. ANDA "submission" occurs only when the FDA has accepted the ANDA as substantially complete. Letter from Gary Buehler in FDA Dkt. Nos. 2007P-0249 and 2007N-0445 (May 7, 2008).

regulations requiring an applicant to amend a certification that is "no longer accurate,"[340] a final, non-appealable judgment that the applicant infringes a patent that was the subject of a paragraph IV certification would apparently require the applicant to change its certification from a paragraph IV to a paragraph III certification for that patent (that is, "the patent will expire on ____").[341] And if the first applicant amends or withdraws its paragraph IV certification for *all* of the patents as to which it made such a certification, it forfeits its right to 180-day exclusivity.[342]

In *Teva Pharmaceuticals USA, Inc. v. Sebelius*,[342.1] the D.C. Circuit rejected the FDA's interpretation of 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(CC), under which a "first applicant" forfeits 180-day exclusivity if it fails to market its ANDA product within seventy-five days after the patent that had provided the basis for its paragraph IV certification had been "delisted." It held that the forfeiture provision did not apply because the NDA holder (Merck) withdrew the patent on its own initiative, without any litigation ever having been commenced. Relying on its prior ruling in the pre-MMA case of *Ranbaxy Laboratories Ltd. v. Leavitt*,[342.2] the court in effect confined the forfeiture to instances in which the patent had been withdrawn as a result of a counterclaim to "correct" patent information.

[B] First Filer's ANDA Is Withdrawn or Rejected

If the first generic applicant has no hope of obtaining FDA approval, there is no reason to grant it exclusivity. Therefore, under section 355(j)(5)(D)(i)(II), the first applicant's exclusivity is forfeited if its ANDA is withdrawn or if the FDA finally determines that its ANDA cannot satisfy the FD&C Act's requirements for safety and effectiveness.

[C] First Filer's ANDA Is Not "Tentatively Approved" Within Thirty Months

Under FDA regulations that implemented the original Hatch-Waxman Act, a first filer risked losing its exclusivity if the FDA

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340. 21 C.F.R. § 314.94(a)(12)(viii)(C) (2005).

341. *See* Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1282–83 (D.C. Cir. 2004). The *Mylan* court suggested that FDA could have required the ANDA to be re-certified upon entry of the district court judgment, even though that judgment had been appealed. But the FDA has not required re-certification until a final non-appealable judgment has been rendered.

342. 21 U.S.C. § 355(j)(5)(D)(i)(III).

342.1. Teva Pharm. USA, Inc. v. Sebelius, 595 F.3d 1303 (D.C. Cir. 2010).

342.2. Ranbaxy Labs. Ltd. v. Leavitt, 469 F.3d 120 (D.C. Cir. 2006).

concluded that it was "not actively pursuing approval" of its ANDA.[343] But the regulations placed no time limit on how long the applicant had to resolve all scientific and manufacturing issues the FDA had raised about its ANDA.

Under the MMA, section 355(j)(5)(D)(i)(IV), the first applicant forfeits its 180-day exclusivity if it has not obtained "tentative approval" within thirty months of the ANDA's filing, unless it can show that the issues preventing approval have arisen because of some new regulatory requirement that was imposed only after the ANDA was submitted.[344]

The FDAAA provided ANDA applicants some protection against forfeiture where FDA consideration of a pending "citizen petition" has preceded FDA's review of the ANDA. These amendments added a new section 505(q) to the FD&C Act that adds to the thirty-month period an additional period of time equal to the time that elapsed between FDA's receipt of the citizen petition and FDA's final action on that petition.[344.1] Additionally, section 1133 of the FDA Safety and Innovation Act (FDASIA) extended the time to obtain tentative approval, and thus avoid forfeiture, to forty months for the limited class of ANDAs that were first submitted to FDA between January 9, 2010, and July 9, 2012.[344.2]

[D] All Challenged Patents Have Expired

The MMA, in section 355(j)(5)(D)(i)(VI), codifies the FDA's pre-2003 position that 180-day exclusivity cannot survive the expiration of the patent(s) upon which that exclusivity was based.[345]

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343. 21 C.F.R. § 314.107(c)(3) (2006).

344. The FDA calculates the thirty-month period from the date it accepts the ANDA as "substantially complete," rather than the date the ANDA is first received. Letter from Gary Buehler in Dkt. Nos. 2007P-0249 and 2007N-0445 (May 9, 2008). The term "tentative approval" refers to the FDA's determination that an ANDA meets the requirements for approval but for another applicant's marketing exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv)(II)(dd)(AA). In Ranbaxy Labs., Ltd. v. Burwell, 82 F. Supp. 3d 159, 179 (D.D.C. 2015), the ANDA "first applicant" had obtained tentative approval in less than thirty months, but the FDA later withdrew that approval because of the applicant's serious manufacturing and reporting violations. The district court upheld the FDA's conclusion that the tentative approval withdrawal resulted in a forfeiture of exclusivity. *Id*. at 196–99.

344.1. 21 U.S.C. § 355(q)(1)(G).

344.2. FDA Safety & Innovation Act, Pub. L. No. 112-144, § 1133, 126 Stat. 993, 1122 (2012).

345. The D.C. Circuit upheld the FDA's pre-2003 interpretation in Ranbaxy Labs. Ltd. v. FDA, 96 F. App'x 1 (D.C. Cir. 2004), *aff'g* 307 F. Supp. 2d 15 (D.D.C.).

[E] First Applicant Withdraws All Paragraph IV Certifications

Even prior to the MMA, FDA regulations provided that if an ANDA filer withdrew a certification, its ANDA would "no longer be considered to contain" that certification.[346] Where an ANDA filer withdrew all of its paragraph IV certifications, for example, in connection with a settlement, the FDA interpreted the regulation to mean the first filer lost its claim to exclusivity.

Codifying the FDA's pre-2003 position, the MMA states that if the first applicant amends or withdraws its paragraph IV certification for all of the patents as to which it made such a certification, it forfeits its 180-day exclusivity.[347]

[F] Collusive Agreement

Finally, under section 355(j)(5)(D)(i)(V), if the first applicant enters into an agreement with a competing ANDA filer, the NDA holder or the patent owner that the FTC or a court finds to violate the federal antitrust laws, and that antitrust determination is either not appealed or cannot be appealed, the applicant's 180-day exclusivity is forfeited. The provision reflects a congressional desire to deter settlements of ANDA disputes that improperly deter competition.[348]

Another section of the MMA requires almost all agreements between ANDA filers and competing applicants, NDA holders, or patent owners to be submitted to the FTC and the Department of Justice for review within ten days of execution.[349] Although failure of these agencies to object to one of these agreements will not bar a later enforcement action, it is reasonable to anticipate that few agreements will survive initial agency review if they are so objectionable that they would ultimately result in a forfeiture of exclusivity.[350]

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346. 21 C.F.R. § 314.94(a)(12)(viii) (2005).
347. 21 U.S.C. § 355(j)(5)(D)(i)(III).
348. *See* Statement of Federal Trade Commission before Senate Special Committee on Aging at 2 (July 20, 2006).
349. 117 Stat. 2461–63.
350. The FTC's most recent review of settlements submitted to it in the 2012 fiscal year led it to conclude that "the number of potentially anticompetitive patent dispute settlements between branded and generic drug companies [had] increased significantly," and the FTC has challenged several of these in court. Press Release, FTC, FTC Study: In FY 2012, Branded Drug Firms Significantly Increased the Use of Potential Pay-for-Delay Settlements to Keep Generic Competitors Off the Market (Jan. 17, 2013), www.ftc.gov/news-events/press-releases/2013/01/ftc-study-fy-2012-branded-drug-firms-significantly-increased.

§ 8:2.7 180-Day Exclusivity Under the Pre-MMA Hatch-Waxman Act

Under section 1102(b)(1) of the MMA,[351] the new law's exclusivity rules generally do not apply to drugs for which *any* ANDA with a paragraph IV certification had been submitted prior to December 8, 2003. Since many new ANDAs continue to be filed for such drugs, the pre-2003 requirements remain applicable and important.

[A] Pre-MMA Statutory Text

Prior to the 2003 amendments, 21 U.S.C. § 355(j)(5)(B)(iv) read as follows:

> (iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing [sic] such a certification, the application shall be made effective not earlier than one hundred and eighty days after—
>
> (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

[B] Exclusivity for Pre-MMA ANDAs

Between the Hatch-Waxman Act's enactment and 1998, only a handful of ANDAs ever qualified for exclusivity, because FDA regulations required, as a precondition for exclusivity, that the ANDA applicant first have "successfully defended" a patent infringement lawsuit. However, the D.C. Circuit definitively held in *Mova Pharmaceutical Corp. v. Shalala*[352] that there is no "successful defense" requirement under the statute, and that the FDA had no authority to impose such a requirement.

Rejection of the "successful defense" requirement did not, however, clarify how the statute should be applied in practice; to the contrary, it led to a considerable amount of controversy and litigation about the meaning of the statutory language.

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351. 117 Stat. 2460.
352. Mova Pharm. Corp. v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998).

[B][1] "patent-by-patent" Exclusivity

The statutory text indicates that approval of an ANDA containing a paragraph IV certification will be subject to the exclusivity of a "previous" ANDA containing "such a certification." The language is easy to apply when both ANDAs contain a single paragraph IV certification with respect to the same patent, but the language is more difficult to apply when the ANDAs contain certifications as to multiple patents.

Two approaches have been identified for applying the Hatch-Waxman Act exclusivity provision to paragraph IV certifications challenging multiple patents. Under one approach, which the FDA calls the "one first-applicant" approach, the ANDA applicant's 180-day exclusivity period begins to run when a court determines that *any* of the patents it challenged is invalid or not infringed. Under a second approach, which the FDA calls a "patent-by-patent" approach, the exclusivity period does not begin until the challenges to *all* of the patents have been resolved. The practical difference between these two approaches can be very substantial where, as frequently happens, additional patents claiming the pioneer drug are issued and appear in the Orange Book after the first ANDA is submitted. For example, challenges to some of the patents claiming Prilosec® were decided against the pioneer in 2001, but others remain to be adjudicated. Under the circumstances, did the first applicant's exclusivity period begin—and end—in 2001, or has it not yet begun.[353]

In 1999, the FDA issued a letter ruling that it would recognize exclusivity on a "patent-by-patent" basis.[354] The letter explained that 21 C.F.R. § 314.107(c), the FDA's regulation governing exclusivity, appeared to follow a patent-by-patent approach. That regulation read as follows (with emphasis added by FDA):

> If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the **same patent** was invalid, unenforceable, or would not be infringed, approval of the subsequent abbreviated new drug application will be made effective no sooner than 180-days from [commercial marketing or a court decision].

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353. In Apotex, Inc. v. FDA, 414 F. Supp. 2d 61 (D.D.C. 2006), *aff'd mem.*, 2007 U.S. App. LEXIS 4270 (D.C. Cir. Feb. 23, 2007), the district court upheld FDA's conclusion that the exclusivity period had not yet begun.

354. Letter from Janet Woodcock to Robert Green, FDA Dkt. 99P-1271 (Aug. 2, 1999) (on file with author).

Within a week, the FDA proposed to amend its regulations to award 180-day exclusivity only to the "first applicant," defining the "first applicant" as "the applicant submitting the first substantially complete abbreviated new drug application (ANDA) for a particular listed drug that contains 'a paragraph IV certification' to *any* patent for the listed drug . . . ."[355] However, the FDA never finalized this proposed rule.

In 2002, the FDA announced that it would continue to "regulate directly from the statute and applicable FDA regulations,"[356] and it has continued to recognize exclusivity on a "patent-by-patent" basis. In 2007, the D.C. Circuit finally upheld the FDA's interpretation.[357]

[B][2] "shared" Exclusivity

While its 1999 rulemaking proposal was still pending, the FDA was confronted with a case in which its patent-by-patent approach threatened to delay generic entry indefinitely. Two ANDA applicants each claimed 180 days of exclusivity in which to market a generic version of the same drug, based on each having been the first to submit a paragraph IV certification (albeit for different patents). In the FDA's view, the patent-by-patent approach would lead to an indefinite "exclusivity standoff," a result that the FDA deemed to be inconsistent with the Hatch-Waxman Act's underlying policy of promoting generic competition. ANDA *A* could not be given final approval until ANDA *B*'s exclusivity for one patent had run; but ANDA *B* could not be given final approval until *A*'s exclusivity for a different patent had run. To resolve this standoff, the FDA ruled that ANDAs *A* and *B* would "share" 180-day exclusivity. That is,

(a) *both* ANDAs would be eligible for final approval without regard to the other's 180-day exclusivity;

(b) *both* would be entitled to 180-day exclusivity periods as against other any other ANDAs; and

(c) the exclusivity periods of both would begin simultaneously, on the day that *either* of them launched or on the day that any "court decision" of non-infringement or invalidity was rendered as to *any* of the patents which had qualified either of them for exclusivity.[358]

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355. Proposed 21 C.F.R. § 314.107(a)(2), 64 Fed. Reg. 42,873, 42,885 (Aug. 6, 1999) (emphasis added).
356. 67 Fed. Reg. 66,593, 66,594 (Nov. 1, 2002).
357. Apotex, Inc. v. FDA, 2007 U.S. App. LEXIS 4270 (D.C. Cir. Feb. 23, 2007), *aff'g* 414 F. Supp. 2d 61 (D.D.C. 2006).
358. Letter from Gary Buehler to Andrx Pharmaceuticals, Inc. regarding ANDA 73-347 (Nov. 16, 2001) ("Omeprazole Letter"), www.fda.gov/cder/ogd/shared_exclusivity.htm.

In a subsequent ruling, the FDA clarified that exclusivity will be "shared" only if the two ANDAs would potentially block each other's entry. Where, for example, ANDA *B* makes a paragraph IV certification with respect to a patent for which *A* was the "first applicant," but *A* did not make a paragraph IV certification with respect to the patent for which ANDA *B* was the "first applicant," then the FDA does not require exclusivity to be shared. In such a case, approval of ANDA *B* will be blocked by *A*'s 180-day exclusivity, but approval of ANDA *A* will not be blocked by *B*'s exclusivity.[359]

[C] When Does 180-Day Period Begin?

For ANDAs that are not governed by the MMA, the 180-day period begins when the first of the following two "trigger" events occurs: (1) "the . . . first commercial marketing of the drug under the previous application"; or (2) "a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed. . . ."[360]

[C][1] "first commercial marketing"

FDA regulations define "first commercial marketing" to mean the first introduction into interstate commerce "outside the control" of the manufacturer.[361] The statutory reference to "the drug under the previous application" seems to refer to the drug that the "first applicant" markets under its FDA-approved ANDA. Nevertheless, the FDA has treated as a "first commercial marketing" the first ANDA applicant's sales of an "authorized generic" under the pioneer's NDA, and a district court has found the FDA's interpretation to be not unreasonable.[362]

[C][2] "a decision of a court . . . holding"

[C][2][a] What "Holding"?

Because the statutory language requires a court decision "holding" that the patent subject to the paragraph IV certification is invalid or not infringed, a court-ordered dismissal, based upon a settlement of

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359. Letter from Gary Buehler to Barr Laboratories regarding ANDA 76-236 (Apr. 14, 2005), www.fda.gov/cder/foi/appletter/2005/076236ltr.pdf.

As noted in section 8:2.7[B][1], *supra*, the FDA's patent-by-patent and shared exclusivity policies have been the subject of litigation, but have not been definitively upheld or rejected by the courts.

360. 21 U.S.C. § 355(j)(5)(B)(iv)(I) & (II).

361. 21 C.F.R. § 314.107(c)(4) (2005).

362. Mylan Pharm., Inc. v. Thompson, 207 F. Supp. 2d 476 (N.D. W. Va. 2001).

the dispute, should not begin the exclusivity period, because the court has made no "holding" about the validity of the patent or whether that patent has been infringed; the court has simply determined not to decide those issues in the now-dismissed case.

However, FDA regulations also state that the 180-day period begins upon a court holding of patent unenforceability. In *Teva Pharmaceuticals USA, Inc. v. FDA*,[363] the D.C. Circuit suggested that where a dismissal has the effect of precluding the patent owner from subsequently enforcing the patent against the other party to that suit, such a dismissal does begin the 180-day period, because the dismissal has the effect of holding the patent to be unenforceable against that party.

Seven years later, however, another panel of the same appellate court read that court's earlier *Teva* opinion as merely suggesting a possible line of analysis that the FDA might consider, rather than an authoritative judicial interpretation of the statute. The FDA subsequently ruled that a "triggering 'court decision' must include an actual 'holding' . . . evidenced by language on the face of the court's decision showing that the determination of invalidity, non-infringement, or unenforceability has been made by the court," and in *Apotex, Inc. v. FDA*,[364] the D.C. Circuit upheld the FDA's ruling.

[C][2][b] What Parties?

In *Teva Pharmaceuticals USA*, the D.C. Circuit held that the requisite "holding" that triggers the commencement of the 180-day exclusivity period may occur in any litigation holding the relevant patent to be invalid, unenforceable or not infringed—even if the alleged infringer in that litigation is someone other than the "first applicant" entitled to the exclusivity.[365] Therefore, for example, a judgment that another party's ANDA product does not infringe may trigger the commencement of the first applicant's exclusivity period, regardless of differences between the different ANDA products.

[C][2][c] What Products?

Although the 180-day period may be triggered by a court holding in favor of any ANDA, the ANDA must be for the same "drug" as the one for which the "first applicant" has exclusivity. The FDA views each dosage form (for example, a capsule) of a marketed drug product as different from every other dosage form (for example, a tablet).

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363. Teva Pharm. USA, Inc. v. FDA, 182 F.3d 1003 (D.C. Cir. 1999).
364. Apotex, Inc. v. FDA, 449 F.3d 1249 (D.C. Cir. 2006).
365. In Minn. Mining & Mfg. Co. v. Barr Labs., Inc., 289 F.3d 775 (Fed. Cir. 2002), the Federal Circuit endorsed the D.C. Circuit's position.

Furthermore, the FDA views each strength of a marketed drug product as a separate "drug." The FDA's policy has been upheld in court.[366]

[C][2][d] What Court?

Prior to the enactment of the MMA, it was unclear which "court" decision—the district court's or the appellate court's—triggered the commencement of the 180-day exclusivity period. The FDA initially took the position that a district court decision subject to appeal did *not* trigger the commencement of the 180-day exclusivity period; the exclusivity was triggered only by a non-appealable court decision. Then, in 2000, the FDA changed its interpretation after a district court read the statutory language to begin the exclusivity period upon *any* judgment of invalidity or non-infringement, even if the judgment was the subject of an appeal.[367]

These uncertainties were cleared up by the MMA. The MMA reinstated the FDA's pre-2000 policy, and it did so retroactively as to all ANDAs whose exclusivity period had not begun as of the MMA's December 8, 2003, effective date.[368] Therefore, it is now settled that the court decision triggering the 180-day period is one from which no appeal has been or can be taken (which is typically the decision of the court of appeals). When the "decision" is that of the court of appeals, the exclusivity period begins to run when the appellate court mandate issues.[369]

[D] Loss of Exclusivity

Under pre-MMA law, as under the MMA, a "first applicant" is entitled to exclusivity only as long as it properly maintains a paragraph IV certification as to the patent that made it eligible for exclusivity. Thus, exclusivity does not survive the expiration of the patent, because upon patent expiration, the paragraph IV certification is no

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366. Apotex, Inc. v. Shalala, 53 F. Supp. 2d 454 (D.D.C.), *aff'd*, 1999 WL 956686 (D.C. Cir. Oct. 8, 1999).

367. 65 Fed. Reg. 43,233 (July 13, 2000) (citing Mylan Pharm. Inc. v. Shalala, 81 F. Supp. 2d 30 (D.D.C. 2000)).

368. Pub. L. No. 108-173, § 1102(b)(3), 117 Stat. 2460.

369. In Mylan Labs., Inc. v. Leavitt, 484 F. Supp. 2d 109 (D.D.C.), *appeal dismissed*, 2007 U.S. App. LEXIS 24964 (D.C. Cir. Oct. 23, 2007), the district court upheld an FDA ruling that the six-month period of pediatric exclusivity created by 21 U.S.C. § 355a(c) remained in effect until the court of appeals issued its mandate vacating a district court judgment in favor of the patent, based upon the agency's interpretation of the phrase "the court determines." But the FDA's interpretation, which the district court found to be allowable, was based in part on a reading of "determine" to mean "fix conclusively," rather than merely "decide."

longer accurate, and the FDA may regard the certification as having been converted to a "paragraph II" certification that the patent "has expired."[370] Similarly, a paragraph IV certification does not survive the entry of a final, non-appealable judgment of infringement against the first applicant, because upon entry of that judgment the paragraph IV certification has been judicially determined to be inaccurate.[371]

§ 8:2.8 Waiver and Transfer of Exclusivity

Neither the Hatch-Waxman Act, nor the MMA, nor FDA regulations authorize an ANDA filer to transfer its exclusivity to another ANDA. Nevertheless, as a matter of policy, the FDA has allowed "first applicants" to "waive" their exclusivity rights, either generally as to all subsequent ANDAs or specifically in favor of one or more particular ANDAs.[372] Under the FDA's policy, a "selective" waiver of exclusivity may be effected only after the first applicant's 180-day period has already begun, but a total "relinquishment" of exclusivity may be made at any time.[373]

§ 8:3 "Data" Exclusivity Under the FD&C Act

§ 8:3.1 Introduction

Beginning with the Orphan Drug Act in 1983, Congress created a series of incentives, apart from patent rights, to compensate pharmaceutical companies for the expense and risk of performing clinical

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370. Ranbaxy Labs. Ltd. v. FDA, 96 F. App'x 1 (D.C. Cir. 2004).

371. In Mylan Labs., Inc. v. Thompson, 389 F.3d 1272, 1283 n.10 (D.C. Cir. 2004), the court of appeals suggested that the FDA could regard the paragraph IV certification as void upon entry of a district court judgment of infringement, even if that judgment was subject to appeal. However, the FDA has continued to recognize paragraph IV certifications as effective until the entry of a non-appealable judgment.

372. A legal defense of the FDA's policy appears in a July 2004 letter in which the FDA denied a "citizen petition" that had challenged the policy. Letter from William K. Hubbard to Bert Rein, Docket No. 04-0227 (July 2, 2004), www.fda.gov/ohrms/dockets/dailys/04/july04/070704/04p-0227-pdn0001.pdf.

373. *Id*. at 5 n.5. Applying this policy, the FDA allowed Teva to "relinquish" its exclusivity for its generic version of Accupril®, for which it was the first to submit a paragraph IV certification, after its ANDA product had already been found by a district court to infringe the patent in question. Letter from Gary Buehler to Ranbaxy, Inc., re: ANDA No. 76-607 (Dec. 15, 2004), www.fda.gov/cder/foi/appletter/2004/076607ltr.pdf. The patent owner, which had not sued Ranbaxy, thereupon sued and obtained a preliminary injection. Pfizer, Inc. v. Teva Pharm. USA, Inc., 429 F.3d 1364 (Fed. Cir. 2005).

studies and developing data to support the approval of novel drugs or new uses of existing drugs. These incentives generally take the form of various exclusivity periods, mostly independent of patent rights, during which the FDA may not approve competing products.

Table 8-1 lists the different types of non-patent FDA exclusivities.

> There are two general categories of regulatory exclusivity: (1) data exclusivity, which precludes applicants from relying on the reference product's clinical data to demonstrate the safety and effectiveness of the follow-on product; and (2) marketing exclusivity, which precludes FDA from approving any other application for an identical or biosimilar product for the same use, even if the applicant has generated its own data.[374]

In addition, there is pediatric exclusivity, which extends other statutory exclusivities. A more detailed description of each type of exclusivity is set forth below.

Table 8-1[374.1]

Types of FDA Exclusivity (for non-biologics)

Type of Exclusivity	Description	Statute
New Chemical Entity (NCE) Exclusivity	5 years' data exclusivity for NDAs covering new chemical entities	§ 355(c)(3)(e)(ii) and (j)(5)(F)(ii)
Other Significant Changes (OSC) Exclusivity	3 years' data exclusivity for NDAs and supplemental NDAs for new indications or new dosage forms of existing drugs	§ 355(c)(3)(E)(ii), (j)(5)(F)(ii) & (u)
Orphan Drug Exclusivity	7 years' marketing exclusivity for drugs that FDA designates as Orphan Drugs which treat rare diseases	§§ 355(c)(3)(E) (iii) & (iv), (j)(5)(F)(iii) & (iv)

374. CONG. RESCH. SERV., DRUG PRICING AND THE LAW: REGULATORY EXCLUSIVITIES (May 17, 2019), https://sgp.fas.org/crs/misc/IF11217.pdf.

374.1. See section 13:4.4 for a description of exclusivities applying to biologics. Also see section 8:2 for a discussion of first paragraph IV filer(s)' 180-day exclusivity.

Type of Exclusivity	Description	Statute
Pediatric Exclusivity	6-month extension to patent or data exclusivities for all drug products and dosage forms of the same "active moiety"; obtained by submission and acceptance of pediatric studies in response to an FDA request	§ 360cc
Qualified Infections Disease Product (QIDP)	5-year extension to patent or data exclusivities for drugs designated by the FDA as QIDP (antibacterial/antifungal that treats serious infections)	§ 355f

§ 8:3.2 New Chemical Entity Exclusivity

[A] Statutory Basis: Section 355(c)(3)(E)(ii) and Section 355(j)(5)(F)(ii)

"Facing the classic question of the appropriate trade-off between greater incentives for the invention of new products and greater affordability of those products," the Hatch-Waxman Act provided "the original drug producer a specified period of market exclusivity depending primarily on the pharmaceutical novelty of a drug."[375] The currently applicable legislative tradeoff appears in the ANDA and "paper NDA" sections of the Hatch-Waxman Act, 21 U.S.C. § 355(c)(3)(E)(ii) and § 355(j)(5)(F)(ii). As implemented by FDA's regulations, these sections generally prohibit the *submission* of an ANDA for five years after the FDA has issued an "approval letter" for the pioneer's NDA.[375.1] If, however, the ANDA contains a paragraph IV certification, it may be submitted four years after NDA approval (but in that case,[376] the "30-month" stay of FDA approval during the pendency of patent litigation terminates 7½ years from NDA approval, rather than thirty months from service of the statutory notice).

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375. Abbott Labs. v. Young, 920 F.2d 984, 985 (D.C. Cir. 1990).

375.1. Under FDA's interpretation, an "approval letter" does not necessarily mean that the product covered by the latter may be lawfully marketed. In Eisai, Inc. v. FDA, 14-cv-1346, 2015 U.S. Dist. LEXIS 133222, at *10–12, *49–50 (D.D.C. Sept. 30, 2015), the district court upheld FDA's ruling that the five-year exclusivity period had started to run even though the drug covered by the "approval letter" could not be lawfully marketed, because another regulatory agency, the Drug Enforcement Administration, had not yet "scheduled" the drug under the Controlled Substances Act.

376. *See supra* section 8:1.6.

[B] Eligibility Criteria for NCE Exclusivity

The drug product for which exclusivity is claimed must be "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been [previously] approved in any [new drug] application. . . ."[377] Thus, a new formulation of a previously approved active ingredient is not eligible for NCE exclusivity.[378]

[B][1] "Active Ingredient" Means "Active Moiety"

Under the FDA's regulations governing data-based exclusivity, the "active ingredient" that must not have been previously approved is the "active moiety."[379] In lay terms, the FDA has described an "active moiety as "the part of the drug that makes the drug work the way it does."[380] The FDA's regulations define "active moiety" as:

> the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[381]

The FDA adopted this narrow interpretation of the statutory term "active ingredient" to avoid overcompensating drug makers who had merely made "minor variations of previously approved chemical compounds."[382] Significantly, however, the statute itself does not expressly limit the "active ingredients" eligible for NCE exclusivity to "active moieties." Indeed, before the FDA officially adopted its narrow interpretation, a district court rejected the "active moiety" restriction as contrary to the "plain meaning" of the statutory text. However, the district court's ruling was itself vacated by the D.C. Circuit, which remanded the question to the FDA for further consideration.[383]

Notwithstanding the uncertain legal status of interpreting "active ingredient" to be the "active moiety," the FDA has adhered to that interpretation without additional challenge for fifteen years.[384] Thus,

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377. 21 U.S.C. § 355(j)(5)(F)(iv).
378. Sections 8:3.2[B][1]–[B][3], *infra*, explain this requirement.
379. 21 C.F.R. § 314.108 (2006).
380. 64 Fed. Reg. 47,719, 47,721 (Sept. 1, 1999).
381. 21 C.F.R. § 314.108(a) (2006).
382. 54 Fed. Reg. 28,872, 28,898 (July 10, 1989).
383. Abbott Labs. v. Young, 691 F. Supp. 462 (D.D.C. 1988), *vacated and remanded*, 920 F.2d 984 (D.C. Cir. 1990).
384. Pfizer, Inc. v. Dr. Reddy's Labs., Ltd., 359 F.3d 1361 (Fed. Cir. 2004) (citing FDA's regulations with approval in construing the Hatch-Waxman Act's patent extension provision, 35 U.S.C. § 156).

for example, the FDA denied exclusivity to a new drug tablet in which the active compound was formulated as a salt, because the same "active moiety"—in an acid form—had been approved several years before for administration by injection.[385] The FDA's interpretation may need to be reevaluated, however, in light of *Amarin Pharmaceuticals Ireland Ltd. v. FDA*.[385.1] In that case, involving an NDA for a naturally derived mixture of ingredients, the district court rejected the FDA's "active moiety" interpretation as both unreasonable under the facts presented and contrary to the statutory text. Nevertheless, although the FDA did not appeal, it has not yet acted on the court's remand, and pending that action, and possible appeals of the district court judgment by intervenors, it has declined to retreat from its "active moiety" interpretation.[385.2]

[B][2] Novel Combinations

The FDA has for many years interpreted the word "drug," for which no "active moiety" has been previously approved, to mean the finished "drug product," so that a new product that consists of a combination of two previously approved active ingredients is not eligible for NCE exclusivity, even though the combination represents a significant therapeutic advance. Likewise, the FDA did not accord NCE exclusivity to newly approved combinations, even though one of the active ingredients in the novel combination had not previously received FDA approval. In 2014, however, in response to several "citizen petitions," and "[i]n light of the increasing importance of fixed-combination products to treat serious diseases and conditions," FDA reversed itself and agreed that fixed-combination drugs should be eligible for NCE exclusivity if any of the active ingredients in the combination had not been previously approved. FDA has further proposed to implement its new policy prospectively, so that only those combination products that receive FDA approval after the proposal is finalized (after public comment) will be eligible for NCE exclusivity.[385.3]

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385. *Abbott*, 691 F. Supp. at 465.

385.1. Amarin Pharm. Ir. Ltd. v. FDA, 14-cv-324, 2015 U.S. Dist. LEXIS 68723 (D.D.C. May 28, 2015).

385.2. *See* Letter from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER) to William H. Carson, et al. (Oct. 5, 2015), Dkt. No. FDA-2015-P 2482, http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2482-0015.

385.3. FDA, Draft Guidance, *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products* (Feb. 2014), www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf; *see also* Letter from Janet Woodcock, Director, Ctr. for Drug Evaluation & Research, to David M. Fox et al. (Feb. 21, 2014) (in FDA Dkts. 2013-P-0058, 2013-P-0019, and 2013-P-0471).

[B][3] New Forms of Previously Approved Ingredients

[B][3][a] Polymorphs

In general, the FDA regards a "polymorph"[386] to be the "same" as a previously approved active ingredient—and thus ineligible for NCE exclusivity—if the finished drug product containing the polymorph performs the same as the previously approved product in terms of such characteristics as dissolution or solubility.[387]

[B][3][b] Stereoisomers

Isomers are compounds that have the same elements in the same proportion (that is, the same chemical formula) but whose atoms are arranged differently. Stereoisomers are isomers that also have the same chemical bonds between the atoms but different spatial arrangements.[388] Enantiomers are stereoisomers that are mirror images of each other. Enantiomers coexist in nature in equal proportions; a mixture of enantiomers in equal proportions is called a "racemic mixture."

However, different enantiomers of the same compound may have different biological properties. Increasing attention has been devoted to studying these potentially differing effects, because drugs consisting primarily of one enantiomer, rather than the other, may have therapeutic or other advantages.

When the FDA issued regulations governing eligibility for exclusivity, it took the position that "a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity."[389] In 1997, however, the FDA expressed its intention to reconsider the issue, and requested further comment.[390] In 2007, after the FDA had not yet acted on its 1997 notice, Congress amended the FD&C Act to provide limited NCE exclusivity for "new" enantiomers. Under section 1113 of the Food and Drug Administration Amendments of 2007, a newly approved drug will be entitled to NCE exclusivity if (i) the newly approved drug's active ingredient is a single enantiomer that had not

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386. The FDA uses the term "polymorphs" broadly, to include chemicals with different crystalline structures, amorphous structures, solvates, and different degrees of hydration.

387. *See* 68 Fed. Reg. 36,676, 36,678 (June 18, 2003) (explaining why the FDA will accept patents claiming polymorphs as claiming "same active ingredient" where the polymorphs have been shown to act in the same fashion).

388. *See In re* May, 574 F.2d 1082, 1085 (C.C.P.A. 1978) (briefly describing stereoisomerism).

389. 59 Fed. Reg. 50,338, 50,359 (Oct. 3, 1994).

390. 62 Fed. Reg. 2167 (Jan. 15, 1997).

been approved in any previous NDA, except as a constituent of a racemic mixture, and (ii) the newly approved drug is approved only for use in a therapeutic category that is different from the category for which the racemic mixture has previously been approved.[391]

[C] Extra Exclusivity for Certain New Antibiotics

In the recent Generating Antibiotic Incentives Now (GAIN) Act, adopted as part of the 2012 FDASIA, Congress created an additional incentive to makers of important new antibiotics. Under new section 505E of the FD&C Act, an antibiotic that the Secretary of HHS has designated as a "qualified infectious disease agent" is entitled to five years of exclusivity beyond the period in which NCE exclusivity would otherwise expire.[391.1]

§ 8:3.3 "Other Significant Changes" Exclusivity

[A] Statutory Basis: Section 355(j)(5)(F)(iii) and (iv)

Drugs that do not qualify for five-years of exclusivity as "new chemical entities" may nevertheless qualify for some protection. If an NDA or supplemental NDA is approved for a new indication for a previously approved drug (for example, treatment of hair loss rather than hypertension), or a new dosage form for that drug (for example, a transdermal patch, rather than a capsule), then ANDAs for a drug containing the same active ingredient may not be approved in that dosage form or for that newly approved indication for three years after the NDA or NDA supplement was approved. "Other Significant Changes" (OSC) exclusivity bars FDA approval during the exclusivity period; it does not bar submission of an ANDA during the exclusivity period for approval immediately upon that period's expiration.

[B] Eligibility Criteria for OSC Exclusivity

The statute granting OSC Exclusivity requires that the NDA or supplemental NDA contain reports of:

- "new clinical investigations"
- "conducted or sponsored by the applicant"
- "essential to the approval"[392]

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391. Pub. L. No. 110-85, § 113, to be codified at 21 U.S.C. § 355(u).
391.1. FDA Safety & Innovation Act, Pub. L. No. 112-144, § 801, 126 Stat. 993, 1077 (2012) (codified at 21 U.S.C. § 355f).
392. 21 U.S.C. § 355(j)(5)(iii) & (iv).

[B][1] "new clinical investigations"

OSC eligibility is intended to reward innovators who make a significant investment in developing improved versions of already-marketed drugs or in identifying new therapeutic uses for those drugs. To qualify for exclusivity, the innovator must have conducted "new clinical investigations," which FDA interprets to mean safety or efficacy studies in humans. Bioavailability studies do not qualify.[393]

Although the statute requires that the studies be "new," the regulations require only that the studies be "new" to the FDA, that is, that the studies not have been previously relied upon to support the safety or efficacy of a drug.[394]

[B][2] "conducted or sponsored by the applicant"

In keeping with the policy of encouraging investment by the innovator, the "new" clinical investigations must have been conducted or "sponsored" by the NDA applicant or holder, who must ordinarily have contributed at least 50% of the study's cost.[395]

[B][3] "essential to approval"

Whether new studies have been "essential" to the FDA's approval can be subject to dispute, because there is no clear-cut line between information that is "essential" and information that is merely "useful" or "confirmatory." For example, the FDA denied exclusivity to Rogaine®, whose manufacturer had submitted additional studies to obtain the FDA's approval for sale of the product without a prescription. Although one high-ranking FDA reviewer appears to have regarded the study as "essential" to his recommendation, his boss did not regard the study as "essential" to his approval. The reviewing court deferred to the FDA, finding the issue of whether the study was "essential" to be "fundamentally a scientific dispute in an area where this Court lacks expertise."[396]

[C] "Carve-Out" Option for ANDAs

The value of OSC three-year exclusivity for new use indications is limited because FDA regulations allow an ANDA applicant to "carve out" from its application indications for use that are subject to the innovator's patent or data exclusivity.[397] To substantially overcome

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393. 21 U.S.C. § 355(j)(5)(F)(iii) & (iv); 21 C.F.R. § 314.108(a) (2006).
394. 21 C.F.R. § 314.108(a) (2006).
395. *Id*.
396. Upjohn Co. v. Kessler, 938 F. Supp. 439, 445 (W.D. Mich. 1996).
397. The regulation appears at 21 C.F.R. § 314.94(a)(8)(iv) (2006). Thus, the three-year OSC exclusivity has been held to protect the pioneer against

the OSC exclusivity, a generic applicant need only omit from its labeling the indication for which the pioneer has received exclusivity.

The omission of the protected use from the generic's label will often have little practical effect. Although the generic manufacturer will be prohibited from promoting its product for the protected use, its product still can, and will, be prescribed and dispensed for that use. That is because once a drug product is on the market, there is nothing to stop physicians from prescribing that product for *any* use, including the use that is supposedly protected by the pioneer's three-year exclusivity. Moreover, under most state laws, the pharmacist is required to fill a prescription for the pioneer's product with the generic substitute, regardless of the indication for which it is prescribed.

As long as an ANDA product contains the appropriate "carve out" for the use protected by OSC exclusivity, the FDA does not consider whether the exclusivity will have any practical effect in the market. Thus, for example, the FDA approved an ANDA for generic ribavirin, labeled to be sold in combination with interferon, even though it was almost certain that most of the ANDA drug would be used in connection with pegelated interferon, a specific use covered by the pioneer's exclusivity.[398]

§ 8:3.4 "Orphan Drug" Exclusivity

[A] Statutory Basis: Sections 360aa–360cc

The "Orphan Drug Act"[399] was enacted in 1983, a year before the Hatch-Waxman Act, for the limited but important purpose of encouraging drug manufacturers to invest in developing drugs for relatively rare but serious diseases, even though the revenues from the sale of these drugs, in a fully competitive market, might not justify the cost of developing them.[400] Although the Act does not itself use the word "orphan," the statute applies to a drug "[f]or . . . [a] rare disease or condition," which the Act defines as one that "affects less than 200,000 persons in the United States," or that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States

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the "manufacture of a generic substitute using the pioneer's proprietary research undertaken to obtain approval for a supplemental indication." Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

398. Letter from Steven Galson, Acting Director, CDER, to David Fox, No. 03P-0321 (Apr. 6, 2004), www.fda.gov/ohrms/dockets/dailys/04/apr04/04D804/03p-0321-pdn0001.pdf.

399. Now codified at 21 U.S.C. §§ 360aa–360cc.

400. Pub. L. No. 97-414 § 1(b), codified at 21 U.S.C. §§ 360aa–360cc.

a drug for such disease or condition will be recovered from sales in the United States of such drug."[401] The Orphan Drug Act provides tax incentives and grant funding for the expensive clinical trials needed to support approval of NDAs for drugs to treat these relatively rare conditions. However, the principal carrot is the award of seven years of exclusive marketing rights for a drug that the FDA designates as an "Orphan Drug."

[B] "Orphan Drug" Eligibility Criteria for Exclusivity

The FDA designates a drug as an "orphan drug" upon review of the "sponsor's" written request. FDA regulations require that the request describe the rare disease or condition for which the drug is being investigated, explain why the drug is thought to have potential for treating or (if a vaccine) for preventing the disease or condition, and document that the disease or condition is sufficiently "rare" to satisfy the statutory criteria.[402] Under FDA policy, embodied in its most recent regulations, if an orphan drug is the same as a previously approved non-orphan drug, FDA will not accord it exclusivity unless the sponsor has shown that it is clinically superior to the earlier approved drug.[402.1] A recent district court decision has found FDA's policy to be contrary to the clear language of the statute.[402.2] A previously approved drug may qualify for "orphan" status with respect to a new use, if the sponsor conducts investigations on using the drug to treat a rare disease or condition. For example, although caffeine is not exactly a "new" drug, the FDA has designated it as an orphan drug for the treatment of apnea in premature infants.[403]

The FDA maintains a list of designated orphan drugs, which now contains over 1400 drugs. The list of approved orphan drugs is much shorter, about 280 as of April 2006.[404]

[C] Scope of Orphan Drug Exclusivity

The Orphan Drug Act prohibits the FDA from approving "another application under section 505(b)" or another biologics license under section 351 of the PHSA "for such drug for such disease or condition" for seven years from the date on which the FDA approves the NDA

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401. 21 U.S.C. § 360bb(a)(2).
402. 21 C.F.R. § 316.20 (2006).
402.1. 21 C.F.R. § 316.34(c).
402.2. Depomed, Inc. v. Dep't Health & Human Servs., 66 F. Supp. 3d 217 (D.D.C. 2014), *appeal dismissed*, 2014 U.S. App. LEXIS 21700 (D.C. Cir. Nov. 7, 2014).
403. FDA Orphan Drug Designations and Approvals, www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=031288.
404. *Id*.

(or supplement) or BLA for the designated orphan drug.[405] Unlike the Hatch-Waxman Act exclusivities discussed above, Orphan Drug Act exclusivity bars approval of subsequent NDAs. However, the FDA has interpreted the second phrase, "for such disease or condition," to limit the exclusivity to applications that seek approval for treating the disease or condition upon which orphan designation was made. Thus, the competitor can obtain FDA approval of the drug for treating other diseases or conditions, and then benefit from the likely substitution of its product for the Orphan Drug sponsor's product for *all* uses. One appellate court upheld the FDA's interpretation notwithstanding the Orphan Drug sponsor's showing that the use accounting for the orphan designation was responsible for more than 80% of the drug's market.[406]

[C][1] "same drug"

The statute does not define when a subsequent drug is regarded as the "same" as the Orphan Drug, and therefore blocked by the Orphan Drug sponsor's exclusivity. The issue is addressed by FDA regulations, which look both to the chemical structure and to the clinical performance of the two drugs.

[C][1][a] "same" Structure

The FDA regards drugs consisting of small molecules to be the "same" if they have the same "active moiety."[407] A district court has found the FDA's interpretation sufficiently plausible to deny a preliminary injunction against enforcement of that interpretation.[408]

In contrast, for large molecules such as proteins, the FDA regards a subsequent drug as the "same" as the approved Orphan Drug if it "contains the same *principal* molecular structural features," (emphasis added) even if not all of the structural features are the same.[409]

[C][1][b] "same" Clinical Performance

However, the FDA will *not* regard a subsequent drug as the "same" as a previously approved Orphan Drug, even if it is structurally "the same," if the FDA concludes that the subsequent drug is "[c]linically superior," that is, that it provides a "significant therapeutic advantage."[410] This "significant therapeutic advantage" may manifest itself in a

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405. 21 U.S.C. § 360cc(a)(2).
406. *See* Sigma-Tau Pharm., Inc. v. Schwetz, 288 F.3d 141 (4th Cir. 2002).
407. 21 C.F.R. § 316.3(b)(13)(i) (2006).
408. Baker-Norton Pharm., Inc. v. FDA, 132 F. Supp. 2d 30 (D.D.C. 2001).
409. 21 C.F.R. § 316.3(b)(13)(ii) (2006).
410. 21 C.F.R. § 316.3(b)(3) (2006).

better safety profile or superior efficacy as to some (even if not all) clinical endpoints.[411]

The FDA applied these criteria to approve subsequent versions of the protein beta interferon for the treatment of multiple sclerosis despite the Orphan Drug designation of Betaseron®. In the first instance, the FDA concluded, based on studies of a third product that the FDA deemed "comparable," that Biogen's beta interferon product Avonex® caused less swelling at the injection site.[412] Thus, Avonex® was not blocked by Betaseron®'s designation as an Orphan Drug. Moreover, Avonex® was itself designated as an Orphan Drug. The FDA then approved still another beta interferon product, Rebif®, based on a head-to-head clinical trial showing that Rebif® was more effective than Avonex® with respect to a single clinical endpoint—without regard to whether Rebif® was more effective, equally effective, or even less effective with respect to other endpoints. The greater effectiveness with respect to just one endpoint was enough for the FDA to conclude that Rebif® was not the "same" as Avonex® and therefore was not blocked by Avonex®'s Orphan Drug exclusivity.[413]

§ 8:3.5 *Pediatric "Exclusivity"*

[A] Statutory Basis: 21 U.S.C. § 355a

Children suffer from many of the diseases and conditions that afflict adults. However, prior to 1997, few drugs were accompanied by labeling setting forth the suitability and proper dosing regimen of the drugs in children, because clinical trials in children had not been performed. In effect, most children were being treated on an "off-label" basis.

As part of an overall "modernization" effort in 1997, Congress created a new incentive for drug makers to determine the safety, effectiveness, and conditions of use of their drug products in children. This new incentive, originally enacted as part of FDAMA, was re-authorized in slightly modified form in the Best Pharmaceuticals for Children Act of 2002 (BPCA).[414]

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411. FDA's policy is articulated in a March 7, 2002, memorandum, Office of Orphan Products Development (OOPD) Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif [hereinafter OOPD Analysis], www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm094512.pdf.

412. Berlex Labs., Inc. v. FDA, 942 F. Supp. 19 (D.D.C. 1996) (declining to overturn the FDA's scientific judgment).

413. *See* OOPD Analysis, *supra* note 411.

414. Pub. L. No. 107-109, 115 Stat. 1408 (2002), codified in pertinent part at 21 U.S.C. § 355a.

The 1997 and 2002 statutes did not *require* manufacturers to undertake any studies of their products in children. Instead, the statutes offered those manufacturers who did conduct pediatric studies a six-month extension of any patent or data exclusivity protection to which they were otherwise entitled.[415] Although this legislative carrot is commonly referred to as "pediatric exclusivity," it is important to remember that this "exclusivity" applies only where there is some *other* statutory exclusivity to which it can attach. If the pioneer has no remaining patent protection and no available data exclusivity, the "pediatric exclusivity" provides it no benefit.

[B] Eligibility for Pediatric Exclusivity

Pediatric exclusivity is earned by submitting the results of pediatric studies that the FDA has requested, and the FDA's acceptance of those studies. The formal process begins when the FDA writes to the holder of an approved NDA to request that the "sponsor," that is, the NDA holder, study the pediatric use of its approved drug product. The request will identify the "indication" of the drug that the FDA wants studied, the population (for example, infants) to be studied, and the time frame for completion of the studies.[416] Indications for which the FDA has made written requests run the gamut from mild pain to meningitis.[417]

The response to a written request is due in thirty days, but is voluntary. If a sponsor chooses to undertake the requested study, and submits the study results as requested, then upon the FDA's acceptance of those results the sponsor is granted pediatric exclusivity—that is, if the sponsor is otherwise entitled to patent or data exclusivity protection, the existing protection period is automatically extended by six months.[418]

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415. FDA efforts to require NDA applicants and holders to determine the appropriateness of their products for pediatric use suffered a judicial set back in 2002, after which Congress adopted the "Pediatric Research Equity Act of 2003," which gave the FDA authority to require such studies. Pub. L. No. 108-155, 117 Stat. 1936 (2003), codified at 21 U.S.C. § 355b.

416. 21 U.S.C. § 355a(c).

417. A list of written request conditions appears on the FDA's website at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050007.htm.

418. If the NDA holder does not respond to the FDA's request for pediatric studies, the FDA may contract with another entity (for example, a hospital or university) to conduct the studies. 42 U.S.C. § 284m.

[C] Interim Extension

Under the BPCA, the FDA may make a written request for pediatric studies even if the "sponsor" has little or no remaining data exclusivity or patent protection left. Sponsors who submit the results of requested pediatric studies toward the end of their exclusivity periods may qualify for an "interim extension" of those exclusivity periods for up to ninety days while FDA reviews the study results.[419]

This interim extension serves only to preserve the sponsor's eligibility for the six-month extension. Thus, if the FDA accepts the study on the ninetieth day, the six-month period will end ninety days later.

[D] Label Revision Not Required

In view of the public interest in determining whether an existing drug is safe and effective in children, FDA acceptance of the requested pediatric studies entitles the sponsor to the six-month extension regardless of whether or not the studies actually demonstrate that the drug is safe and effective in the pediatric population studied. Nor is the sponsor obliged to take any further action based upon the studies, for example, to submit an NDA amendment to add labeling directions for pediatric use.

However, if the FDA does approve an NDA amendment based upon these studies, the sponsor will be entitled to OSC exclusivity for that additional indication, and the exclusivity period will total three years and six months (the regular three-year OSC data exclusivity, plus the six-month extension afforded by the pediatric exclusivity).[420] As discussed above,[421] competitors may nonetheless obtain FDA approval for their products by "carving out" the newly approved pediatric information from their labeling, although the FDA is authorized to require that their labeling disclose that the product has not been approved for use in children.[422]

[E] Scope of Pediatric Extension

Unlike data-based exclusivity, the scope of the pediatric extension is not limited to the particular drug product that was the subject of the pediatric studies. Rather, the FDA interprets the extension as applying to all drug products in all dosage forms that contain the

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419. 21 U.S.C. § 355a(e).
420. 21 U.S.C. § 355a(*l*)(3).
421. *See supra* section 8:3.3[C].
422. 21 U.S.C. § 355a(*l*)(2).

same "active moiety" that was present in the product that was studied for pediatric use.[423]

[E][1] Extension of Data-Based Exclusivity

As discussed directly above, the pediatric extension extends the period of otherwise-applicable exclusivities by an additional six months. Thus, the five-year NCE exclusivity becomes 5½ years; the three-year OSC exclusivity becomes 3½ years; and the seven-year Orphan Drug exclusivity becomes 7½ years.

[E][2] Extension of Patent Protection

In enacting the BPCA, Congress did not authorize the FDA to extend the life of any patent.[424] If a patent claiming an active ingredient of a drug expires in July 2007, that patent will still expire on that date after the FDA accepts a pediatric study conducted on a drug containing that ingredient. However, the BPCA requires the FDA to continue for six months after patent expiration the protections against approval of competing products that applied prior to patent expiration.

The BPCA's pediatric extension provision and the Hatch-Waxman Act's patent protection provisions are awkwardly connected, requiring judicial melding. The effect of the pediatric extension is relatively straightforward when an ANDA filer has made a certification under "paragraph II" (that is, the patent "has expired") or under "paragraph III" (that is, the "patent will expire on ___"). In such cases, the FDA may not approve the ANDA for six months after the patent expires.

The effect of the pediatric extension where the ANDA filer has challenged the relevant patents with a "paragraph IV" certification is not as clear. Section 355a(b)(2)(B) of title 21 of the U.S. Code provides:

> [I]f the drug is the subject of a listed patent for which [a paragraph IV certification] has been submitted and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the

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423. Although the FDA has never promulgated regulations to govern the pediatric extension, it has issued a "Guidance" that sets forth in some detail how the FDA interprets the relevant statute. "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act" (Sept. 1999) [hereinafter Qualifying for Pediatric Exclusivity], www.fda.gov/OHRMS/DOCKETS/98fr/980265gd.pdf. A district court upheld the FDA's interpretation in Nat'l Pharm. All. v. Henney, 47 F. Supp. 2d 37 (D.D.C. 1999).

424. *See* Qualifying for Pediatric Exclusivity, *supra* note 423.

> period during which an application may not be approved under [21 U.S.C. § 355] (j)(5)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

Thus, where the ANDA filer has made a paragraph IV certification, the pediatric extension applies only when, in "the patent infringement litigation resulting from the [paragraph IV] certification," the court determines that the patent is valid and infringed. When the court makes such an infringement determination, the period under which the ANDA may not be approved under section 355(j)(5)(B) [that is, before patent expiration] is extended for six months after patent expiration.

The pediatric extension does not, however, extend the thirty-month stay. If the patent has not yet expired, there is nothing in the BPCA that precludes FDA approval once the thirty-month period has expired. However, if FDA has not yet approved the ANDA when the patent expires, the paragraph IV certification will automatically be "converted" to a "paragraph II" certification (that is, that the patent "has expired"), and FDA approval must be postponed for six months after patent expiry.[425] If FDA approves the ANDA before patent expiry the pediatric extension will not attach unless the patent is subsequently found to be infringed. If the district court finds infringement, the FDA's approval will automatically be suspended for six months after patent expiration. If the ANDA holder has already launched before the district court judgment is entered, its ANDA will no longer be considered to possess an effective approval, and it may not continue to distribute its product in commerce.[426]

§ 8:4 Patent Term Restoration*

§ 8:4.1 Introduction

The patent term restoration portion of the Hatch-Waxman Act (formally named the "Drug Price Competition and Patent Term

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425. Ranbaxy Labs. Ltd. v. FDA, 307 F. Supp. 2d 15 (D.D.C.), *aff'd*, 96 F. App'x 1 (D.C. Cir. 2004). In Mylan Labs., Inc. v. Leavitt, 484 F. Supp. 2d 109 (D.D.C.), *appeal dismissed*, 2007 U.S. App. LEXIS 24964 (D.C. Cir. Oct. 23, 2007), an ANDA filer was allowed to market its product because the district court judgment enforcing a patent against it had been stayed before the patent expired.

426. Mylan Labs., Inc. v. Thompson, 389 F.3d 1272 (D.C. Cir. 2004). Indeed, the D.C. Circuit held that the six-month extension applied even though the plaintiff had neglected to commence its action within the forty-five-day window.

* Written by Allan Kassenoff.

Restoration Act of 1984")[427] was enacted to remedy the effective loss of patent term due to delays in the regulatory approval process for pharmaceutical and other products that were subject to laborious pre-market review. In *Eli Lilly & Co. v. Medtronic, Inc.*,[428] the Supreme Court explained some of the concerns that led Congress to enact the Hatch-Waxman Act:

> The holder of a patent relating to such products would as a practical matter not be able to reap any financial rewards during the early years of the term. When an inventor makes a potentially useful discovery, he ordinarily protects it by applying for a patent at once. Thus, if the discovery relates to a product that cannot be marketed without substantial testing and regulatory approval, the "clock" on his patent term will be running even though he is not yet able to derive any profit from the invention.[429]

The following example, Fig. 8-2, illustrates how the FDA approval process can shorten the effective life of a patent.

Section 156 of title 35 of the U.S. Code contains provisions that extend the term of an eligible patent to restore this time lost by the patentee.

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427. Codified at 35 U.S.C. § 156.

428. Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990).

429. *Id*. at 669–70; *see also* Pfizer, Inc. v. Dr. Reddy's Labs., Ltd., 359 F.3d 1361, 1364 (Fed. Cir. 2004) ("By restoring a portion of the patent term that is consumed during the approval phase, the incentive to develop and market products that require lengthy pre-marketing approval is intended to be preserved."); Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568 (Fed. Cir. 1997) (noting that section 156 provided "patent holders with limited extensions of patent term in order to recover a portion of the market exclusivity lost during the lengthy process of development and FDA review"); H.R. REP. NO. 98-857, pt. I at 15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2670 ("The incentive is the restoration of some of the time lost on patent life while the product is awaiting pre-market approval.").

Fig. 8-2
Shortened Patent Life Without Extension*

* U.S. Patent No. 3,975,536 as discussed in *Fisons plc v. Quigg,* 8 U.S.P.Q. 2d (BNA) 1491 (D.D.C. 1988).

§ 8:4.2 Eligibility for Patent Term Restoration

[A] Threshold Requirement

Section 156 only permits extension of a single patent per regulatory review period for a product.[429.1] "[N]othing in the statute restricts the patent owner's choice for patent term extension among those patents whose terms have been partially consumed by the regulatory review process."[429.2]

Not all patents are eligible to receive a patent term restoration. Extensions are available only for patents that "claim":

- "a product,"
- a "method of using a product," or
- a "method of manufacturing a product."[430]

This threshold requirement is not satisfied unless the patent actually "claims" the product (or method of its use) that was the subject of regulatory review (defined by section 156(a) as the "approved product").[431] That the use of an approved product may result in infringement of a patent does not necessarily mean that the patent "claims" the product. In *Hoechst-Roussel Pharmaceutical, Inc. v. Lehman*,[432] the Federal Circuit upheld the PTO's rejection of a term extension to a patent that claimed 1-hydroxy-tacrine, a metabolite of the salt, tacrine hydrochloride, because the patent did not "claim" tacrine hydrochloride, the "product" that FDA had approved. Judge Newman further observed that the panel's holding did not address whether, to be eligible for extension, the patent must "claim" the product literally or whether the statute allows an extension for a patent for which infringement can be shown only through the doctrine of equivalents.[433]

The term "product" does not carry its commonly understood meaning. Section 156(f) defines the term "product" to mean a "drug product" or a "medical device, food additive, or color additive subject to regulation under the Federal Food, Drug, and Cosmetic Act."

429.1. No more "than one patent [shall] be extended under subsection (e)(1) for the same regulatory review period for any product." 35 U.S.C. § 156(c).

429.2. Novartis AG v. Ezra Ventures LLC, 909 F.3d 1367, 1372–73 (Fed. Cir. 2018) (fact that extension of a compound patent "effectively" extended the term of a method patent claiming using of that compound did not prevent patentee from extending the compound patent).

430. 35 U.S.C. § 156(a).

431. Hoechst-Roussel Pharm., Inc. v. Lehman, 109 F.3d 756, 759 (Fed. Cir. 1997).

432. *Hoechst-Roussel Pharm., Inc.*, 109 F.3d 756.

433. *Id.* at 764 n.2 (Newman, J., concurring).

Furthermore, the term "drug product," does *not* mean the finished drug product (for example, an aspirin tablet) that is administered to the patient.[434] Instead "product" "means the active ingredient of . . . a new drug, antibiotic drug, or human biological product . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient."[435] As explained in the subsequent sections, the statutory definition of "product" had led to many disputes.

[B] Five Conditions for Extension Eligibility

In addition to the above-described threshold requirement that the patent "claim" the approved "product," section 156(a) sets forth five conditions that must also be met for a patent to be eligible for a term extension:

(1) The application for term extension must be filed prior to the patent's expiration.[436]

(2) The patent term cannot have been previously extended under subsection (e)(1) of section 156.[437]

(3) The patent owner (or its agent) must have submitted an application to the U.S. Patent & Trademark Office (PTO) for an extension that sets forth the information required by subsection (d) of section 156.[438]

(4) The product claimed by the patent for which an extension is being sought must have been subject to a "regulatory review period" prior to its commercial marketing or use.[439]

(5) The regulatory approval received by the product must be the "first permitted commercial marketing or use of the product."[440]

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434. Shortly before the Hatch-Waxman Act was adopted, the Supreme Court had used the phrase "drug product" to describe the "complete" product composed of both "active ingredients" and "excipients." United States v. Generix Drug Corp., 460 U.S. 453, 461 (1983). *See generally supra* section 8:1.1[C].
435. 35 U.S.C. § 156(f)(1)–(2).
436. 35 U.S.C. § 156(a)(1).
437. 35 U.S.C. § 156(a)(2).
438. 35 U.S.C. § 156(a)(3).
439. 35 U.S.C. § 156(a)(4).
440. 35 U.S.C. § 156(a)(5)(A). This last requirement differs slightly for animal drugs/veterinary biological products (35 U.S.C. § 156(a)(5)(C)) and methods of manufacturing products which primarily use recombinant DNA technology (35 U.S.C. § 156(a)(5)(B)). When Congress extended

Section 156(a) provides that the patent term "shall be extended" if the patent owner has satisfied these five conditions. The Federal Circuit has declined to read a further limitation into the statutory scheme.[441] Because the patent in question had been issued subject to a terminal disclaimer the defendant argued that extending the patent's term under section 156 would effectively reward double-patenting, but the court refused to read into the text of section 156(a) a limitation that Congress had failed to write. The court buttressed its "plain language" analysis of the Hatch-Waxman patent term extension for regulatory delay with the extension of the patent term provided under section 154 for delays occurring during prosecution of the patent. The latter provision, unlike section 156(a) specifies that a patent that is subject to a terminal disclaimer "shall not be eligible for extension under this paragraph."[442]

[C] The "First Permitted Commercial Marketing or Use of the Product"

This fifth condition of eligibility, "the first permitted commercial marketing or use of the product" requirement, has been the subject of much litigation.

[C][1] Need Not Be the First Product Covered by the Patent to Receive Regulatory Approval

The Federal Circuit has held that the product upon which an extension application is based (that is, the "approved product") need not be the first product covered by the claims of the patent to receive regulatory approval. In other words, even if another product covered by the patent for which an extension is being sought had received regulatory approval prior to the "approved product," so long as the regulatory approval received by the "approved product" was the first such approval for *that* product, an extension may be based on it. For example, the patent at issue in *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*[443] claimed a cardiac defibrillator that automatically selected the most appropriate corrective shock. FDA approval

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the Hatch-Waxman compromise to animal drugs in 1988, it gave the patent owner the option of seeking an extension based either upon the first approval for use in non-food animals or in food animals.

441. Merck & Co. v. Hi-Tech Pharmacal Co., 482 F.3d 1317 (Fed. Cir. 2007).

442. *See also supra* section 5:8.5[E][4].

443. Cardiac Pacemakers, Inc. v. St. Jude Med., Inc., 381 F.3d 1371 (Fed. Cir. 2004).

of the patent owner's device occurred after two other defibrillators, produced under license from the plaintiff, had been approved. The defendants argued that the patent was ineligible for extension because the plaintiff's device was not the first to have been approved. The Federal Circuit ruled, however, that the plaintiff had not based its extension request on these approvals and it was not required to do so, because the licensed devices were different "products" from the plaintiff's product and that nothing in the statute required a patentee to "rely on a licensee's device as the basis for the extension."[444]

[C][2] Patent Cannot Merely Claim a New Formulation of a Previously Approved Active Ingredient

As discussed directly above, however, if the same "product" claimed by the patent had previously received a regulatory approval, then the patent will not be eligible for extension based upon a later approval of that same product. In the context of drugs, the statutory definition of "product" to mean an "active ingredient" means that "products" may be considered the "same" even though their formulations are very different. In *Fisons plc v. Quigg*,[445] the Federal Circuit read the statutory definition of "product" to require the denial of an extension to a patent claiming an aqueous solution of cromolyn sodium, even though FDA testing and approval requirements had prevented the patent owner from marketing the patented solution during the first eight years of the patent term. Because another cromolyn sodium drug had been approved by FDA in the 1970s, a patent claiming a new formulation of cromolyn sodium was not eligible for extension because the "product," that is, the active ingredient, cromolyn sodium, had previously been approved. In *Ortho-McNeil Pharmaceutical, Inc. v. Lupin Pharmaceuticals, Inc.*,[445.1] the Federal Circuit, following longstanding FDA and PTO practice, held that an entiomer was a different active ingredient from the previously approved racemic mixture of which it was a part.

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444. *Id*. at 1385.

445. Fisons plc v. Quigg, 876 F.2d 99 (Fed. Cir. 1989). The facts appear in the district court opinion, Fisons plc v. Quigg, 8 U.S.P.Q.2d (BNA) 1491 (D.D.C. 1988).

445.1. Ortho-McNeil Pharm., Inc. v. Lupin Pharm., Inc., 603 F.3d 1377 (Fed. Cir. 2010).

[C][3] Patent Cannot Claim an Active Ingredient If Any Salt or Ester of That Active Ingredient Has Been Previously Approved

As noted above, 35 U.S.C. § 156(f) not only defines a drug "product" to mean the "active ingredient," it also includes in the definition of "product" any "salt or ester" of that active ingredient. Given the definition of "product" it is clear that a patent claiming, for example, an acid would not be eligible for extension if FDA had previously approved an NDA for a drug whose active ingredient was a salt of that acid. In *Glaxo Operations UK Ltd. v. Quigg*,[446] the Federal Circuit confronted a variation of the example just presented. The patent for which an extension was sought claimed an ester, cefuroxime axetil, an active ingredient in the antibiotic Ceftin®. Although Ceftin® was the first approved cefuroxime *ester* drug, the FDA had previously approved antibiotic drugs whose active ingredient consisted of cefuroxime *salts*. The PTO denied the extension request, believing that because Congress clearly had not allowed an extension for a salt if the first approved product had been that salt's acid, it could not have meant to allow an extension where the first approved product was a salt and the patent claimed an ester. The Federal Circuit ruled, however, that the unambiguous statutory language foreclosed the PTO's interpretation. It held that "section 156(f)(2)'s terms, 'active ingredient of a new drug . . . including any salt or ester of the active ingredient,' all have a plain meaning. . . . In particular, the terms 'active ingredient,' 'salt,' and 'ester' had well-defined, ordinary, common meanings when Congress enacted the Act."[447] Based on such "plain meaning," the Federal Circuit agreed that Ceftin® was the "first permitted commercial marketing" of the "product" and, thus, the patentee was entitled to an extension.

[C][4] Patent Cannot Claim Combination of Two Previously Approved Drugs

The Federal Circuit affirmed the PTO's denial of an application for patent term extension for a combination of two previously approved drugs because the application "did not comply with the 'first commercial marketing' requirement of § 156(a)(5)(A)."[448]

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446. Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392 (Fed. Cir. 1990).
447. *Id*. at 395.
448. Arnold P'ship v. Dudas, 362 F.3d 1338, 1339 (Fed. Cir. 2004) (denying patent term extension application for Vicoprofen, a combination of ibuprofen and hydrocodone, because they were both previously approved).

The Federal Circuit explained that it must "examine a drug product patent's eligibility for extension on a component-by-component, or an ingredient-by-ingredient basis."[449] The patentee argued that although *both* ingredients in its combination had previously been approved, the *combination* of ingredients claimed by its patent had never been previously approved. This combination, it argued, should be viewed as "an active ingredient within the meaning of § 156" that had never been previously approved.[450]

The Federal Circuit rejected this argument, as foreclosed by the plain statutory language.

> [T]he statute places a drug product with two active ingredients, *A* and *B*, in the same category as a drug product with a single active ingredient. In both instances, those active ingredients individually qualify for examination under the first permitted marketing requirement. To extend the term of a patent claiming a composition comprising *A* and *B*, either *A* or *B* must not have been previously marketed. In other words, at least one of the claimed active ingredients must be new to the marketplace as a drug product.[451]

[D] Section 156 and the Uruguay Round Agreements Act

Congress enacted the GATT Uruguay Round Agreements Act (URAA)[452] in 1994 to harmonize the term of U.S. patents with foreign patents. Prior to June 8, 1995, the effective date of the URAA, the term for U.S. patents was seventeen years from issuance. The URAA changed the term to twenty years from the filing date as illustrated below in Fig. 8-3.

Patents in force on June 8, 1995, and patent applications filed prior to that date, were subject to the following transitional provision:

> The term of a patent that is in force on or that results from an application filed before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act shall be the greater of the 20-year term as provided in subsection (1), or 17 years from grant, subject to any terminal disclaimers.[453]

449. *Id.* at 1341.
450. *Id.* at 1339.
451. *Id.* at 1341.
452. *See* 35 U.S.C. § 154.
453. 35 U.S.C. § 154(c)(1).

The Federal Circuit confronted the interplay of section 156 with the URAA[454] in *Merck & Co. v. Kessler*.[455] The court addressed the applicability of a term extension to patent terms that were recalculated under the URAA. The plaintiffs in *Merck* were owners of patents that had each already received a two-year term extension and were in force on June 8, 1995. Five of the patents in suit were in force on June 8 only because their term had already been extended pursuant to section 156. The PTO decided that each of the plaintiffs was entitled to a patent term of seventeen years from issuance plus an extension or to a patent term of twenty years from filing (but no term extension), whichever was longer.[456] The Federal Circuit rejected the PTO's argument and concluded that "pre-June 8, 1995, patents are entitled to add on the restoration extension to a twenty-year from filing term regardless of when such extension is granted except for those patents kept in force on June 8, 1995, only because of a restoration extension."[457]

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454. *Id*.

455. Merck & Co. v. Kessler, 80 F.3d 1543 (Fed. Cir. 1996).

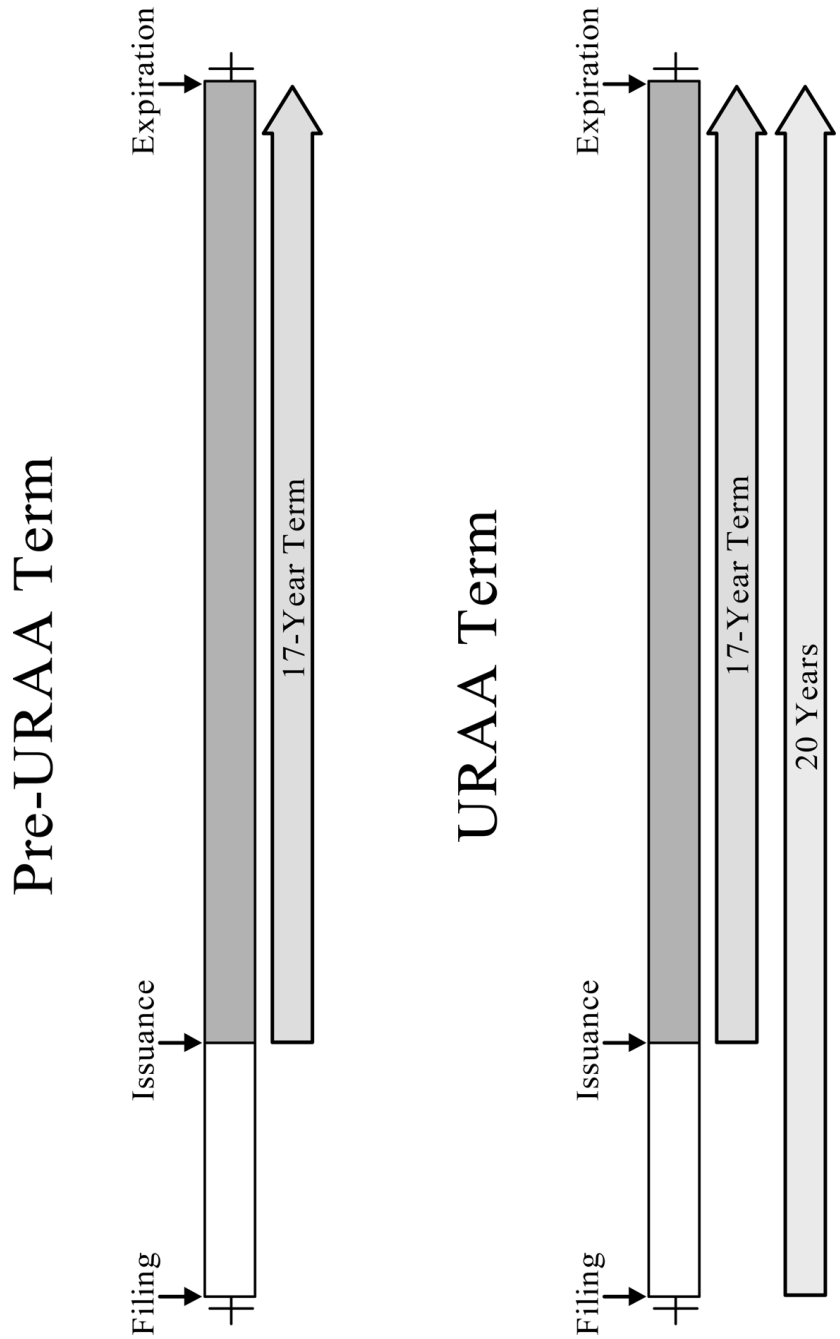
456. *Id*. at 1548.

457. *Id*. at 1550. The court reasoned that the patents that were in effect on June 8 only as a result of a previously issued extension should be treated differently:

> Section 156(a)(2) provides that a restoration extension may be given provided "the term of the patent has never been extended under subsection (e)(1) of this section." The terms of these five patents have once been extended under subsection (e)(1). Indeed, it is only because of actual use of the restoration extension that the patentees can even make their arguments under the Hatch-Waxman Act. A reapplication of the restoration extension would constitute a second extension contrary to the statute.

Id. at 1552.

Fig. 8-3
Effect of URAA on Patent Term



§ 8:4.3 Scope of Protection During Restoration Period

A patent that has received an extension under section 156 cannot be asserted against all acts that fall within the scope of its claims after expiration of its normal (unextended) term. The scope of protection during the restoration period is limited by section 156(b)(1). That section limits the scope of protection during the restoration period for a patent that claims a product "to any use approved for the product." The Hatch-Waxman Act's legislative history explains, "[I]f a chemical is subjected to regulatory review for new drug uses, but is also marketed for other commercial uses, the patent term extension would apply only to the new drug uses for which regulatory review was required."[458] Similarly, the scope of protection during the restoration period for a patent that claims a method of using a drug product is limited to the methods of use claimed in the patent and approved for the drug.[459] The scope of protection during the restoration period for a patent claiming a method of manufacturing a product is likewise limited to the method as used in making the approved product.[460]

[A] The Scope of Protection During the Extension Period

The Federal Circuit's opinion in *Merck v. Kessler* described section 156(b)(1) as extending the source of an extended patent "only to the product on which the extension was based."[461] The quoted passage was not necessary to the judgment and does not fully track the statutory text, which limits the scope of the extension not to the "product" on which the extension was based (the "approved product") but rather to "any *use* approved for the product" (emphasis added). In *Pfizer, Inc. v. Dr. Reddy's Laboratories, Ltd.*,[462] the district court applied the *Merck* dictum to limit the scope of an extension that had been awarded to a patent claiming "amlodipine and its pharmaceutically acceptable salts" to the single salt form, amlodipine besylate, whose approval by FDA, as the drug Norvasc®, had formed the basis of Pfizer's extension request. The drug for which Dr. Reddy sought FDA approval was intended for the very same uses as the previously approved amlodipine product, but Dr. Reddy's drug used a different

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458. H.R. REP. NO. 97-696, at 10 (1982).
459. 35 U.S.C. § 156(b)(2).
460. 35 U.S.C. § 156(b)(3).
461. *Merck*, 80 F.3d at 1547.
462. Pfizer, Inc. v. Dr. Reddy's Labs., Ltd., 67 U.S.P.Q.2d (BNA) 1525 (D.N.J. 2002), *rev'd*, 359 F.3d 1361 (Fed. Cir. 2004).

salt form—amlodipine maleate. Relying on *Glaxo Operations UK Ltd. v. Quigg*,[463] the district court ruled that Dr. Reddy's "active ingredient" was different from that in Norvasc®, and, relying on *Merck v. Kessler*, it ruled further that because the "products" were not the same the patent could not be enforced against Dr. Reddy's proposed product after its initial term expired. The Federal Circuit reversed, stating that *Merck v. Kessler* was "not relevant" and that the district court's reliance on it was "inappropriate."[464] It is not clear, however, that the court was now rejecting entirely *Merck*'s interpretation of section 156(b) as limiting the scope of a term extension to a single "product," because the majority (Chief Judge Mayer dissented) ruled that the active ingredient in Dr. Reddy's drug was amlodipine. Because "the statutory definition of 'drug product' is met by amlodipine and its salts," the Federal Circuit concluded that the term extension encompassed claims for all amlodipine salts.[465] In so ruling, the majority cited with approval the FDA's definition of "active ingredient," when used, (as it is in section 156) as part of the phrase "active ingredient, including any salt or ester of the active ingredient" to mean "active moiety," that is, "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, [or] salt . . . ."[466] The majority opinion did not mention that in *Glaxo Operations UK Ltd. v. Quigg*, a previous panel had rejected the FDA's definition of "active ingredient."[467] The Federal Circuit recently clarified that *Glaxo Operations UK Ltd. v. Quigg* remains good law. In *PhotoCure ASA v. Kappos*,[468] the court held that a patent claiming an ester of a previously approved drug qualified for extension because the ester was "a different chemical compound from" the previously approved drug, "warranting separate patentability and separate regulatory approval."[468.1]

The Federal Circuit, in *Biogen International GmbH v. Banner Life Sciences, LLC*, held that a de-esterified (monomethyl ester) form of the approved (double ester) product is not covered by a 35 U.S.C. § 156 extension "because the scope of a patent term extension . . . only includes the active ingredient of an approved product, or an ester or

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463. Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392 (Fed. Cir. 1990).
464. *Dr. Reddy's Labs.*, 359 F.3d at 1366–67.
465. *Id*. at 1366.
466. *Id*.
467. Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392 (Fed. Cir. 1990).
468. PhotoCure ASA v. Kappos, 603 F.3d 1372 (Fed. Cir. 2010).
468.1. *Id*. at 1375.

salt of that active ingredient, and the product at issue does not fall within one of those categories."[468.2]

§ 8:4.4 Mechanics of Patent Term Restoration

To receive a patent term extension, the patent holder must submit an application for extension to the Director of the PTO within sixty days after regulatory approval is given for the product.[469]

[A] Application for a Patent Term Restoration

Under the PTO regulations,[470] the following items must be contained in an application for restoration.

- Information sufficient to identify the approved product.[471]
- The statute under which the product was approved.[472]
- The date on which the product received regulatory approval.[473]
- For a patent claiming a drug product, the applicant must identify each active ingredient and provide a statement that each active ingredient has not been previously approved; or, if it has been approved, a statement of when such active ingredient was approved, the use for which it was approved, and under what provision of law it received approval.[474]
- A statement that the application is being submitted within the sixty-day period permitted under 35 U.S.C. § 156(d)(1).[475]
- The patent for which extension is sought, with a complete copy of such patent, as well as any related documents (such as certificates of correction, terminal disclaimers, reexamination certificates, etc.).[476]
- A statement showing that the patent claims the approved product or a method of using or manufacturing the claimed product.[477]

468.2. Biogen Int'l GmbH v. Banner Life Scis. LLC, 956 F.3d 1351, 1353 (Fed. Cir. 2020).
469. 35 U.S.C. § 156(d)(1).
470. 37 C.F.R. § 1.740(a) (2006).
471. 37 C.F.R. § 1.740(a)(1) (2006).
472. 37 C.F.R. § 1.740(a)(2) (2006).
473. 37 C.F.R. § 1.740(a)(3) (2006).
474. 37 C.F.R. § 1.740(a)(4) (2006).
475. 37 C.F.R. § 1.740(a)(5) (2006).
476. 37 C.F.R. § 1.740(a)(6)–(8) (2006).
477. 37 C.F.R. § 1.740(a)(9) (2006).

- The relevant dates necessary to compute the regulatory review period (in order to determine the length of the extension).[478]
- A statement that the applicant believes that the patent is eligible for an extension, the length of the extension, an explanation of how the extension was calculated as well as an acknowledgment that the applicant knows of its duty to disclose all information that is material to the determination of entitlement to the sought extension.[479]
- The name, address, and telephone number for the person to whom inquiries regarding the application should be directed, the prescribed application fee, and two additional copies of the application.[480]

[B] Roles of PTO and FDA in Handling Patent Term Restoration Applications

Within sixty days of receiving a complete application for a term extension in the case of a patent claiming a human drug or medical device, the PTO must notify the FDA and provide it with a copy of the application.[481] The FDA then has thirty days to consider the regulatory review dates contained in the application and compute the "regulatory review period." This period is *not* limited to the period of time during which an approval application (for example, an NDA) was actually pending before the FDA. Rather the regulatory review period is comprised of a "testing" period and an "approval" period. For a human drug product or biologic product the "testing" period begins on the date upon which human testing of the drug was authorized to be conducted under an Investigational New Drug Application (IND) and it ends on the date an NDA, or in the case of a biologic, a BLA, is "initially submitted," that is, in FDA's judgment "contains sufficient information to allow the FDA to commence review of the application."[482] The second portion of the regulatory review period

478. 37 C.F.R. § 1.740(a)(10)–(11) (2006).
479. 37 C.F.R. § 1.740(a)(12)–(13) (2006).
480. 37 C.F.R. § 1.740(a)(14)–(15) (2006).
481. 35 U.S.C. § 156(d)(2)(A).
482. 35 U.S.C. § 156(g)(1)(B)(i); 21 C.F.R. § 60.23(f) (2006). The statute says "the date an application was initially submitted for such drug product under section 351 [of the Public Health Service Act], 505, or 507." The last of these statutory references is to the now-repealed section of the FDCA that governed the approval of antibiotic drugs until FDAMA was enacted in 1997.

(the approval period) begins "on the date the [new drug or biological license] application was initially submitted for the approved product . . . and end[s] on the date such application was approved . . . ," that is, the date on which FDA mails an approval letter.[483]

Once these two periods are determined, any portion of either period that occurred prior to the issuance of the patent is subtracted.[484] The patent term extension, however, restores only a portion of the patent life that was consumed by regulatory review. In the first place the applicant receives credit for only one half of the testing period. Second, although each day of patent life during the approval period may be "restored," the PTO must deduct any time during the approval period for which FDA finds that the applicant failed to act with "due diligence."[485] The statute requires FDA to publish a notice of its proposed due diligence determination in the *Federal Register* and provide an opportunity for a hearing at the request of any interested person.[486] Finally, Congress limited the maximum extension available to any patent. The maximum extension for any patent issued after September 24, 1984, that claims a human drug is the *shorter* of fourteen years after the NDA was approved or five years.[487] An example of how the patent extension compensates for a portion of the regulatory delay is provided below in Fig. 8-4.

[C] Interim Extensions

Patents may also be eligible for two different types of interim extensions. First, if the patent owner

> reasonably expects that the applicable regulatory review period . . . that began for a product that is the subject of such patent may extend beyond the expiration of the patent term in effect, the owner or its agent may submit an application . . . for an interim extension during the period beginning 6 months, and ending 15 days, before such term is due to expire.[488]

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483. 35 U.S.C. § 156(g)(1)(B)(ii); 21 C.F.R. § 60.22(f) (2006).
484. 35 U.S.C. § 156(c) ("The term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued . . . .").
485. 35 U.S.C. § 156(c)(1) ("each period of the regulatory review period shall be reduced by any period determined under subsection (d)(2)(B) during which the applicant for the patent extension did not act with due diligence during such period of the regulatory review period").
486. 35 U.S.C. § 156(d)(2)(B)(ii); 21 C.F.R. § 60, subpts. D & E.
487. 35 U.S.C. § 156(c)(3) & (g)(6)(A).
488. 35 U.S.C. § 156(d)(5)(A).

If the extension application has still not received approval during this interim extension, the patent owner may apply for subsequent extensions.[489] However, "[i]n no event will the interim extensions granted under this section be longer than the maximum period of extension to which the applicant would be entitled under 35 U.S.C. § 156(c)."[490] Second,

> [i]f the term of a patent for which an application has been submitted . . . would expire before a certificate of extension is issued or denied . . . respecting the application, the Director shall extend, until such determination is made, the term of the patent for periods of up to one year if he determines that the patent is eligible for extension.[491]

Again, however, "[i]n no event will the interim extensions granted under this section be longer than the maximum period of extension to which the applicant would be eligible."[492]

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489. 37 C.F.R. § 1.790(a) (2006).
490. *Id*.
491. 35 U.S.C. § 156(e)(2).
492. 37 C.F.R. § 1.760 (2006).

Fig. 8-4
Patent Extension Time Line*

* Source: U.S. Patent No. 4,472,909 discussed in 58 Fed. Reg. 7893 (Feb. 10, 1993).

Chapter 9. Claim Construction

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Chapter 9

Claim Construction

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§ 9:1 General

§ 9:1.1 The Purpose of Claims

Section 112, paragraph 2, of the Patent Act requires that "[t]he specification [of a patent] shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."[1] Claims of a patent are the legal definition of the right to exclude others from practicing the claimed invention.[2] Like the language in a deed (or land patent) that describes the "metes and bounds" of real property, patent claims describe the metes and bounds of the legal right to exclude others from practicing the invention.[3] The scope of patent claims

1. 35 U.S.C. § 112, ¶ 2.
2. *See* Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) ("It is a 'bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.'"); Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004).
3. *See* Corning Glass Works v. Sumitomo Elec. USA, Inc., 868 F.2d 1251, 1257 (Fed. Cir. 1989) ("A claim in a patent provides the metes and bounds of the right which the patent confers on the patentee to exclude others from making, using, or selling the protected invention."); Zenith Lab., Inc. v.

often determines the patent's validity and whether it covers an allegedly infringing activity. Construing the claims, therefore, is usually a critical component of any patent dispute.

§ 9:1.2 Role of Jury, District Court, and Appellate Courts

[A] Claim Construction Is a Matter of Law

Since the U.S. Supreme Court decision in *Markman v. Westview Instruments, Inc.*,[4] claim construction is decided as a question of law. In a jury trial, the court construes the claim and instructs the jury on the meaning of the claim terms just as it instructs the jury on the meaning of the law. The claim construction hearing is often called a "Markman hearing" after this leading case. A district court's claim construction is reviewed by appellate courts de novo as a legal question without deference to the district court's findings.[5]

"When the disputed words describe technology, the terse usage of patent claims often requires 'construction' in order to define and establish the legal right."[5.1] If the parties dispute the scope of a claim based on the meaning of claim terms, the court should construe those terms so the jury is not left to resolve that dispute.[5.2] Furthermore, if the parties dispute the meaning of a proposed construction, the court may need to construe the construction to avoid giving claim construction disputes to the jury.[5.3]

Bristol-Myers Squibb Co., 19 F.3d 1418, 1424 (Fed. Cir. 1994); *In re* Warmerdam, 33 F.3d 1354 (Fed. Cir. 1994); *In re* Braat, 937 F.2d 589, 594 (Fed. Cir. 1991) ("[A] claim often does not describe any particular thing but instead defines the boundary of patent protection . . . .").

4. Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996).

5. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448 (Fed. Cir. 1998).

5.1. Fenner Invs., Ltd., v. Cellco P'ship, 778 F.3d 1320, 1323 (Fed. Cir. 2015).

5.2. O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., 521 F.3d 1351, 1360 (Fed. Cir. 2008) ("When the parties raise an actual dispute regarding the proper scope of these claims, the court, not the jury, must resolve that dispute."); Every Penny Counts, Inc. v. Am. Express Co., 563 F.3d 1378, 1383 (Fed. Cir. 2009) ("the court's obligation is to ensure that questions of the scope of the patent claims are not left to the jury. . . . [T]o fulfill this obligation, the court must see to it that disputes concerning the scope of the patent claims are fully resolved."); Omega Patents, LLC v. CalAmp Corp., 920 F.3d 1337, 1346–47 (Fed. Cir. 2019) ("The court is not absolved of this duty to construe the actually disputed terms just because the specification of the patent defines the term. Even if the parties had agreed to the construction, the district court was still obligated to give that construction to the jury in its instructions.").

5.3. *O2 Micro Int'l Ltd.*, 521 F.3d at 1360 ("Thus, there was nothing improper about the fact that the court interpreted EPC's (quite slippery) proposed

[B] Standards of Review for Claim Constructions

As explained in the sections that follow, courts may consider both intrinsic and extrinsic evidence, as appropriate, when construing patent claims. In some cases, where claim construction is limited to the intrinsic record, appellate courts review the construction de novo.[5.4] In other cases, claim construction will require resolution of an underlying factual dispute such as when opposing expert witnesses differ on the meaning of a term used by those skilled in the art.[5.5] Appellate courts must apply a "clear error" standard of review for these underlying fact disputes,[5.6] however it still applies the de novo standard for "the district court's ultimate construction of the claim."[5.7]

§ 9:1.3 *Claim Construction Is a Predicate for Infringement and Invalidity*

Claim construction, the process of determining what the claims mean, is central to determining whether claims are infringed, and whether they are valid. Claim construction is often the most crucial step in a patent litigation, and it can be dispositive of the entire litigation in many cases.

Claim construction has a major impact on most patent litigation issues. Infringement, for example, is determined in a two-step process: (1) the claims are construed, and (2) the accused product is compared to the properly construed claims.[6] Accordingly, "any articulated

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construction. As Michel de Montaigne has said, there are times when '[w]e need to interpret interpretations more than to interpret things.' Jacques Derrida, *Structure, Sign and Play in the Discourse of the Human Sciences, in Writing and Difference* 278 (Alan Bass, trans. 1980) (quoting Montaigne).").

5.4. Teva Pharm. USA, Inc. v. Sandoz, Inc., 135 S. Ct. 831, 841 (2015) ("[W]hen the district court reviews only evidence intrinsic to the patent (the patent claims and specifications, along with the patent's prosecution history), the judge's determination will amount solely to a determination of law, and the Court of Appeals will review that construction de novo.").

5.5. *Id*. ("In some cases . . . the district court will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period.").

5.6. *Id*. at 835 ("We hold that the appellate court must apply a 'clear error,' not a *de novo*, standard of review" when reviewing underlying factual disputes.).

5.7. *Id*. at 841.

6. Atl. Thermoplastics Co. v. Faytex Corp., 974 F.2d 1299, 1300 (Fed. Cir. 1992); Vitronics Corp. v. Conceptronics, Inc., 90 F.3d 1576, 1581–82 (Fed. Cir. 1996).

definition of a claim term ultimately must relate to the infringement questions that it is intended to answer."[6.1] Claim construction is also an essential first step in almost every validity analysis.[7] This is necessarily the case because the claim defines the invention to which the rules of validity must be applied. For example, determining whether a claim is anticipated by the prior art requires determination of whether a single prior art reference discloses every limitation of the claim. That analysis necessarily entails a construction of the claim to determine what limitations must be found in the prior art reference for it to anticipate. Likewise, whether a patent claim is invalid for lack of written description support again requires that the claim be construed, and then compared to the patent specification to determine if what has been claimed is described. Whether a claim is invalid for obviousness-type double patenting over the claim of an earlier commonly owned patent requires the construction of the claims of each patent before the claims are compared.[8]

Claims must have the same meaning for both infringement and validity. The claims cannot be defined one way for purposes of infringement in order to cover the accused product, but more narrowly when considering validity in order to avoid encompassing prior art.[9]

6.1. E-Pass Tech., Inc. v. 3Com Corp., 473 F.3d 1213, 1219 (Fed. Cir. 2007); *see also Every Penny Counts, Inc.*, 563 F.3d at 1383 ("A court may not use the accused products for the sole purpose of arriving at a construction of the claim terms that would make it impossible for the plaintiff to prove infringement" but it may consider "the accused products only to elicit the parties' views about what the claim term means in the context of a concrete transaction involving these products."); Aero Prods. Int'l, Inc. v. Intex Recreation Corp., 466 F.3d 1000, 1012 n.6 (Fed. Cir. 2006) ("Although the court revealed an awareness of the accused device, the court's awareness of the accused device is permissible."); Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1326 (Fed. Cir. 2006) ("[T]he legal function of giving meaning to claim terms always takes place in the context of a specific accused infringing device or process.").

7. Akamai Tech., Inc. v. Cable & Wireless Internet Servs., Inc., 344 F.3d 1186, 1192 (Fed. Cir. 2003) ("The first step in any invalidity analysis is claim construction . . . .").

8. *See* Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955 (Fed. Cir. 2001).

9. SmithKline Beecham Corp. v. Apotex, Inc., 439 F.3d 1312 (Fed. Cir. 2006); Amgen, Inc. v. Hoechst Marion Rousell, Inc., 314 F.3d 1313 (Fed. Cir. 2003); W.L. Gore & Assocs., Inc. v. Garlock, 842 F.2d 1275, 1279 (Fed. Cir. 1988).

§ 9:1.4 Procedure for Claim Construction

The Federal Circuit has not imposed any procedural rule regarding when a claim construction hearing must be held.[10] The court has discretion to decide when and how to construe claims, as long as they are construed before or at the same time as instances of infringement (or other issues that depend on claim construction) are decided. In jury trials, the claims must be construed before the case is given to the jury.

The court may, and typically does, hold a claim construction *Markman* hearing to construe claims. The hearings are sometimes merely oral argument based on a submitted paper record including, at times, affidavits of expert witnesses. Some hearings involve live testimony of witnesses, typically experts. Other courts forego a hearing, and construe claims as part of a ruling on a summary judgment motion.[11] "If the district court considers one issue to be dispositive, the court may cut to the heart of the matter and need not exhaustively dismiss all the other issues presented by the parties."[12]

The Northern District of California has set out local rules that prescribe an orderly procedure for the construction of claims, and it requires the parties to set forth in advance the terms to be construed, their proposed construction, and the evidence on which they will rely to support the construction. These rules are occasionally adopted by judges in other districts for use in particular cases. Other districts have followed the Northern District of California's lead and enacted their own sets of local patent rules. "The application of local patent rules is governed by the law of this court and '[d]ecisions enforcing local rules in patent cases will be affirmed unless clearly unreasonable, arbitrary, or fanciful; based on erroneous conclusions of law; clearly erroneous; or unsupported by any evidence.'"[12.1]

Since claim construction is purely a legal issue that affects so many other issues, one might expect a claim construction to occur early in a case. Many judges, however, prefer to construe the claims

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10. Ballard Med. Prod. v. Allegiance Healthcare Corp., 268 F.3d 1352, 1358 (Fed. Cir. 2001).
11. Schoenhaus v. Genesco, Inc., 440 F.3d 1354 (Fed. Cir. 2006) (construing claims in a summary judgment opinion proper); Elec. Planroom, Inc. v. McGraw-Hill Co., 135 F. Supp. 2d 805, 832 n.25 (E.D. Mich. 2001) (finding "it unnecessary to conduct a separate *Markman* hearing before ruling on the pending [summary judgment] motions").
12. *Ballard Med.*, 268 F.3d at 1358.
12.1. Shire LLC v. Amneal Pharm., LLC, Nos. 2014-1736, 2014-1737, 2014-1738, 2014-1739, 2014-1740, 2014-1741, 2015 WL 5603864, at *3 (Fed. Cir. Sep. 24, 2015) (quoting O2 Micro Int'l Ltd. v. Monolithic Power Sys., Inc., 467 F.3d 1355, 1366–67 (Fed. Cir. 2006)).

late in the proceedings and shortly before trial. The rationale for that approach is that often the issues on claim construction are not sharpened until after discovery is conducted and the parties develop their positions fully. A construction before that time can be too vague or general to address the actual point of a dispute. On the other hand, when claims are construed late in a case, the statement of positions in expert reports and other documents must often be made in the alternative to account for more than one possible claim construction.

§ 9:2 Sources for Interpreting Claims

Claim construction is a legal issue. A court decides the meaning of a claim as a matter of law in a way similar to deciding the meaning of a statute. In reaching the decision, however, the court needs to examine issues that are factual in nature, such as how persons of ordinary skill in the art would understand technical terms used in the patent claims. That inevitably requires that the court consider some source of evidence for the definition of a technical term, and a general understanding of the technology involved in the patent so that a construction is made in context.

§ 9:2.1 *Precedent Prior to* Phillips v. AWH[13]

[A] Hierarchy of Evidence

Early in the history of *Markman* hearings, the Federal Circuit set forth some general guidelines on the types of evidence that should be relied on construing claims. In *Vitronics Inc v. Conceptronics Inc.*,[14] the Federal Circuit set forth a hierarchy of evidence, dividing the evidence for claim construction into two broad categories: "intrinsic" and "extrinsic."

The rules of preference for intrinsic evidence are not rules of admissibility, but rather of weight. Extrinsic evidence, if offered, should always be considered.[15] Occasionally, extrinsic evidence will

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13. Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005), is discussed in section 9:2.2, *infra*.
14. Vitronics, Inc. v. Conceptronics, Inc., 90 F.3d 1576 (Fed. Cir. 1996).
15. *See* Key Pharm. v. Hercon Labs Corp., 161 F.3d 709, 716 (Fed. Cir. 1998) ("This court has made strong cautionary statements on the proper use of extrinsic evidence, which might be misread by some members of the bar as restricting a trial court's ability to hear such evidence. We intend no such thing. To the contrary, trial courts generally can hear expert testimony for background and education on the technology implicated by the presented claim construction issues, and trial courts have broad discretion in this regard.") (citation omitted).

be essential where the intrinsic evidence is insufficient to resolve the meaning of a term with enough precision.[16]

[A][1] Intrinsic Evidence

Intrinsic evidence includes the following:

- the language of the claims;
- the patent specification;
- the prosecution file history;
- prior art cited in a patent or the file history.

Intrinsic evidence, particularly the claims and specification, is the most important type of evidence. The patent specification is given particular importance because "[u]sually, it is dispositive; it is the single best guide to the meaning of a disputed term."[17]

The prosecution history of the claim at issue can shed light on the meaning of claim terms.[18] In addition, "[a]bsent qualifying language in the remarks, arguments made to obtain the allowance of one claim are relevant to interpreting other claims in the same patent."[19] Statements made in a prosecution of one patent may also be relevant to the interpretation of common terms that appear in other applications stemming from the same parent application.[20] Other intrinsic evidence includes prior art that is cited in the patent or prosecution history.[21]

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16. *See* Kumar v. Ovonic Battery Co., 351 F.3d 1364, 1372 (Fed. Cir. 2003) ("We conclude that testimony from those skilled in the art is required to establish the meaning of the term 'long range order' . . . ."); *Phillips v. AWH Corp.*, 415 F.3d at 1318–19.
17. *Vitronics*, 90 F.3d at 1582.
18. Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc., 262 F.3d 1258, 1268 (Fed. Cir. 2001) (courts "must also examine the prosecution history to determine whether the patentee has relinquished a potential claim construction in an amendment to the claim or in an argument to overcome or distinguish a reference").
19. Dig. Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1347 (Fed. Cir. 1998).
20. Microsoft Corp. v. Multi-Tech Sys., Inc., 357 F.3d 1340, 1349 (Fed. Cir. 2004).
21. V-Formation, Inc. v. Benetton Grp. SpA, 401 F.3d 1307, 1311 (Fed. Cir. 2005) ("The Meibock patent is prior art that was listed as a reference on the face of the '466 patent and in an Information Disclosure Statement. This prior art reference to Meibock is not extrinsic evidence."); Kumar v. Ovonic Battery Co., 351 F.3d 1364, 1368 (Fed. Cir. 2003) ("Our cases also establish that prior art cited in a patent or cited in the prosecution history of the patent constitutes intrinsic evidence."); Arthur A. Collins, Inc. v. N. TeleCom, Inc., 216 F.3d 1042, 1045 (Fed. Cir. 2000).

[A][2] Extrinsic Evidence

Extrinsic evidence consists of materials such as prior art publications,[21.1] dictionaries, expert testimony, or other evidence that was not part of the official Patent Office record. The court places the greatest value on intrinsic evidence because this is the evidence to which the public, examining the patent to determine its scope, would have ready access. In addition, section 112 of the Patent Act, by requiring that the specification describe the invention and that the claims "particularly point out and distinctly claim[ ]" the invention, links intrinsic evidence of claim terms and specification to the requirements for patentability.

Inventor testimony may be relevant to claim construction as evidence of skill in the art and to provide background on the technology, but not for the inventor's subjective intent in drafting the claims.[22]

[B] Superseded Focus on Ordinary Meaning

In *Texas Digital Systems, Inc. v. Telegenix, Inc.*,[23] an alternative approach was developed for claim construction. Relying on the general principle that a patent claim should be given its ordinary meaning

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21.1. Laryngeal Mask Co. v. Ambu A/S, 618 F.3d 1367, 1373 (Fed. Cir. 2010) (relying on two prior art patents which use the same term and list the same inventor as the patent being construed).

22. Voice Tech. Grp., Inc. v. VMC Sys., Inc., 164 F.3d 605, 615 (Fed. Cir. 1999) ("Although in *Markman* this court stated that 'the subjective intent of the inventor when he used a particular term is of little or no probative weight in determining the scope of a claim,' this statement does not disqualify the inventor as a witness, or overrule the large body of precedent that recognizes the value of the inventor's testimony. . . . An inventor is a competent witness to explain the invention and what was intended to be conveyed by the specification and covered by the claims. The testimony of the inventor may also provide background information, including explanation of the problems that existed at the time the invention was made and the inventor's solution to these problems."); Hoechst Celanese Corp. v. BP Chem. Ltd., 78 F.3d 1575, 1580 (Fed. Cir. 1996) ("the inventor's testimony reads as that of an expert in the field"); Oakley, Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1342 n.2 (Fed. Cir. 2003) (admissions during inventor's deposition testimony of "little value" to claim construction).

23. Tex. Dig. Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193 (Fed. Cir. 2002); *see also* Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999) (stating that as a "general rule . . . terms in the claim are to be given their ordinary and accustomed meaning"); *but see* Scimed Life Sys., Inc. v. Advanced Cardio-Vascular Sys., Inc. (Fed. Cir. 2001) ("the written description can provide guidance as to the meaning of the claims, thereby dictating the manner in which the claims are to be construed, even if the guidance is not provided in explicit definitional format"); Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp., 493 F.3d 1358

to one of skill in the art, the Federal Circuit panel in *Texas Digital* looked first to dictionaries, encyclopedias, and technical treatises to determine the ordinary meaning of the words in the claim. Only if the specification indicated a clear intention to adopt a different meaning were the dictionary-type definitions to be rejected. The Federal Circuit has moved away from a complete focus on plain meaning.[24]

§ 9:2.2 Phillips v. AWH

[A] Rejecting "Dictionary First" Approach

In *Phillips v. AWH Corp.*,[25] a much-awaited rehearing en banc ruling, the Federal Circuit attempted to address the conflicting views of cases like *Vitronics*, which gave primacy to intrinsic evidence, and those following *Texas Digital*, which gave primacy to dictionaries.[26] The majority opinion in *Phillips* followed the approach adopted by the prior majority panel decision, which is the *Vitronics* approach giving primacy to intrinsic evidence. The court rejected the panel dissent, which had adopted the "dictionary first" approach. Ironically, however, the en banc court agreed with the outcome of the dissent, whose method they rejected, and rejected the panel majority's construction, although approving of their method. This result reveals a fundamental truth about claim construction: regardless of the method employed, there is much room for disagreement and the outcome can be unpredictable. A dissent in *Phillips* pointed to these uncertainties, and attacked the controlling law that claim construction was an issue of law, rather than a question of fact.

[B] Method for Construing Claims

The *Phillips* majority reiterated the general approach to claim construction that had been expressed in *Vitronics*. In summary, the main points of its approach to claim construction are the following:

(1) The claims of the patent define the invention. The *Phillips* court reiterated what it said in a prior decision: "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled to the right to exclude."[27] The court should look to the words of the claims

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(Fed. Cir. 2007) (construing term based on specification, not dictionary, when term used in manner contrary to plain meaning).

24. *See infra* section 9:2.2.
25. Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005). The *Phillips* opinion reviews much of the Federal Circuit's history on claim construction.
26. *Id*. at 1312.
27. *Id*. at 1312 (citing Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004)).

themselves and their plain import in construing the scope of the invention.

(2) Claim terms should be construed in a manner in which they would be understood by a person of ordinary skill in the art at the time of the invention.[28] This principle assigns the role of fact finder to the construing court, and requires evidence that may be found outside the four corners of the patent.[29]

(3) The person of ordinary skill in the art is deemed to understand the claim terms in the context of the entire patent specification, as well as the prosecution history. This principle requires that the claim terms be understood in the context of the specifications and prosecution history, including specific definitions that may appear in the specification.[30]

(4) Claims are not necessarily limited to the examples in the patent specification. (In *Phillips*, all examples had baffles at oblique angles, but the claims also covered baffles at right angles.)

(5) The claims of the patent themselves also provide a context for understanding a particular term. Thus, for example, a narrow term qualifying a broader term in a dependent claim (for example, "the baffle is made of steel") implies that the broader term alone is not limited to the narrower modifying term that appears in only a dependent claim (for example, the term "baffle," by itself in a broader independent claim, would not be limited to steel baffles).[31]

(6) The meaning of a term in one claim should be consistent with its meaning in another claim.[32]

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28. *Phillips*, 415 F.3d at 1313.
29. A dissent by Judges Mayer and Neuman acknowledged this paradox: "Claim construction is, or should be, made in context—a claim should be interpreted both from the perspective of one of ordinary skill in the art and in view of the state of the art at the time of the invention. These questions, which are critical to the correct interpretation of a claim, are inherently factual." *Id*. at 1332 (citation omitted).
30. *Id*. at 1313.
31. *Id*. at 1314.
32. *Id*.; *see also* Callicrate v. Wadsworth Mfg., Inc., 427 F.3d 1361, 1372 (Fed. Cir. 2005) ("Of course this court interprets claim terms consistently throughout various claims of the same patent."); Arthur A. Collins v. N. Telecom, 216 F.3d 1042, 1044 (Fed. Cir. 2000) (court "determined that a common construction of" a limitation in the claims of two related patents "was appropriate").

(7) Courts are authorized in their discretion to admit and to rely on extrinsic evidence that "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises."[33] Of these, learned treatises are particularly helpful, and expert testimony generated for litigation may be the most suspect.

(8) While expert testimony is useful to provide technical background, conclusory opinions about the meaning of the term are not helpful.[34]

(9) If, after applying all other tools of claim construction, a claim remains ambiguous, a court may construe the claim to preserve validity if possible in view of the claim language.[34.1]

The *Phillips* case adds nothing substantially new to the approach taken in *Vitronics*. A dissent by Judges Mayer and Newman disputed the premise that claim construction was a legal question devoid of factual issues. They bemoaned what they saw as ineffective standards for construction, arguing that the majority "merely restate what has become the practice over the last ten years—that we will decide cases according to whatever mode or method results in the outcome we desire, or at least allows us a seemingly plausible way out of the case."[35] There are reasons to sympathize with this criticism. One finds the cases filled with claim construction rules or maxims, but for each maxim there is a counter-maxim that can lead to the opposite result. There is much room for discretion to select the construction principle that leads one to one result or another.

§ 9:2.3 *Post*-Phillips *Rules of Claim Construction*

Many of the rules, or rules of thumb, for construing claims expressed in the pre-*Phillips* case law remain valid and have been used in the post-*Phillips* era. The following sections summarize many of these rules.

[A] Patentee Acting As a Lexicographer

Phillips continues to recognize the possibility that the patentee, in drafting the specification, may have acted as a lexicographer and provided a special definition to a claim term.[35.1] "In such cases, the

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33. *Phillips*, 415 F.3d at 1317–18.
34. *Id*. at 1318.
34.1. *Id*. at 1327–28; *see also supra* section 5:1.3.
35. *Id*. at 1330.
35.1. *Phillips*, 415 F.3d at 1316 ("[O]ur cases recognize that the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess.").

inventor's lexicography governs."[35.2] One indication that the patentee intended to act as a lexicographer is by using quotation marks around a term.[35.3] Another indication that the patentee intended to act as a lexicographer is use of the word "is."[35.4]

Failing "to introduce a dictionary definition for" a disputed claim term "does not preclude a conclusion that there exists a plain meaning to one of skill in the art."[35.5] The Federal Circuit refused "to adopt a categorical rule that absence of a dictionary definition means that the applicant must be held to have acted as his own lexicographer and is therefore constrained to the preferred embodiment."[35.6] If a claim term has no plain meaning, one must look at the specification to discern the meaning.[35.6.1]

[B] Extrinsic Evidence

"A court may look to extrinsic evidence so long as the extrinsic evidence does not contradict the meaning otherwise apparent from the intrinsic record."[35.7] Expert declarations, however, have little value

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35.2. *Id*. at 1316.

35.3. Sinorgchem Co. v. Int'l Trade Comm'n, 511 F.3d 1132, 1136 (Fed. Cir. 2007) ("The term 'controlled amount' is set off by quotation marks–often a strong indication that what follows is a definition."; finding that patentee acted as a lexicographer); Cultor Corp. v. A.E. Staley Mfg. Co., 224 F.3d 1328, 1331 (Fed. Cir. 2000) ("water-soluble polydextrose" was expressly defined in the specification).

35.4. *Sinorgchem*, 511 F.3d at 1136; Abbott Labs. v. Andrx Pharm., Inc., 473 F.3d 1196, 1210 (Fed. Cir. 2007) (the word "is" may "signify that a patentee is serving as its own lexicographer").

35.5. *Laryngeal Mask*, 618 F.3d at 1373.

35.6. *Id*.

35.6.1. Novartis Pharm. Corp. v. Abbott Labs., 375 F.3d 1328, 1334–35 (Fed. Cir. 2004) (holding that "[i]f the disputed claim term 'is a term with no previous meaning to those of ordinary skill in the art[,] its meaning, then, must be found [elsewhere] in the patent.'") (citation omitted); *see also* Virnetx, Inc. v. Cisco Sys., Inc., 767 F.3d 1308, 1317 (Fed. Cir. 2014) ("As an initial matter, we note that there is no dispute that the word 'secure' does not have a plain and ordinary meaning in this context, and so must be defined by reference to the specification."); JT Eaton & Co. v. Atl. Paste & Glue Co., 106 F. 3d 1563, 1570 (Fed. Cir. 1997) ("In this case, the dispositive claim limitation is a term unknown to those of ordinary skill in the art at the time the patent application was filed. It thus fell to the applicants, as a duty, to provide a precise definition for the 120°F limitation.").

35.7. Helmsderfer v. Brobrick Washroom Equip., Inc., 527 F.3d 1379, 1382 (Fed. Cir. 2008); Intel Corp. v. VIA Techs., 319 F.3d 1357, 1367 (Fed. Cir. 2003) ("When an analysis of intrinsic evidence resolves any ambiguity in a disputed claim term, it is improper to rely on extrinsic evidence to contradict the meaning so ascertained.").

if they conflict with the intrinsic evidence or lack support by "independent sources" such as "industry publications."[35.8]

"When the intrinsic evidence is silent as to the plain meaning of a term, it is entirely appropriate for the district court to look to dictionaries or other extrinsic sources for context—to aid in arriving at the plain meaning of a claim term."[35.9]

[C] Disclosed Embodiments

Courts do "not normally interpret a claim term to exclude a preferred embodiment."[35.10] "This rule has particular force where the claims as construed do not encompass any disclosed embodiments."[35.11] When "multiple embodiments are disclosed," the Federal Circuit has "interpreted claims to exclude embodiments where those embodiments are inconsistent with unambiguous language in the patent's specification or prosecution history."[35.12]

[D] Construction Preferably Does Not Render Terms Superfluous or Differences in Terminology Meaningless

"A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."[35.13] "[D]ifferent claim

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35.8. *See* Network Commerce, Inc. v. Microsoft Corp., 422 F.3d 1353, 1361 (Fed. Cir. 2005) (rejecting claim construction expert declaration for failing to support "conclusion with any references to industry publications or other independent sources" and for being "at odds with the intrinsic evidence").

35.9. *Helmsderfer*, 527 F.3d at 1382.

35.10. Primos, Inc. v. Hunter's Specialties, Inc., 451 F.3d 841, 848 (Fed. Cir. 2006).

35.11. *Sinorgchem*, 511 F.3d at 1138; Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1355 (Fed. Cir. 1998) ("A patent claim should be construed to encompass at least one disclosed embodiment in the written description portion of the patent specification.").

35.12. *Sinorgchem*, 511 F.3d at 1138; *see also* Rheox, Inc. v. Entact, Inc., 276 F.3d 1319, 1327 (Fed. Cir. 2002) ("[W]here the prosecution history requires a claim construction that excludes some but not all of the preferred embodiments such a construction is permissible."); *Helmsderfer*, 527 F.3d at 1383; ("It is true that . . . claims 6-7 do not cover the preferred embodiment or the other illustrated embodiments. However, this does not mean that these embodiments are all excluded from the scope of the invention, but rather that they are excluded from the scope of these particular claims. . . . [W]e note that none of the other independent claims of the '928 patent recite the term 'the platform top surface is partially hidden from view.'").

35.13. Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1372 (Fed. Cir. 2005); Stumbo v. Eastman Outdoors, Inc. 508 F.3d 1358, 1362 (Fed. Cir. 2007)

terms are presumed to have different meanings."[35.14] "That assumption, however, carries less weight when comparing a term in the claim to a term in the specification, especially where, as here, the specification only describes one embodiment."[35.15]

[E] Order of Method Steps

The steps of a method may be construed so that they must be performed in order, depending on the claim language and other sources for construing claims. When method steps are expressed in a sequential manner or method steps refer to the completed results of prior steps, the claim should ordinarily be construed so that the steps are performed in order.[35.16]

[F] Range Claims

Depending on the claim language, specification and other sources for construing claims, a claimed range may be construed as limited

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(rejecting construction because it would render some claim phrases "superfluous, a methodology of claim construction that this court has denounced").

35.14. *Helmsderfer*, 527 F.3d at 1382; Applied Med. Res. Corp. v. U.S. Surgical Corp., 448 F.3d 1324, 1333 n.3 (Fed. Cir. 2006) ("[T]he use of two terms in a claim requires that they connote different *meanings* . . . ."); CAE Screenplates Inc. v. Heinrich Fiedler GmbH, 224 F.3d 1308, 1317 (Fed. Cir. 2000) ("In the absence of evidence to the contrary, we must presume that the use of these different terms in the claims connotes different meanings.").

35.15. SEB S.A. v. Montgomery Ward & Co., 594 F.3d 1360, 1369 (Fed. Cir. 2010).

35.16. E-Pass Tech., Inc. v. 3Com Corp., 473 F.3d 1213, 1222 (Fed. Cir. 2007) ("because the language of most of the steps of its method claim refer to the completed results of the prior step, E-Pass must show that all of those steps were performed in order"; for example, claim 1 required "transferring a data set . . .; storing said transferred data set"); Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc., 152 F.3d 1368, 1376 (Fed. Cir. 1998) ("the sequential nature of the claim steps is apparent from the plain meaning of the claim language and nothing in the written description suggests otherwise"); Oak Tech., Inc v. Int'l Trade Comm'n, 248 F.3d 1316, 1324 (Fed. Cir. 2001) ("According to the plain language of the claim, the 'assembled data' is processed by the 'error correction circuitry' and converted into 'corrected assembled data.' This 'corrected assembled data' is then processed by the 'cyclic redundancy checker,' which finally provides 'corrected data.'"; therefore, the court concluded that "the plain language of the claim . . . explicitly describes a sequential process"); Techsearch L.L.C. v. Intel Corp., 286 F.3d 1360, 1376 (Fed. Cir. 2002) ("We conclude, however, that where, as in this case, the claim recites steps of a method, each dependent upon the other, we cannot interpret the limitations so loosely.").

to the precise endpoints of the claimed range,[35.17] or may be construed to be somewhat broader.[35.18]

[G] Disavowal or Disclaimer

The Federal Circuit has "found disavowal or disclaimer [of claim scope] based on clear and unmistakable statements by the patentee that limit the claims," including:

- "the present invention includes . . ."
- "the present invention is . . ."
- "all embodiments of the present invention are . . ."[35.19]

Other examples include:

- for "successful manufacture," a particular step was "require[d]."[35.20]
- the invention used "pushing (as opposed to pulling) forces," and "pushing forces" are "an important feature of the present invention"[35.21]
- prior art embodiment was "antiquated," having "inherent inadequacies"[35.22]
- "very important feature . . . in an aspect of the present invention," and disparaged alternatives to that feature.[35.23]

35.17. U.S. Philips Corp. v. Iwasaki Elec. Co., 505 F.3d 1371, 1376 (Fed. Cir. 2007) (rejecting construction of "between 10^{-6} and 10^{-4} μmol/mm^3" as expressing a range of orders of magnitude in favor of meaning precisely "between 1×10^{-6} and 1×10^{-4} μmol/mm^3" because the "overall phrase—'a quantity between ___ and ___'—is a construction that implies a specific range").

35.18. Viskase Corp. v. Am. Nat'l Can Co., 261 F.3d 1316, 1320–21 (Fed. Cir. 2001).

35.19. Pacing Techs., LLC v. Garmin Int'l, Inc., 778 F.3d 1021, 1024 (Fed. Cir. 2015).

35.20. Andersen Corp. v. Fiber Composites, LLC, 474 F.3d 1361, 1367 (Fed. Cir. 2007).

35.21. SafeTCare Mfg., Inc. v. Tele-Made, Inc., 497 F.3d 1262, 1269–70 (Fed. Cir. 2007).

35.22. Chi. Bd. Options Exch., Inc. v. Int'l Sec. Exch., LLC, 677 F.3d 1361, 1372 (Fed. Cir. 2012).

35.23. Inpro II Licensing, S.A.R.L. v. T-Mobile USA Inc., 450 F.3d 1350, 1354–55 (Fed. Cir. 2006).

- patentee "describes the features of the 'present invention' as a whole" and state "this description limits the scope of the invention"[35.24]
- "Summary and Objects of the Invention"[35.25]

[H] Dependent Claims Can Inform Scope of Independent Claim

A construction of an independent claim should not generally exclude an embodiment covered explicitly by a dependent claim.[35.26] The Federal Circuit refused to construe "antibody" to mean "a specific antibody consisting of two identical heavy chains and two identical light chains or an antibody that only binds the antigen that induced its synthesis or very similar antigens" because this would exclude chimeric, humanized, and bispecific antibodies—all of which are specifically claimed by dependent claims.[35.27]

§ 9:3 Interpretation of Common Claim Terms

Certain rules apply to the interpretation of claims based on their format. Claims sometimes have the following format: preamble followed by a transition and a body. For example, in the claim, "A composition comprising *A* as the active ingredient, and *B*, *C* and *D* as diluents," the preamble is "A composition," the transition is "comprising," and the body is "*A* as the active ingredient, and *B*, *C* and *D* as diluents." The following sections describe preambles, various transition phrases and the articles "a" and "the."

§ 9:3.1 Preambles

"No litmus test defines when a preamble limits claim scope. Some guideposts, however, have emerged from various cases discussing the preamble's effect on claim scope."[36]

35.24. Regents of Univ. of Minn. v. AGA Med. Corp., 717 F.3d 929, 936 (Fed. Cir. 2013) (citing Verizon Servs. Corp. v. Vonage Holdings Corp., 503 F.3d 1295, 1308 (Fed. Cir. 2007)).

35.25. *Pacing Techs.*, 778 F.3d at 1025.

35.26. *See* Baxalta Inc. v. Genetech, Inc., 972 F.3d 1341 (Fed. Cir. 2020); *see also* Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1361–62 (Fed. Cir. 2008) (rejecting a construction that would "render several dependent claims meaningless").

35.27. *Id*. at 1345–46.

36. Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002).

[A] Preamble Recites Essential Structure

A preamble "is regarded as limiting if it recites essential structure that is important to the invention or necessary to give meaning to the claim."[37] "[I]f the claim drafter 'chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects.'"[38] On the other hand, "a preamble is not limiting 'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use of the invention.'"[39]

[B] Preamble Recites Important Steps

Another guidepost used by courts to determine when a preamble limits a claim is whether the preamble recites important steps. "[W]hen reciting additional . . . steps underscored as important by the specification, the preamble may operate as a claim limitation."[40]

[C] Preamble Provides Antecedent Basis

Another one of the guideposts used by courts to determine if a preamble is a limitation is whether the preamble provides the antecedent basis for limitations in the body of the claim. "[W]hen the limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention."[41]

The Federal Circuit, for example found the "method for transmitting *a packet* . . . said packet including a source address and a destination address" to be limiting.[42] The body of the claim contained two elements that referred to "said packet," thereby relying on the preamble for antecedent basis.[43] The patentee argued that the preamble

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37. Bicon, Inc. v. Strauman Co., 441 F.3d 945, 952 (Fed. Cir. 2006) (holding that the preamble limited the claim because the body derived antecedent basis from the preamble); Phillips Petroleum Co. v. Huntsman Polymers Corp., 157 F.3d 866, 873 (Fed. Cir. 1998).
38. Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp., 55 F.3d 615, 620 (Fed. Cir. 1995).
39. Poly-America, L.P. v. GSE Lining Tech., Inc., 383 F.3d 1303, 1310 (Fed. Cir. 2004).
40. *Catalina Mktg.*, 289 F.3d at 808.
41. *Bicon*, 451 F.3d at 952; *Catalina Mktg.*, 289 F.3d at 809.
42. Bell Commc'ns Research v. Vitalink Commc'ns, 55 F.3d 615 (Fed. Cir. 1995).
43. *Id*. at 621 ("assigning, by said source device, one of said trees to broadcast said packet and associating with said packet an identifier indicative of said trees").

was not a limitation. The Federal Circuit disagreed, holding that the reference to "said packet" in the body of the claim incorporated the entire description of the packet from the preamble into the claim as limitations:

> These two steps of the claimed method, by referring to "*said* packet," expressly incorporate by reference the preamble phrase "said packet including a source address and a destination address." As a result, only a method for transmitting packets that have *both* source *and* destination addresses can literally infringe [the claim].[44]

[D] Reliance on Preamble During Prosecution

In addition to the above guideposts, "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention."[45]

§ 9:3.2 *Transition Phrases*

Three types of transitions are typically used in claims: "comprising," "consisting essentially of," and "consisting of."

[A] "Comprising"

"Comprising" generally means including or having, and that an infringing product can have features in addition to the elements set forth in the body of the claim.[46] The term "comprised of" is also generally construed in the same manner as "comprising."[46.1] The

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44. *Id.*; *see also* Electro Sci. Indus. v. Dynamic Details, Inc., 307 F.3d 1343, 1348 (Fed. Cir. 2002) ("References throughout the rest of the claim to 'circuit boards' rely upon and derive antecedent basis from this preamble language. Therefore, this preamble definition limits the term 'circuit boards' throughout the claim.").
45. *Catalina Mktg.*, 289 F.3d at 808.
46. Gillette Co. v. Energizer Holdings, Inc., 405 F.3d 1367, 1371 (Fed. Cir. 2005); Genentech, Inc. v. Chiron Corp., 112 F.3d 495 (Fed. Cir. 1997), *rev'd*, 220 F.3d 1345 (Fed. Cir. 2000); Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) ("The word 'comprising,' . . . as is well-established, permits inclusion of other moieties.").
46.1. Cias, Inc. v. All. Gaming Corp., 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("Although 'comprised of' is not used as regularly as 'comprising,' and 'comprised of' is sometimes used other than as a 'transition phrase,' nonetheless it partakes of long-standing recognition as an open-ended term. . . . The usual and generally consistent meaning of 'comprised of,' when it is used as a transition phrase, is, like 'comprising,' that the ensuing elements or steps are not limiting.").

term "comprising," however, does not permit a claim to be open to additional elements or steps that negate the very structural features recited in, and therefore required by, the claim. The Federal Circuit has held that the "open-ended transition 'comprising' does not free the claim from its own limitations."[47] "'Comprising' is not a weasel word with which to abrogate claim limitations."[48] "While the term 'comprising' in a claim preamble may create a presumption that a list of claim elements is nonexclusive, it 'does not reach into each [limitation] to render every word and phrase therein open-ended.'"[48.1]

Claims occasionally use the term "having," which courts not infrequently construe as open, like "comprising";[48.2] however, it depends on context.[48.3] In some cases, having may be construed as being closed.[48.4]

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47. Kustom Signals, Inc. v. Applied Concepts, Inc., 264 F.3d 1326, 1332 (Fed. Cir. 2001) ("Although Kustom is correct that 'comprising' means that the claims do not necessarily recite all of the elements and limitations of a device, or steps of a method, the clause imposing the limiting term 'or' requires the exclusion of devices whose memory search includes magnitude and frequency."); Spectrum Int'l, Inc. v. Sterlite Corp., 164 F.3d 1372, 1379–80 (Fed. Cir. 1998) (rejecting attempt to use the term "comprising" to open the claim to additional elements that negated the recited and required claim elements); Becton Dickinson & Co. v. C.R. Bard, Inc., 922 F.2d 792, 796–97 (Fed. Cir. 1990) (rejecting argument that "comprising" be construed to cover a feature of an accused device "as an 'additional element beyond those recited in the claims'" where such a "position would require disregarding not additional structure in the accused device but specific limitations . . . set forth in the claim"); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1271 (Fed. Cir. 1986).

48. *Spectrum*, 164 F.3d at 1379.

48.1. Promega Corp. v. Life Tech. Corp, 773 F.3d 1338, 1350 (Fed. Cir. 2014) (quoting Dippin' Dots, Inc. v. Mosey, 476 F.3d 1337, 1343 (Fed. Cir. 2007)).

48.2. Lampi Corp. v. Am. Power Prods., Inc., 228 F.3d 1365, 1376 (Fed. Cir. 2000) ("The specification in this case indicates that the patentee intended the word 'having' in claim 11 to be open [because] [t]he patent states that 'the housing preferably consists of two separable half-shells,'" indicating that it may include other parts); Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1573 (Fed. Cir. 1997) (the term "having" in a claim to "A DNA transfer vector comprising an inserted cDNA having a[DNA] sequence coding for human [PI]" construed to "permit[ ] inclusion of other moieties"); Mobil Oil Corp. v. Amoco Chems. Corp., 779 F. Supp. 1429, 1450–51 (D. Del. 1991).

48.3. The Manual of Patent Examining Procedure states that transitional phrases such as "having" "must be interpreted in light of the specification to determine whether open or closed claim language is intended." M.P.E.P. § 2111.03(iv).

48.4. *See* Pieczenik v. Dyax Corp., 76 F. App'x 293, 296 (Fed. Cir. 2003) (defining the gene "having" an oligonucleotide population of a length from

[B] "Consisting of"

"Consisting of" means that an infringing product must have exactly the elements set forth in the body of the claim, and no additional features.[49]

[C] "Consisting essentially of"

"Consisting essentially of" has a scope that falls in between the open language of "comprising" and the closed language of "consisting of," and means that an infringing product includes the elements recited in the claim body and some additional elements, but excludes additional unspecified elements that affect the basis and novel characteristics of the product defined by the claim.[50] A patentee, however, can alter the meaning of "consists essentially of" by statements in the specification or prosecution history.[50.1]

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four to twelve nucleotide triplets closed the term because equating "having" to "comprising" would read the upper bound (about twelve) out of the claim); Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l Inc., 246 F.3d 1336, 1348 (Fed. Cir. 2000) ("'having' in transitional phrase 'does not create a presumption that the body of the claim is open'").

49. AFG Indus., Inc. v. Cardinal IG Co., Inc., 239 F.3d 1239 (Fed. Cir. 2001); Ga.-Pac. Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1327–28 (Fed. Cir. 1999) ("the terms 'comprise' and 'consist' have different meanings; . . . 'comprising' . . . is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. . . . 'comprise' is broader than 'consist'"). *See also* Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp., No. 2015-1420, 2016 WL 4137673, at *6 (Fed. Cir. 2016) ("The presumption that a claim term set off by the transitional phrase 'consisting of' is closed to unrecited elements is at least a century old"; "to overcome [this] exceptionally strong presumption . . ., the specification and prosecution history must unmistakably manifest an alternative meaning.").

50. Water Techs. Corp. v. Calco, Ltd., 850 F.2d 660, 666 (Fed. Cir. 1988); PPG Indus. v. Guardian Indus. Corp., 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("consisting essentially of" generally means the claim "necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention").

50.1. Ecolab, Inc. v. FMC Corp., 569 F.3d 1335, 1343–44 (Fed. Cir. 2009) ("a patentee can alter" the "typical meaning" of "consists essentially of"); *PPG Indus.*, 156 F.3d at 1355 (patentee can "define[ ] the scope of the phrase 'consisting essentially of' . . . by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention"); *Water Techs.*, 850 F.2d at 666.

[D] "Group of," "Group consisting of," *Markush* Group

The phrase "group of" is presumptively open in meaning, while the phrase "group consisting of" is closed.[51] The phrase "group consisting of" is used to introduce a "*Markush* group"—that is, a claim element defining a limited number of members from which a selection must be made.[52]

Normally, a *Markush* group is limited to the members of the group and excludes combinations of those members unless specifically recited in the *Markush* group. "If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim."[52.1] Nevertheless, "[a]ll patent claims, including Markush claims, must be construed in view of 'the words of the claims, the specification, the prosecution history, and any relevant extrinsic evidence.'"[52.2]

Accordingly, a *Markush* group may in rare cases cover nonrecited elements to be included for "aspects unrelated to the invention."[52.3]

[E] "Whereby," "Wherein"

"Whereby" clauses are frequently used in the body of claims to introduce a result that follows from practicing the steps of the invention. Whether the matter introduced by the whereby clause limits the claim is often an issue in claim construction. In one case the court determined that "a 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."[53] With regard to the "whereby" clause of the

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51. *Gillette*, 405 F.3d at 1372; *see also* Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274 (Fed. Cir. 2003); *In re* Harnisch, 631 F.2d 716, 724 (C.C.P.A. 1980); M.P.E.P. § 2173.05(h).
52. *Gillette*, 405 F.3d at 1372.
52.1. *Abbott*, 334 F.3d at 1281.
52.2. *Multilayer*, 2016 WL 4137673, at *10–11 ("the intrinsic evidence . . . is unequivocal that the inner layers described in element (b) . . . are open, not closed, to blends of the recited resins" because the listed resins "do not constitute four entirely different species but instead overlap to some extent.").
52.3. Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1331 (Fed Cir. 2004); *see also* Shire Dev., LLC v. Watson Pharm., 848 F.3d 981, 986 (Fed. Cir. 2017) (reversing finding of infringement because the nonrecited magnesium stearate present in the accused ANDA product "structurally and functionally relates to the invention, and its presence in the outer matrix violates the 'consisting of' requirement in claim 1(b)").
53. Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n, 988 F.2d 1165 (Fed. Cir. 1993).

claims at issue, the court found that it "merely describe[s] the result of arranging the components of the claims in the manner recited in the claims," and did "not contain any limitation not inherent to the process found in [the] claims."[54] Furthermore, "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."[55] The court concluded that this would be the case with the patent-in-suit, because the used term 'efficiently' "does not inform the mechanics of how the trade is executed, and nothing in the specification or the prosecution history suggests otherwise." Rather, the term 'efficiently' was understood as a laudatory one "characterizing the result of the executing step."[56]

On the other hand, a "whereby" clause can introduce claim limitations when the subject matter that follows is material to patentability.[57]

§ 9:3.3 *Articles and Conjunctions*

[A] "a" or "an"

The words "a" and "an" ordinarily mean "one or more."[58] "That 'a' or 'an' can mean 'one or more' is best described as a rule, rather than merely as a presumption or even a convention. The exceptions to this rule are extremely limited: a patentee must 'evince[ ] a clear intent' to limit 'a' or 'an' to 'one.'"[58.1] However, where "the claims and written description . . . make clear that the singular meaning applies," courts will not apply the rule that "a" or "an" means "one or more."[58.2]

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54. *Id*. at 1172 (citing Israel v. Cresswell, 166 F.2d 153, 156 (C.C.P.A. 1948)).
55. Minton v. Nat'l Ass'n of Sec. Dealers, Inc., 336 F.3d 1373 (Fed. Cir. 2003).
56. *Id*. at 1381.
57. Hoffer v. Microsoft, 405 F.3d 1326, 1330 (Fed. Cir. 2005); Allergan Sales, LLC v. Sandoz, Inc., 935 F.3d 1370, 1376 (Fed. Cir. 2019) (wherein clause found to be limited because "[t]he prosecution history thus demonstrates that the formulation's efficacy and safety—as reflected in the disputed 'wherein' clauses—were expressly relied on to define the claimed methods and distinguish them from the prior art").
58. Collegenet v. Applyyourself, Inc., 418 F.3d 1225, 1231 (Fed. Cir. 2005); *see also* KJC Corp. v. Kinetic Concepts, Inc., 223 F.3d 1351, 1356 (Fed. Cir. 2000) ("[t]his court has repeatedly emphasized that an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising'").
58.1. Baldwin Graphic Sys., Inc. v. Siebert, Inc., 512 F.3d 1338, 1342 (Fed. Cir. 2008) (citations omitted).
58.2. TiVo, Inc. v. Echostar Commc'ns Corp., 516 F.3d 1290, 1303 (Fed. Cir. 2008) (distinguishing *Baldwin* because here the claim "refers to 'assembl[ing] said video and audio components into an MPEG stream,'

The first time a claim refers to an object, it is often preceded by the indefinite article *a* or *an* to establish the "antecedent basis" for subsequent references to that object. Subsequent references can then be modified with either *the* or *said*, for example, "the lever" or "said lever," because the referent for the noun has been identified. If "the lever" was used in the claim as the first reference to a lever, the term would lack proper antecedent basis.[59] The fact that a claim uses "the" as in "the lever" to refer back to a prior instance of "a lever" does not mean that "a lever" refers to only one lever.[59.1]

[B] "the"

Use of the word "the" refers to the previous instance of the thing described.[60] Refer to the prior section for a discussion of the relationship between "a" and "the."

[C] "and"/"or"

When the specification or claim requires "and" to be a disjunctive to make sense, "and" will be construed to mean "or."[60.1] However, when "the written description can be interpreted to support either construction," the term "and" should be given its plain and ordinary meaning to mean "and" instead of "or."[60.2]

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which in context clearly indicates that two separate components are assembled into a single stream" and the specification provides similar support).

59. M.P.E.P. § 2173.05(e); *Baldwin*, 512 F.3d at 1343 ("Section 2173.05(e) describes the need, in most cases, for claim terms to have proper antecedent bases."); NTP, Inc. v. Research in Motion, Ltd., 418 F.3d 1282, 1306 (Fed. Cir. 2005).

59.1. *Baldwin*, 512 F.3d at 1343 ("Because the initial indefinite article ('a') carries either a singular or plural meaning, any later reference to that same claim element merely reflects the same potential plurality. In grammatical terms, the instances of 'said fabric roll' in the claim are anaphoric phrases, referring to the initial antecedent phrase. Because the initial phrase carries no definitive numerosity, the anaphoric phrases do not alter that meaning in the slightest.").

60. M.P.E.P. § 2173.05(e); *NTP*, 418 F.3d at 1306 ("It is a rule of law well established that the definite article 'the' particularizes the subject which it precedes.").

60.1. Ortho McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1361–62 (Fed. Cir. 2008) ("In light of . . . the specification, . . . this court sustains the trial court's ruling that . . . claim 1's use of and means or" because "as used in [the] claim, and conjoins mutually exclusive possibilities.").

60.2. Medgraph, Inc. v. Medtronic, Inc., 843 F.3d 942, 949 (Fed. Cir. 2016).

§ 9:4 Construction of Means-Plus-Function Claims

Under section 112, paragraph 6, a claim may be written as a means-plus-function claim whereby a claim term specifies a function to be performed without specifying a structure that will perform the function. In construing such a claim, the statute limits the means to those that are set forth in the specification and "equivalents thereof." This provision does not allow one to claim an open-ended "means" for achieving some goals regardless of the means employed.

It is not always easy to determine whether a claim is a means-plus-function claim, because some general functional terms may be used in a claim where the functions are correlated with well-known structures. There is, however, a rebuttal presumption that a claim is a means-plus-function claim when it specifically recites the word "means."[61] For the claim to be a means-plus-function claim, there must be a purely functional term used without providing the structure that performs the function.[62]

§ 9:5 Disclaimer of Subject Matter That Literally Falls Within Claim Language

While the disclaiming of subject matter during patent prosecution is an issue that typically arises in the context of prosecution history estoppel when infringement under the doctrine of equivalence is asserted, the Federal Circuit has also accepted that disclaimed subject matter can be relevant to the construction of a claim.[63]

A disclaimer of subject matter must be "explicit" and use words of "manifest exclusion."[64]

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61. Cross Med. Prods., Inc. v. Medtronics Sofamor Danek, Inc., 424 F.2d 1293 (Fed. Cir. 2005); Personalized Media Commc'ns, LLC v. Int'l Trade Comm'n, 161 F.3d 696, 703–04 (Fed. Cir. 1998); Rodine PLC v. Seagate Tech., Inc., 174 F.3d 1294, 1302 (Fed. Cir. 1999).
62. Watts v. XL Sys., Inc., 232 F.3d 877, 880–81 (Fed. Cir. 2000).
63. SciMedLife Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337 (Fed. Cir. 2001) (the express statements in the patent specification and prosecution history had disclaimed a particular side-by-side arrangement of lumen in balloon dilation catheters even though the claim language was broad enough to include it); *see also* Microsoft Corp. v. Multi-Tech Sys., Inc., 357 F.3d 1340, 1347–49 (Fed. Cir. 2004) ("We cannot construe the claims to cover subject matter broader than that which the patentee itself regarded as comprising its inventions and represented to the PTO."); Biodex Corp v. Loredan Biomed, Inc., 946 F.2d 850, 862 (Fed. Cir. 1991).
64. *Gillette*, 405 F.3d at 1374; Libel-Florsheim Co. v. Medrad, Inc., 358 F.3d 898 (Fed. Cir. 2004).

§ 9:6 Pharmaceutical Patents

§ 9:6.1 *Planning for Claim Construction During Prosecution*

Because of the prime importance of claim language and the specification in interpreting the claims of a patent, the patent applicant has great opportunity to influence the construction the claims will have. Indeed, the patent applicant can dictate the construction of a claim term by expressly defining it in the specification.

Certainly, careful thought should be given to defining any term in a claim that is potentially open to interpretation or dispute. The difficulty is, however, that it is not possible to always foresee which terms will be disputed, or the way in which they will be disputed, because accused infringers often develop surprising proposed definitions for terms. Also, one cannot always foresee how changes in technology will develop so that a narrow definition might exclude something later developed that would logically be considered as falling within the meaning of a claim term if it were specifically considered when the claim was drafted. There is also a danger that the express definition may be too broad, and might cover prior art that was not intended to be included if the specific issue were known when the claim was drafted.

Finally, a definition that is written without a particular fact situation in mind may still itself leave open questions of whether a particular embodiment is included in the definition. In such a situation, the construction problem is moved from the claim term to terms used in an express definition in the specification.[65]

Although not a panacea to claim construction problems, a patent applicant should think very carefully about the terms that will be used in the claims and consider what express definitions might be developed to promote clarity and achieve the interpretation that would be most helpful. One must remember to consider not only infringement issues, but also prior art, definiteness, and enablement in formulating claim term definitions.

Because claims are often amended during prosecution, new terms might be introduced that are not specifically defined in the original specification. In that case, explanations of the meaning of the new terms could be added to the remarks section of the amendment, or

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65. *See, e.g.*, Kumar v. Ovonic Battery Co., 351 F.3d 1364 (Fed. Cir. 2003) (definition known in the art of amorphous meter as one without a long range order, required still further definition to determine what was meant by "long range order").

by amendment to the specification if new matter problems would not thereby be introduced.

§ 9:6.2 Common Construction Issues in Pharmaceutical Patents

Claims to the active pharmaceutical molecule present some common problems that might be addressed in the initial drafting. A claim to an active drug molecule can take account of the various forms in which the molecule could be administered, for example, a salt, an ester, or pro-drug. If the active drug molecule is a base, for example, the base can be made into a salt by addition of an acid. When ingested, however, the salt separates into ions, and the base portion of the drug provides the therapeutic effect. In claiming the compound, one can make sure that such modifications of the active drug form are covered by, for example, claiming the molecule and salts thereof.

One approach to achieve literal coverage of modifications of the drug compound that are discarded *in vivo* (such as a pro-drug where the pro-drug metabolizes into the claimed drug) is to claim the use of the active chemical moiety regardless of how delivered. For example, a claim may involve a method of treatment where the method entails delivery of the active compound "X" or the delivery of another compound that metabolizes into the active molecule "X" or ions thereof. A method claim may be more generally defined as a method of treatment by causing compound "X" to enter into or be produced in the bloodstream.

Definitions can also address possible disputes about whether changes in a physical form of a compound—such as hydrates, polymorphs, amorphous, or crystal forms are within the claims to the compound. These can be addressed by definitions that make clear that all forms are included when appropriate, particularly by drafting the claims to address the method of treatment by the active chemical entity, regardless of the physical or chemical form in which it may be administered.

In the end, however, claim construction remains an imprecise art where the many specific rules do not lead one to a particular result. While careful thought about the issue during drafting of the patent and conducting the prosecution can help greatly, and is undoubtedly superior to leaving the construction to after-the-fact analysis, there will likely always be room for argument and uncertainty about the construction that the court will ultimately adopt.

Chapter 10. Patent Infringement

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Chapter 10

Patent Infringement

David K. Barr

§ 10:1 Introduction

A U.S. patent is infringed by certain unauthorized acts specified in section 271 of the Patent Act.[1] A determination of infringement requires a two-step analysis. First, the asserted patent claims are construed as a matter of law.[2] Second, the allegedly infringing product or process is compared to the properly construed claims.[3] Determining whether the properly construed claim is infringed by an accused product or process is an issue of fact,[4] and the patent owner bears the burden of proving infringement by a preponderance of the evidence.[5]

Infringement can either be "direct" or "indirect." The term "direct" infringement is used to characterize unauthorized conduct by an entity that by itself satisfies all of the requirements of the patent claim. The term "indirect" infringement is used to characterize

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1. 35 U.S.C. § 271. A discussion of remedies for patent infringement, including enhanced damages for willful infringement, can be found *supra* in section 1:8.2.
2. See *supra* chapter 9 for a discussion of claim construction.
3. Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc., 467 F.3d 1370, 1375 (Fed. Cir. 2006). *See supra* chapter 9 (Claim Construction).
4. *Abraxis Bioscience Inc.*, 467 F.3d at 1375.
5. Seal-Flex, Inc. v. Athletic Track & Court Constr., 172 F.3d 836, 842 (Fed. Cir. 1999).

Chapter 11. Willful Infringement and the Advice of Counsel Defense

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Chapter 11

Willful Infringement and the Advice of Counsel Defense

David K. Barr

Patent infringement complaints are often accompanied by allegations not only that the defendant has infringed a patent but also that the infringement was "willful." The consequences of a finding of willful infringement could lead to awards of up to treble damages and having to pay the patent owner's attorneys' fees. This chapter will discuss the elements of willful infringement and the defenses to allegations of willful infringement, particularly in light of the decisions of the Court of Appeals for the Federal Circuit and the U.S. Supreme Court.

The U.S. patent statute, 35 U.S.C. § 284, provides for the award of damages for patent infringement.[1] Section 284 further provides

1. 35 U.S.C. § 284.

that "[t]he court may increase damages up to three times the amount found or assessed."[2] Although the statute itself does not specify the circumstances under which damages can be increased, courts have done so based on a finding that the infringement was "willful."[3] Similarly, section 285 of the patent statute provides that "[t]he court in exceptional cases may award reasonable attorneys' fees to the prevailing party," and although the statute does not specify which circumstances should be considered "exceptional," a finding of willful infringement has formed the basis for an award of attorneys' fees.[4]

Willful infringement is an issue for the jury to decide when patent infringement is tried to a jury[5] and is a question of fact reviewed for substantial evidence.[6] However, the decision to enhance damages is for the court[7] and is reviewed under an abuse-of-discretion standard.[8]

Upon a finding of willful infringement, the court considers a variety of factors, as set forth in the Federal Circuit's 1992 *Read v. Portec* decision, in deciding whether to enhance damages.

> The court must consider factors that render defendant's conduct more culpable, as well as factors that are mitigating or ameliorating: (1) whether the infringer deliberately copied the ideas or design of another; (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed; (3) the infringer's behavior as a party to the litigation;

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2. *Id*.
3. Read Corp. v. Portec, Inc., 970 F.2d 816, 827 (Fed. Cir. 1992) ("While no statutory standard dictates the circumstances under which the district court may exercise its discretion, this court has approved such awards where the infringer acted in wanton disregard of the patentee's patent rights, that is, where the infringement is willful . . . . On the other hand, a finding of willful infringement does not mandate that damages be enhanced, much less mandate treble damages.").
4. *See, e.g.*, Georgetown Rail Equip. Co. v. Holland L.P., No. 6:13-cv-366, 2016 WL 3346084, at *21–24 (E.D. Tex. June 16, 2016) (the district court found that willful infringement alone is a compelling indication that a case is also exceptional and deserves an award of attorneys' fees).
5. WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1341 (Fed. Cir. 2016) ("[T]he factual components of the willfulness question should be resolved by the jury.").
6. Polara Eng'g Inc. v. Campbell Co., 894 F.3d 1339, 1353 (Fed. Cir. 2018).
7. Eko Brands, LLC v. Adrian Rivera Maynez Enters., Inc., 946 F.3d 1367, 1378 (Fed. Cir. 2020) ("The question of enhanced damages is *addressed by the court* once an affirmative finding of willfulness has been made.") (emphasis added).
8. *Polara*, 894 F.3d at 1353 ("We review a district court's ultimate decision whether to enhance damages for abuse of discretion.").

(4) defendant's size and financial condition; (5) closeness of the case; (6) duration of defendant's misconduct; (7) remedial action by the defendant; (8) defendant's motivation for harm; and (9) whether defendant attempted to conceal its misconduct.[9]

§ 11:1 Willful Infringement in the Era of the Federal Circuit

§ 11:1.1 *The* Underwater Devices *Era: 1983–2006*

In an early decision of the Federal Circuit, *Underwater Devices Inc. v. Morrison-Knudsen Co.*,[10] the court addressed the standards for willful infringement. In the case, the accused infringer had actual notice of the asserted patents based on a letter from the patent owner offering a license. The accused infringer's in-house counsel, who was not a patent lawyer, wrote a cursory memorandum that the patents were invalid based on a brief discussion of a single prior art reference without benefit of a review of the file histories. In-house counsel advised the accused infringer that it could proceed, in part, because "Courts, in recent years, have—in patent infringement cases—found the patents claimed to be infringed upon invalid in approximately 80% of the cases."[11] The accused infringer "did not receive the opinion of its patent counsel until . . . long after infringement had commenced and even after the complaint for the instant case was filed."[12]

The Federal Circuit affirmed a judgment of willful infringement and an award of treble damages. "Where, as here, a potential infringer has actual notice of another's patent rights, he has an affirmative duty to exercise due care to determine whether or not he is infringing. . . . Such an affirmative duty includes, inter alia, the duty to seek and obtain competent legal advice from counsel before the initiation of any possible infringing activity."[13] The court concluded that "[t]he appellant clearly failed to exercise its affirmative duty. Accordingly, the district court's finding that infringement was willful, in the totality of the circumstances presented in this case, is not clearly erroneous and the district court did not abuse its discretion in awarding treble damages."[14]

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9. *Read Corp.*, 970 F.2d at 826–27.
10. Underwater Devices Inc. v. Morrison-Knudsen Co., 717 F.2d 1380 (Fed. Cir. 1983).
11. *Id*. at 1385.
12. *Id*. at 1390.
13. *Id*. at 1389–90.
14. *Id*. at 1390.

Thus, under the standard set forth in *Underwater Devices*, once on notice of another's patent rights, there is an affirmative duty of due care before embarking on potentially infringing activity. The *Underwater Devices* decision and its affirmative statement about obtaining "competent legal advice from counsel" cautioned in favor of seeking formal opinions of counsel as part of patent clearance procedures.

§ 11:1.2 *The* Seagate *Era: 2007–2016*

In 2007, the Federal Circuit issued an en banc decision *In re Seagate Technology, LLC*, which overruled *Underwater Devices* and upended the manner in which willful infringement was determined by the courts and consequently how companies conducted their patent clearance procedures.[15] Originating as a petition for a writ of mandamus regarding a district court's discovery order relating to the scope of waiver occasioned by the reliance on the advice of counsel, the full Federal Circuit bench revisited the standard for determining willful infringement and abandoned the affirmative duty of care set forth in *Underwater Devices*, holding that "[b]ecause we abandon the affirmative duty of due care, we also reemphasize that there is no affirmative obligation to obtain opinion of counsel."[16]

In *Seagate*, the Federal Circuit reaffirmed that willful infringement is a predicate for enhanced damages in patent cases: "Absent a statutory guide, we have held that an award of enhanced damages requires a showing of willful infringement."[17] However, the en banc court articulated a new test and standard for finding willful infringement. To prove willful infringement following *Seagate*, a patentee was required to show by clear and convincing evidence (1) "that the infringer acted despite an objectively high likelihood that its actions constituted infringement of a valid patent" and (2) "that this objectively defined risk (determined by the record developed during the infringement proceeding) was either known or so obvious that it should have been known to the accused infringer."[18]

Notably, under *Seagate*, the "objective" threshold prong of the test was determined with reference to the defenses that the accused infringer raised during litigation, without regard to the accused infringer's subjective state of mind at the time of infringement. Accordingly, a finding of willful infringement could be defeated by

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15. *In re* Seagate Tech., LLC, 497 F.3d 1360, 1368 (Fed. Cir. 2007).
16. *Id*. at 1371.
17. *Id*. at 1368.
18. *Id*. at 1371.

the merits of defenses asserted and mounted at trial. Only if the objective prong was satisfied would the trier of fact evaluate the subjective intent of the accused infringer. Subsequent decisions established that objective recklessness was an issue for the court, reviewed de novo on appeal; subjective knowledge was a jury issue, reviewed for substantial evidence; and a court's ultimate decision to award enhanced damages was reviewed under an abuse-of-discretion standard.[19]

§ 11:1.3 35 U.S.C. § 298: Elimination of the Adverse Inference of Not Obtaining Advice of Counsel

As part of the America Invents Act (AIA), in 2011 Congress enacted 35 U.S.C. § 298, which provided: "The failure of an infringer to obtain the advice of counsel with respect to any allegedly infringed patent, or the failure of the infringer to present such advice to the court or jury, may not be used to prove that the accused infringer willfully infringed the patent or that the infringer intended to induce infringement of the patent." Section 298 thus codified the Federal Circuit's pre-*Seagate* determination that "no adverse inference that an opinion of counsel was or would have been unfavorable flows from an alleged infringer's failure to obtain or produce an exculpatory opinion of counsel."[20]

§ 11:1.4 *The* Halo *Era: 2016 to Date*

In 2016, the U.S. Supreme Court overruled *Seagate* when it decided *Halo Electronics, Inc. v. Pulse Electronics, Inc.*[21] The *Halo* decision was based on the Supreme Court's review on writs of certiorari of two Federal Circuit decisions.

The first Federal Circuit decision on review was *Halo Electronics, Inc. v. Pulse Electronics, Inc.*[22] in which the plaintiff patent owner was "a supplier of electronic components and owns . . . patents directed to surface mount electronic packages containing transformers for mounting on a printed circuit board." The defendant Pulse "allegedly knew of the Halo patents as early as 1998." "In 2002, Halo sent Pulse two letters offering licenses to its patents but did not accuse Pulse of infringement in those letters." A Pulse engineer "spent about two hours reviewing the Halo patents and concluded that they were

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19. Bard Peripheral Vascular, Inc. v. W. L. Gore & Assocs., Inc., 682 F.3d 1003, 1005, 1008 (Fed. Cir. 2012); Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1347 (Fed. Cir. 2011).
20. Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp., 383 F.3d 1337, 1341 (Fed. Cir. 2004).
21. Halo Elecs., Inc. v. Pulse Elecs., Inc., 136 S. Ct. 1923 (2016).
22. Halo Elecs., Inc. v. Pulse Elecs., Inc., 769 F.3d 1371 (Fed. Cir. 2014).

invalid in view of prior Pulse products." Notwithstanding its knowledge of Halo's patents, "Pulse did not seek an opinion of counsel . . . and continued to sell its [products]." During trial, a "Pulse witness later testified that she was 'not aware of anyone in the company . . . that made a conscious decision' that 'it was permissible to continue selling' those products."[23]

The jury found that Pulse infringed Halo's patents and rejected Pulse's obviousness defense, awarding Halo $1.5 million in reasonable royalty damages. Moreover, the jury found that "[i]t was highly probable that Pulse's infringement was willful."[24] Post-trial, the district court held that the objective component of *Seagate* had not been satisfied because Pulse "reasonably relied on at least its obviousness defense" and the obviousness defense was not "objectively baseless."[25]

The second Federal Circuit decision on review was *Stryker Corp. v. Zimmer, Inc.*,[26] which involved "the two principal participants in the market for orthopedic pulsed lavage devices." In around 1998, Stryker introduced its Pulsavac Plus products. As the district court stated, "Zimmer had no answer for Stryker's new [patented] technology and saw its market share fall precipitously." In addition, "Zimmer hired an independent contractor with no experience in pulsed lavage devices. In essence, Zimmer handed the independent contractor a copy of Stryker's product and said, 'Make one for us.'" Moreover, Zimmer did not investigate the scope of Stryker's patents, and Zimmer did not stop infringing or change its design after the district court granted summary judgment of infringement on two of Stryker's three patents.[27]

At trial, the jury found that all asserted claims were valid and that Zimmer infringed the third patent (summary judgment of infringement had been granted to Stryker on the first two patents). The jury awarded Stryker $70 million in lost profits damages. Moreover, the jury found that Zimmer's infringement of all three patents was willful.[28]

Post-trial, the district court awarded Stryker treble damages based on the jury's willful infringement finding.

> Zimmer lost every argument it advanced at claim construction, then lost most of the disputed claims on summary judgment.

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23. *Id*. at 1376.
24. *Id*.
25. Halo Elecs., Inc. v. Pulse Elecs., Inc., No. 2:07-cv-00331-PMP-PAL, 2013 WL 2319145, at *15 (D. Nev. May 28, 2013).
26. Stryker Corp. v. Zimmer, Inc., 782 F.3d 649 (Fed. Cir. 2015).
27. Stryker Corp. v. Zimmer, Inc., No. 1:10-cv-1223, 2013 WL 6231533, at *1–2, *11–14 (W.D. Mich. Aug. 7, 2013).
28. *Id*. at *1.

> It lost all of its remaining claims at trial. At the time the jury announced its verdict, Zimmer had not changed its product design. This is consistent with both the market and litigation strategy that Zimmer has followed for years. Zimmer chose a high-risk/high-reward strategy of competing immediately and aggressively in the pulsed lavage market and opted to worry about the potential legal consequences later.[29]

The district court also found the case exceptional under 35 U.S.C. § 285 based on Zimmer's willful infringement and awarded Stryker its attorneys' fees.

On appeal, the Federal Circuit applied the *Seagate* test and reversed the finding of willful infringement and the awards of treble damages and attorneys' fees. The Federal Circuit concluded that the "district court failed to undertake an objective assessment of Zimmer's specific defenses to Stryker's claims." Specifically, the Federal Circuit found that Zimmer relied on claim construction and obviousness arguments that were "not unreasonably founded" and that an "objective assessment of the case shows that Zimmer presented reasonable defenses to all of the asserted claims of Stryker's patents."[30]

The Supreme Court granted the petitions for writ of certiorari in both cases and took the opportunity to expressly overrule *Seagate* and reversed and remanded the judgments of the Federal Circuit in both cases.[31] The Supreme Court reviewed the history of the award of enhanced damages based on willful infringement, noting that enhanced damages were reserved for particularly egregious behavior:

> Awards of enhanced damages under the Patent Act over the past 180 years establish that they are not to be meted out in a typical infringement case, but are instead designed as a "punitive" or "vindictive" sanction for egregious infringement behavior. The sort of conduct warranting enhanced damages has been variously described in our cases as willful, wanton, malicious, bad-faith, deliberate, consciously wrongful, flagrant, or—indeed—characteristic of a pirate.[32]

The Supreme Court concluded that the *Seagate* test was inappropriate for making these determinations:

> The principal problem with *Seagate*'s two-part test is that it requires a finding of objective recklessness in every case before district courts may award enhanced damages. Such a threshold

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29. *Id*. at *2.
30. *Stryker Corp.*, 782 F.3d at 661.
31. *Halo Elecs., Inc.*, 136 S. Ct. at 1935–36.
32. *Id*. at 1932.

> requirement excludes from discretionary punishment many of the most culpable offenders, such as the "wanton and malicious pirate" who intentionally infringes another's patent—with no doubts about its validity or any notion of a defense—for no purpose other than to steal the patentee's business.[33]

In particular, the Supreme Court rejected the notion that objectively meritorious defenses advanced in litigation could insulate an accused infringer who had engaged in egregious behavior from a finding of willfulness. While the *Seagate* test "reflects, in many respects, a sound recognition that enhanced damages are generally appropriate under § 284 only in egregious cases. That test, however, 'is unduly rigid, and it impermissibly encumbers the statutory grant of discretion to district courts'. . . . In particular, it can have the effect of insulating some of the worst patent infringers from any liability for enhanced damages."[34] Thus, "[u]nder *Seagate*, someone who plunders a patent—infringing it without any reason to suppose his conduct is arguably defensible—can nevertheless escape any comeuppance under § 284 solely on the strength of his attorney's ingenuity."[35]

The *Halo* Court also made plain that, for willful infringement, "culpability is generally measured against the knowledge of the actor at the time of the challenged conduct."[36] Accordingly, *Halo* marked a return to the *Underwater Devices* era of establishing good faith as of the time of infringement, not at the time of trial based on defenses developed during litigation.

In addition, *Halo* changed the evidentiary burdens and appellate review standards for willful infringement. First, *Halo* rejected *Seagate*'s clear-and-convincing standard for willfulness and adopted a preponderance-of-the-evidence standard: "[P]atent-infringement litigation has always been governed by a preponderance of the

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33. *Id*.
34. *Id*.
35. *Id*. at 1933.
36. *Id. See also* Pavo Sols. LLC v. Kingston Tech. Co., 35 F.4th 1367, 1378 (Fed. Cir. 2022) (Kingston argued on appeal that infringement could not be willful because the district court had made a judicial correction to the claim language during litigation. The Federal Circuit rejected this argument and affirmed the district court's judgment of willfulness because the judicial correction was to "an obvious minor clerical error." The Federal Circuit also rejected Kingston's argument that the willfulness finding was improper because the PTAB had denied Pavo's correction request during IPR proceedings because the PTAB had not considered the substance of the correction request and "[m]ore importantly, culpability is generally measured against the knowledge of the actor at the time of the challenged conduct.").

evidence standard. . . . Enhanced damages are no exception."[37] Thus, the burden of proof for willful infringement was made the same as the burden for proving infringement itself. Second, *Halo* rejected the Federal Circuit's "tripartite framework" for appellate review of awards of enhanced damages: "Nearly two centuries of exercising discretion in awarding enhanced damages in patent cases, however, has given substance to the notion that there are limits to that discretion. The Federal Circuit should review such exercises of discretion in light of the longstanding considerations we have identified as having guided both Congress and the courts."[38]

In *Halo*, on remand, the Federal Circuit, applying the Supreme Court's new willfulness standard, (1) vacated the district court's determination of no willful infringement under *Seagate* and (2) remanded to the district court to exercise its discretion as to whether to enhance damages "taking into consideration the jury's unchallenged subjective willfulness finding" as well as "what Pulse knew or had reason to know at the time of the infringement of the Halo patents."[39] In turn, on remand, the district court, applying the Supreme Court's decision, decided not to enhance damages notwithstanding the jury's willful infringement determination. In reaching its determination, the district court stated:

> Enhanced damages remain an exceptional tool meant to punish patent "pirates"—companies that intentionally infringe with no regard for a plaintiff's rights. The record reveals that Pulse is no pirate. Its defense strategies were questionable, which is reflected in the jury's verdict against it. But Pulse offers ample evidence that: (1) when it learned of Halo's patent Pulse investigated whether its products infringed, (2) Pulse pursued non-frivolous defenses at trial, and (3) Pulse had a basis to subjectively believe it was not infringing Halo's patent throughout this litigation and prior.[40]

Of note is that the district court in its decision not to enhance damages relied on two opinions of counsel that the patent-in-suit was invalid, even though those opinions had not been produced during discovery. The district court reasoned that those opinions were "powerful evidence that Pulse was not intentionally infringing Halo's

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37. *Halo Elecs., Inc.*, 136 S. Ct. at 1934.
38. *Id*.
39. Halo Elecs., Inc. v. Pulse Elecs., Inc., 831 F.3d 1369, 1381 (Fed. Cir. 2016).
40. Halo Elecs., Inc. v. Pulse Elecs., Inc., 281 F. Supp. 3d 1087, 1089 (D. Nev. 2017).

patent" and decided that the opinions were properly considered in the determination of whether damages should be enhanced, even though they were not produced during discovery.[41]

In *Stryker*, on remand the Federal Circuit, applying the *Halo* willfulness standard, affirmed the jury's finding of willful infringement—Zimmer had not appealed the jury's finding of subjective willfulness under the clear-and-convincing standard—and vacated and remanded the district court's award of treble damages and attorneys' fees for the exercise of its discretion.[42] In turn, on remand the district court reaffirmed its award of treble damages and attorneys' fees based on all of the *Read v. Portec* factors, including evidence that Zimmer had copied and "Zimmer presented no evidence that it investigated the scope of Stryker's patents to form a good faith belief about invalidity or infringement."[43]

§ 11:2 Reliance on the Advice of Counsel and the Waiver of Attorney-Client Privilege

It is a well-established principle that the attorney-client privilege cannot be used as both a sword and a shield such that the holder of the privilege can selectively waive the privilege to rely on helpful aspects of counsel's advice.[44] Accordingly, courts generally rule that reliance on the advice of counsel results in a waiver of the attorney-client privilege beyond the specific advice on which reliance has been placed and "applies to all other communications relating to the same subject matter."[45] This applies with equal force to reliance on advice of counsel to defend against a charge of willful patent infringement such that the waiver extends to communications with counsel relating to the same subject matter: "Once a party announces that it will rely on advice of counsel, for example, in response to an assertion of willful infringement, the attorney-client privileged is waived. 'The widely applied standard for determining the scope of a waiver of attorney-client privilege is that the waiver applies to all other communications relating to the same subject matter.'"[46]

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41. *Id*. at 1091.
42. Stryker Corp. v. Zimmer, Inc., 837 F.3d 1268 (Fed. Cir. 2016).
43. Stryker Corp. v. Zimmer, Inc., No. 1:10-cv-1223, 2017 WL 4286412, at *4 (W.D. Mich. July 12, 2017).
44. *In re* EchoStar Commc'ns Corp., 448 F.3d 1294, 1301, 1303 (Fed. Cir. 2006); Fort James Corp. v. Solo Cup Co., 412 F.3d 1340, 1349 (Fed. Cir. 2005).
45. *Fort James Corp.*, 412 F.3d at 1349.
46. *In re EchoStar Commc'ns Corp.*, 448 F.3d at 1299 (internal citation omitted).

Because the waiver consequences of reliance on the advice of counsel to defend against willful infringement can be far-reaching, a number of jurisdictions have adopted patent local rules governing when in the course of a litigation an accused infringer must decide on whether it will rely on counsel's advice and thus waive privilege to related communications.[47]

The waiver of privilege occasioned by reliance on advice of counsel has both a temporal and subject matter scope and often depends on the specific facts of the case. Waiver has been held to extend to communications with both in-house and outside counsel and to communications occurring both before and after litigation has been commenced.[48] Waiver can also extend to attorney work product relating to the same subject matter that has been communicated to the client or that reflects communications with the client,[49] but not to work product that was not communicated to the client.[50] With regard to subject matter, courts may limit the scope of waiver to the specific subject matter of the relied-on advice. For example, a court may limit waiver to the scope of a non-infringement opinion on which a defendant elects to rely and not extend waiver to a separate invalidity opinion on which the defendant has decided not to rely.[51]

An important consideration is whether waiver is limited to communications with opinion counsel or can extend to communications with trial counsel. As the Federal Circuit stated in *Seagate*, "as a

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47. For example, both the Northern District of California and the District of New Jersey rules provide that the election must be made not later than thirty days after the claim construction order (N.D. Cal. Patent L.R. 3.7; D.N.J. Patent L.R. 3.8). The Eastern District of Texas rules provide that the date of election is set forth in the Docket Control Order, usually a set time after the claim construction order (E.D. Tex. Patent L.R. 3.7).

48. *In re EchoStar Commc'ns Corp.*, 448 F.3d at 1299.

49. *Id*. at 1304 ("Therefore, when an alleged infringer asserts its advice-of-counsel defense regarding willful infringement of a particular patent, it waives its immunity for any document or opinion that embodies or discusses a communication to or from it concerning whether that patent is valid, enforceable, and infringed by the accused. This waiver of both the attorney-client privilege and the work-product immunity includes not only any letters, memorandum, conversation, or the like between the attorney and his or her client, but also includes, when appropriate, any documents referencing a communication between attorney and client.").

50. *Id*. at 1305 ("Here, Merchant & Gould work product that was not communicated to EchoStar or does not reflect a communication is not within the scope of EchoStar's waiver because it obviously played no part in EchoStar's belief as to infringement of the '389 patent.").

51. *See* Barry v. Globus Med., Inc., Civ. No. 17-2998 (E.D. Pa. Oct. 10, 2018), ECF No. 177; *see also* Barry v. Globus Med., Inc., Civ. No. 17-2998 (E.D. Pa. Oct. 18, 2018), ECF No. 185.

general proposition, . . . asserting the advice of counsel defense and disclosing opinions of opinion counsel do not constitute waiver of the attorney-client privilege for communications with trial counsel."[52] However, the court left open the possibility that waiver can be extended to communications with trial counsel in exceptional circumstances: "trial courts remain free to exercise their discretion in unique circumstances to extend waiver to trial counsel, such as if a party or his counsel engages in chicanery."[53]

Waiver may extend to communications from before patent issuance[54] and to communications after litigation has commenced. In particular, it has been held that allegations of ongoing willful infringement create a risk of waiver extending to the period after the filing of the complaint.[55] This risk is increased if opinion counsel continues to have a role after litigation has commenced and has engaged in discussions with trial counsel.[56] In this regard, blurring the line between the roles of opinion counsel and trial counsel also presents a risk of waiver of communications with trial counsel.[57]

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52. *Seagate Tech.*, 497 F.3d at 1374. It should be noted that the aspects of the *Seagate* decision relating to waiver of the attorney-client privilege were not overruled by *Halo*.

53. *Id*. at 1374–75. *See also In re* Alcon Labs., Inc., No. 2018-115, 2018 WL 7485446, at *2 (Fed. Cir. Feb. 14, 2018) (trial courts "remain free to exercise their discretion in unique circumstances to extend waiver to trial counsel."). However, the *Seagate* court also held that "as a general proposition, relying on opinion counsel's work product does not waive work product immunity with respect to trial counsel." *Seagate Tech.*, 497 F.3d at 1376.

54. Johns Hopkins Univ. v. Alcon Labs., Inc. (Stark), No. 15-525-LPS-SRF, 2017 WL 5172395 (D. Del. Nov. 8, 2017), *mandamus denied sub nom. In re* Alcon Labs., Inc., No. 2018-115, 2018 WL 7485446 (Fed. Cir. Feb. 14, 2018) (holding that waiver extended to pre-patent issuance and post-litigation communication).

55. Krausz Indus. Ltd. v. Smith-Blair, Inc., No. 5:12-CV-00570-FL, 2016 U.S. Dist. LEXIS 191859, at *21 (E.D.N.C. Dec. 13, 2016) ("[I]n light of Krausz's claim of ongoing willful infringement, it is appropriate to extend the waiver resulting from the assertion of an advice of counsel defense beyond the filing of the Complaint in this action.").

56. *Id*. at *29 (opinion counsel's "active, on-going involvement in this litigation blurs the lines between the roles of objective advisor and partisan advocate.").

57. *See* Zen Design Grp. Ltd. v. Scholastic, Inc., 327 F.R.D. 155 (E.D. Mich. 2018) (waiver found with respect to trial counsel's pre-suit communications regarding the subject matter of opinion counsel's work as the plaintiff was entitled to discover whether trial counsel, who had also served as pre-suit settlement counsel, had given advice inconsistent with the opinion).

§ 11:3 The Quality of the Opinion of Counsel

To be effective as a defense to willful infringement, an opinion of counsel should reflect careful consideration and attention to detail to show that the opinion was competently rendered by experienced patent counsel. Willfulness is a factor only if the defendant is found to have infringed a valid patent, which necessarily means that the defenses on the merits have been rejected by the jury or the court. Therefore, as the Federal Circuit has pointed out, it is not the correctness of the positions taken by which the opinion is ultimately judged but the competency of advice provided.[58] As the Federal Circuit stated in *Ortho Pharmaceutical Corp. v. Smith*[59]:

> While an opinion of counsel letter is an important factor in determining the willfulness of infringement, its importance does not depend upon its legal correctness. Indeed, the question arises only where counsel was wrong. Rather, counsel's opinion must be thorough enough, as combined with other factors, to instill a belief in the infringer that a court might reasonably hold the patent is invalid, not infringed, or unenforceable. . . .Thus, Ortho's intent and reasonable beliefs are the primary focus of a willful infringement inquiry.
>
> The district court, in finding no willful infringement, concluded that Ortho obtained and reasonably relied upon opinion letters rendered by counsel. . . . This finding is not clearly erroneous. Ortho's opinion letters were obtained from experienced patent counsel.

Accordingly, the trier of fact should be expected to consider the overall thoroughness of the opinion in evaluating the specifics of the opinion (whether directed to non-infringement, invalidity, or both) as well as the competency of the patent counsel providing the opinion. It is also important to consider that the opinion counsel and the client personnel who solicited and relied on the opinion may be witnesses who will have to defend the good faith of both the opinion and the client's reliance on it.

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58. *See* Sunoco Partners Mktg. & Terminals v. U.S. Venture, 32 F.4th 1161, 1177–79 (Fed. Cir. 2023) (The district court awarded enhanced damages based on its finding that the patent counsel authoring the opinion letter relied on by defendant did not have a competent understanding of the technology. The Federal Circuit reversed, concluding that this finding was in error because it was based on an erroneous reading of the counsel's testimony, which in fact demonstrated an understanding of the technology, and further that the district court's error undermined other grounds that the district court relied on to enhance damages.).
59. Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 944 (Fed. Cir. 1992).

In general, a written opinion of counsel should reflect a knowledge and understanding of the patent, its specification, claims, and prosecution history as well as the underlying technology. Opinions on infringement and validity issues should address, to the extent relevant, the construction of the claims which the court will determine in *Markman* proceedings.[60] The opinion should also duly consider the relevant case law on the issues under consideration, including the burdens of proof and evidentiary standards required for each defense addressed.[61] Finally, the opinion should be written with two audiences in mind: (1) the client who requested the advice reflected in the opinion and (2) the trier of fact, who will be evaluating the opinion as a defense to a charge of willful infringement, and a court, which will be deciding whether to enhance damages. The opinion should thus be clear and comprehensible to both potential audiences, while presenting a comprehensive and competent basis for the conclusions reached.

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60. As discussed above, because a court may limit the scope of waiver of privilege to the particular subject matter of the opinion on which a defendant relies, it may be prudent to obtain separate opinions for different potential defenses. *See supra* note 50.

61. For example, the opinion should take into consideration that the patent owner must prove infringement by a preponderance of the evidence, while the patent challenger must prove invalidity by clear-and-convincing evidence. Novartis Pharm. Corp. v. Par Pharm., Inc., 48 F. Supp. 3d 733 (D. Del. 2014) (noting that the patent owner has the burden of proving infringement by a preponderance of the evidence and the challenger has the burden of proving invalidity by clear-and-convincing evidence); Avanir Pharm., Inc. v. Actavis S. Atl. LLC, 36 F. Supp. 3d 475 (D. Del. 2014) (holding that the plaintiffs proved by a preponderance of the evidence that certain asserted claims of the patent are infringed and that the defendants had failed to prove by clear-and-convincing evidence that certain claims of the patents are invalid); Microsoft Corp. v. i4i Ltd. P'ship, 564 U.S. 91 (2011) (the Court adopted the "clear and convincing evidence" standard to prove invalidity, stating that the Patent Act's enactment in 1952 should be read as implicitly incorporating such standard).

unauthorized conduct that either induces another to directly infringe or contributes to the direct infringement by another. While direct infringement does not require intent or knowledge of the patent, there are intent and/or knowledge elements to inducing infringement and contributory infringement.[6]

In addition, infringement can either be "literal" or under the "doctrine of equivalents." Literal infringement requires that "every limitation set forth in a claim must be found in an accused product, exactly."[7] The judicially created doctrine of equivalents allows for a finding of infringement when, although an accused act fails to literally meet an element of the claim, it nevertheless includes an "equivalent" to that element or elements.[8] The doctrine of equivalents was created to "prevent[ ] an accused infringer from avoiding liability for infringement by changing only minor or insubstantial details of a claimed invention while retaining the invention's essential identity."[9]

§ 10:2 Acts Constituting Infringement

Section 271 of the Patent Laws specifies a number of acts that, when unauthorized by the patent owner, constitute infringement:

§ 10:2.1 Direct Infringement

Section 271(a) "sets forth the requirements for a claim of direct infringement of a patent."[10] Section 271(a) provides that one who "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent."[11] There is no intent element to direct infringement and

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6. See *infra* section 10:2.1.
7. Southwall Techs. v. Cardinal IG Co., 54 F.3d 1570, 1575 (Fed. Cir. 1995).
8. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997).
9. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558, 564 (Fed. Cir. 2000), *vacated on other grounds*, 535 U.S. 722 (2002).
10. NTP, Inc. v. Research In Motion, Ltd., 418 F.3d 1282, 1313 (Fed. Cir. 2005), *cert. denied*, 546 U.S. 1157 (2006).
11. 35 U.S.C. § 271(a). In general, direct infringement under § 271(a) is based on the conduct of a single entity. "A party cannot avoid infringement, however, simply by contracting out steps of a patented process to another." BMC Res., Inc. v. Paymentech, 498 F.3d 1373, 1381 (Fed. Cir. 2007). "In those cases, the party in control would be liable for direct infringement." *Id.* (affirming summary judgment of non-infringement "absent evidence that Paymentech also provides instructions or directions regarding the use of those data").

one can infringe without being aware of the patent's existence.[12] In addition, "[s]ection 271(a) is only actionable against patent infringement that occurs within the United States."[13]

§ 10:2.2 Inducing Infringement

[A] Elements of Inducing Infringement

Section 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer."

Inducing infringement requires proof that direct infringement has occurred, along with intent to induce that infringement.[14] In other words, inducing infringement "requires proof that the accused infringer knowingly aided and abetted another's direct infringement of the patent."[15] "While proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice."[16] The Federal Circuit has held that "[a] crucial element of induced infringement is that the inducer must have actual or constructive knowledge of the patent."[17]

The Supreme Court in *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*,[18] in applying the standard for inducing patent infringement in a copyright infringement case, held that inducement can be "shown by clear expression or other affirmative steps taken to

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12. Intel Corp. v. U.S. Int'l Trade Comm'n, 946 F.2d 821, 832 (Fed. Cir. 1991).
13. *NTP, Inc.*, 418 F.3d at 1313.
14. Liquid Dynamics Corp. v. Vaughan Co., 449 F.3d 1209, 1222 (Fed. Cir. 2006) ("A finding of inducement requires both an underlying instance of direct infringement and a requisite showing of intent.") (quoting Fuji Photo Film Co. v. Jazz Photo Corp., 394 F.3d 1368, 1377 (Fed. Cir. 2005)); Limelight Networks, Inc. v. Akamai Techs., Inc., 134 S. Ct. 2111 (2014) ("our case law leaves no doubt that inducement liability may arise 'if, but only if, [there is] . . . direct infringement'") (quoting Aro Mfg. Co. v. Convertible Top Replacement Co., 365 U.S. 336, 341 (1961) (emphasis omitted)).
15. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1363 (Fed. Cir. 2003) (quoting Rodime PLC v. Seagate Tech., Inc., 174 F.3d 1294, 1306 (Fed. Cir. 1999)); *see also* MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp., 420 F.3d 1369, 1378 (Fed. Cir. 2005) (the patentee must show that the "alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement") (quoting Minn. Mining & Mfg. Co. v. Chemque, Inc., 303 F.3d 1294, 1305 (Fed. Cir. 2002)).
16. Water Techs. Corp. v. Calco, Ltd., 850 F.2d 660, 668 (Fed. Cir. 1988).
17. Insituform Techs., Inc. v. Cat Contracting, Inc., 161 F.3d 688, 695 (Fed. Cir. 1998).
18. Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd., 545 U.S. 913 (2005).

foster infringement," and one is then "liable for the resulting acts of infringement by third parties."[19] In *DSU Medical Corp. v. JMS Co.*,[20] the Federal Circuit, en banc, relied on *Grokster* and clarified that "inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities."[21]

In *Global-Tech Appliances, Inc. v. SEB S. A.*,[21.1] the U.S. Supreme Court held that inducing infringement required not only knowledge of the patent, but "knowledge that the induced acts constitute patent infringement." The Supreme Court in *Global-Tech* further held that a defendant's knowledge could be found under the doctrine of "willful blindness," which requires that "(1) the defendant must subjectively believe that there is a high probability that a fact exists and (2) the defendant must take deliberate actions to avoid learning of that fact."[21.2]

In *Commil USA LLC v. Cisco Systems, Inc.*,[21.3] the U.S. Supreme Court reaffirmed its *Global-Tech* decision that inducement of infringement "requires proof the defendant knew the acts were infringing,"[21.4] but also held that a good faith belief that a patent is invalid is not a defense to a claim of inducement of infringement. The Court based its decision in *Commil* by reasoning that "'[v]alidity and infringement are distinct issues, bearing different burdens, different presumptions, and different evidence.'"[21.5] Thus, the Court held that "invalidity is not a defense to infringement, it is a defense to liability. And because

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19. *Id*. at 919.
20. DSU Med. Corp. v. JMS Co., 471 F.3d 1293 (Fed. Cir. 2006).
21. *Id*. at 1306. *See also* Ricoh Co. v. Quanta Comput. Inc., 550 F.3d 1325, 1340–43 (Fed. Cir. 2008) (material issue of fact as to specific intent for active inducement can be based on use of components that have no other use "than the performance of infringing functions under normal use conditions"). Evidence of the existence or absence of an opinion of counsel may be relevant to the specific intent element of inducing infringement. *See DSU*, 471 F.3d at 1307 (counsel's noninfringement opinion considered evidence that there was no intent to infringe); Broadcom Corp. v. Qualcomm Inc., 543 F.3d 683, 699–700 (Fed. Cir. 2008) ("[W]e . . . hold that the failure to procure [an opinion of counsel] may be probative of intent in this context. It would be manifestly unfair to allow opinion-of-counsel evidence to serve an exculpatory function . . . and yet not permit patentees to identify failures to procure such advice as circumstantial evidence of intent to infringe.").
21.1. Global-Tech Appliances, Inc. v. SEB S. A., 131 S. Ct. 2060, 2068 (2011).
21.2. *Id*. at 2070.
21.3. Commil USA, LLC v. Cisco Sys., Inc., 135 S. Ct. 1920 (2015).
21.4. *Id*. at 1928.
21.5. *Id*. at 1929 (quoting Commil USA, LLC v. Cisco Sys., Inc., 720 F.3d 1361, 1374 (opinion of Newman, J.)).

of that fact, a belief as to invalidity cannot negate the scienter required for induced infringement."[21.6]

[B] Inducement Under Section 271(e)(2)

The Federal Circuit has held that claims for inducing infringement of method of treatment claims can be asserted against generic drug manufacturers under section 271(e)(2) of title 35 based on the filing of an Abbreviated New Drug Application (ANDA) where the ANDA is for an FDA-approved use that is claimed in the patent.[22] However, "pursuant to section 271(e)(2), a method of use patent holder may not sue an ANDA applicant for induced infringement of its patent, if the ANDA applicant is not seeking FDA approval for the use claimed in the patent and if the use claimed in the patent is not FDA-approved."[23] In addition, in a claim for inducing infringement of a method of treatment claim under section 271(b), "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven."[24] There must be evidence that the ANDA filer "has or will promote or encourage doctors to infringe" the asserted method of treatment patent.[25]

21.6. *Id*. The Supreme Court in *Commil* did not comment on Federal Circuit decisions to the effect that a good faith belief that a patent is not infringed is a defense to a charge of inducing infringement (*see supra* note 21), although the implication of its decision is that a good faith belief of non-infringement can be used as a defense to a charge of inducing infringement.

22. Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322, 1330–32 (Fed. Cir. 2003) ("[A] patent holder asserting infringement of a patent that claims a FDA-approved method of use for which an ANDA seeks approval will, in many instances, have to prove induced infringement. Therefore, section 271(e)(2) may support an action for induced infringement."). *See also supra* section 8:1.4[B][3][b].

23. *Allergan*, 324 F.3d 1332; *see also Warner-Lambert*, 316 F.3d at 1354–55 ("it is not an act of infringement [under section 271(e)(2)] to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent").

24. *Warner-Lambert*, 316 F.3d at 1364.

25. *Id*.; Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 845 F.3d 1357, 1369 (Fed. Cir. 2017) ("Where the product labeling already encourages infringement of the asserted claims, as it does here, a physician's decision to give patients even more specific guidance is irrelevant to the question of inducement."); Sanofi v. Watson Labs. Inc., 875 F.3d 636, 645 (Fed. Cir. 2017) (finding induced infringement when the label "directs medical providers to information identifying the desired benefit for only patients with the patent-claimed risk factors" and "[t]here was considerable testimony that this label encourages . . . administration of the drug to those

§ 10:2.3 Contributory Infringement

Liability for contributory infringement is governed by section 271(c), which provides:

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.[26]

Contributory infringement under section 271(c) creates a cause of action for infringement based on the sale in the United States of a component of a patented machine or combination even though the component itself does not infringe a claim of the patent. To prove contributory infringement, the patent owner must establish that direct infringement has occurred.[27] The patent owner must also prove that the defendant "'knew that the combination for which its components were especially made was both patented and infringing' and that defendant's components have 'no substantial non-infringing

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patients"); AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1059–60 (Fed. Cir. 2010) (a label instructing patients to use product in an infringing manner was adequate proof of inducement even though some users may not follow the instructions); GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 976 F.3d 1347, 1352–56 (Fed. Cir. 2020) (concluding that circumstantial evidence in the form of promotional materials, press releases, product catalogs and FDA labels supported inducement of infringement of a patented indication by a marketed generic drug, both during the time when the patented indication was carved out of the generic label and after the FDA required the generic label to include the patented indication); GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 7 F.4th 1320, 1326 (Fed. Cir. 2021), *en banc reh'g denied*, 25 F.4th 949 (Fed. Cir. 2022) (noting that the earlier *GlaxoSmithKline LLC v. Teva Pharm. USA, Inc.* decision was "a case in which substantial evidence supports a jury finding that the patented use was on the generic label at all relevant times and that, therefore, Teva failed to carve out all patented indications" and that "[t]his narrow, case-specific review of substantial evidence does not upset the careful balance struck by the Hatch-Waxman Act regarding section viii carve-outs.").

26. 35 U.S.C. § 271(c).

27. Golden Blount, Inc. v. Robert H. Peterson Co. (*Golden Blount I*), 365 F.3d 1054, 1061 (Fed. Cir. 2004).

uses.'"[28] In addition, the patent owner must show that the accused contributory infringer had knowledge of the patent.[29]

§ 10:2.4 Section 271(f): Infringement by Shipment from the United States of Component of a Patented Invention to Be Assembled Abroad

Section 271(f) provides:

> (1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.
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> (2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.[30]

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28. Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1312 (Fed. Cir. 2005) (citation omitted); *see also* Golden Blount, Inc. v. Robert H. Peterson Co. (*Golden Blount II*), 438 F.3d 1354, 1362–63 (Fed. Cir. 2006). In Ricoh Co. v. Quanta Comput. Inc., 550 F.3d 1325, 1336–40 (Fed. Cir. 2008), the Federal Circuit held that contributory infringement is not avoided by bundling a component that has no substantially non-infringing use with other components that do have substantial non-infringing uses.
29. Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1469 n.4 (Fed. Cir. 1990) ("Although not clear on the face of the statute, subsequent case law held that § 271(c) required not only knowledge that the component was especially made or adapted for a particular use but also knowledge of the patent which proscribed that use."); *see also Golden Blount I*, 365 F.3d at 1061 (the patentee "must show that [the accused contributory infringer] 'knew that the combination for which its components were especially made was both patented and infringing'") (citation omitted).
30. 35 U.S.C. § 271(f). See *supra* section 7:1.4[A] for a discussion of section 271(f) in the context of research tool patents.

Section 271(f) was enacted to overrule prior U.S. Supreme Court authority holding that the assembly of a patented machine outside the United States from components shipped from the United States was not an act of infringement.[31] The Federal Circuit has held that infringement under section 271(f) is not limited to patent claims covering physical products, but can also reach the supply of components used in patented methods and processes.[32] The U.S. Supreme Court held in *WesternGeco LLC v. ION Geophysical Corp.* that lost profits are available as a remedy in cases brought under section 271(f).[32.1]

§ 10:2.5 Section 271(g): Infringement of a U.S. Process Patent by Importing into the United States or Offering to Sell, Selling, or Using a Product Made by the Patented Process

Section 271(g) provides:

> Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after—
>
> (1) it is materially changed by subsequent processes; or
>
> (2) it becomes a trivial and nonessential component of another product.[33]

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31. Deepsouth Packing Co. v. Laitrim Corp., 406 U.S. 518 (1972).
32. Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co., 425 F.3d 1366, 1380 (Fed. Cir. 2005) ("because § 271(f) governs method/process inventions, Shell's exportation of catalysts may result in liability under § 271(f)"); *see also* Eolas Techs. Inc. v. Microsoft Corp., 399 F.3d 1325, 1338–39 (Fed. Cir. 2005) (stating that "every form of invention eligible for patenting falls within the protection of section 271(f)" in holding that software code could be a "component" for purposes of § 271(f)). *But see* Standard Havens Prods., Inc. v. Gencor Indus., Inc., 953 F.2d 1360, 1374 (Fed. Cir. 1991) (holding that section 271(f) did not apply in alleged infringement of a method claim for making asphalt by sale to foreign customers of an apparatus for carrying out the method).
32.1. WesternGeco LLC v. ION Geophysical Corp., 138 S. Ct. 2129, 2138–39 (2018).
33. 35 U.S.C. § 271(g).

Under section 271(g), the importation into the United States, or offer to sell, sale, or use within the United States of a product made by a process patented in the United States is an act of infringement.[34] Section 271(g) does not require that the product have been made during the term of the process patent, as long as a specified act occurs during the term of the patent.[35]

Section 271(g) provides that a product will not be considered to be made by the patented process if (1) the product is "materially changed by subsequent processes," or (2) the product "becomes a trivial and nonessential component of another product."[36]

Infringement under 271(g) is limited to the manufacture of physical goods and does not extend to data or knowledge that is generated by a patented process, such as a screening method.[37] Therefore, the transmission into the United States of data generated abroad from a process patented in the United States, such as an assay, has been held not to be an act of infringement under section 271(g).[38]

§ 10:2.6 "Divided" Infringement of Method Claim

Infringement requires proof that all of the elements of a claim are practiced. For method claims, it is possible that different actors can perform different steps of the claimed method such that no one actor performs all of the recited steps.[38.1] In such a case, the courts have had to determine whether there can be liability for infringement of a method claim where the recited steps are "divided" among more than one actor.[38.2]

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34. Bio-Tech. Gen. Corp. v. Genentech, Inc., 80 F.3d 1553, 1560 (Fed. Cir. 1996). See *supra* section 7:1.4[B] for a discussion of section 271(g) in the context of research tool patents.
35. *Id*.
36. 35 U.S.C. § 295 provides that in a case alleging infringement under section 271(g), if a "court finds (1) that a substantial likelihood exists that the product was made by the patented process, and (2) that the plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable to so determine, the product shall be presumed to have been so made, and the burden of establishing that the product was not made by the process shall be on the party asserting that it was not so made."
37. Bayer AG v. Housey Pharm., Inc., 340 F.3d 1367, 1378 (Fed. Cir. 2003).
38. *Id*.
38.1. Mark A. Lemley et al., *Divided Infringement Claims*, 33 AIPLA Q.J. 255 (2005).
38.2. Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1310, 1311 (Fed. Cir. 2005) (surgical implants with an interface "operatively joined" to a part of the bone not infringed by the manufacturer because that party "d[id] not itself make [the] apparatus" joined to the bone); *cf.* LifeNet Health v. LifeCell Corp., 837 F.3d 1316, 1326 (Fed. Cir.

In its *Muniauction* decision, the Federal Circuit held that direct infringement under 35 U.S.C. § 271(a) could be found only where one party exercises "control or direction" over the other parties practicing the steps of the claimed method:

> [W]here the actions of multiple parties combine to perform every step of a claimed method, the claim is directly infringed only if one party exercises "control or direction" over the entire process such that every step is attributable to the controlling party, i.e., the "mastermind.". . . At the other end of this multi-party spectrum, mere "arms-length cooperation" will not give rise to direct infringement by any party.[38.3]

The *Muniauction* court cited its prior decision in *BMC Resources*, which had held that

> [w]hen a defendant participates in or encourages infringement but does not directly infringe a patent, the normal recourse under the law is for the court to apply the standards for liability under indirect infringement. Indirect infringement requires, as a predicate, a finding that some party amongst the accused actors has committed the entire act of direct infringement.[38.4]

In addition, the court in *BMC* held that "the law imposes vicarious liability on a party for the acts of another in circumstances showing that the liable party controlled the conduct of the acting party."[38.5]

In 2012, in *Akamai Technologies, Inc. v. Limelight Networks, Inc.*, the Federal Circuit, sitting en banc, overruled *BMC Resources* and held that a party could be held liable for inducing infringement under 35 U.S.C. § 271(b) in cases in which no one party performed, or controlled the performance of, all of the steps of a claimed method, but where a party knowingly induced others to practice the steps necessary for all of the steps to have been practiced.[38.6] However, the

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2016) ("[T]he non-removal [of placitizer prior to implanting] limitation clarifies that the recited plasticizer has not been removed and, because the plasticizer is biocompatible, can remain in the internal matrix of the tissue graft during transplantation, i.e., it need not ever be removed. This limitation is met without action by a third party. It is satisfied by the graft from the moment it is manufactured unless and until the plasticizer is removed from the internal matrix before transplantation.").

38.3. Muniauction, Inc. v. Thomson Corp., 532 F.3d 1318, 1329 (Fed. Cir. 2008).

38.4. BMC Res., Inc. v. Paymentech, L.P., 498 F.3d 1373, 1379 (Fed. Cir. 2007).

38.5. *Id*.

38.6. Akamai Techs., Inc. v. Limelight Networks, Inc., 692 F.3d 1301 (Fed. Cir. 2012) (en banc).

U.S. Supreme Court granted certiorari and reversed and remanded the en banc Federal Circuit decision in *Limelight Networks, Inc. v. Akamai Technologies, Inc.*[38.7] Assuming the correctness of the Federal Circuit's *Muniauction* decision, the Supreme Court held that "there has simply been no infringement of the method . . . because the performance of all the patent's steps is not attributable to any one person. . . . [W]here there has been no direct infringement, there can be no inducement of infringement."[38.8]

Thus, the Supreme Court in *Limelight* rejected the Federal Circuit's en banc holding that there can be divided infringement for inducement of infringement under section 271(b), even when there can be no divided infringement for direct infringement under section 271(a) because no one party directed or controlled the performance of all of the method steps.

> [T]he reason Limelight could not have induced infringement under § 271(b) is not that no third party is *liable* for direct infringement; the problem, instead, is that no direct infringement was *committed*. *Muniauction* (which, again, we assume to be correct) instructs that a method patent is not directly infringed—and the patentee's interest is thus not violated—unless a single actor can be held responsible for the performance of all steps of the patent. Because Limelight did not undertake all steps of the '703 patent and cannot otherwise be held responsible for all those steps, respondents' rights have not been violated.[38.9]

On remand from the Supreme Court, the Federal Circuit stated that it "will hold an entity responsible for others' performance of method steps in two sets of circumstances: (1) where that entity directs or controls others' performance, and (2) where the actors form a joint enterprise."[38.10] The Federal Circuit also stated "that liability under § 271(a) can also be found when an alleged infringer conditions participation in an activity or receipt of a benefit upon performance of a step or steps of a patented method and establishes the manner or timing of that performance."[38.11] The Federal Circuit has since then applied these factors as part of a two-prong test to determine "divided" infringement liability.[38.12]

38.7. Limelight Networks, Inc. v. Akamai Techs., Inc., 134 S. Ct. 2111 (2014).
38.8. *Id*. at 2117.
38.9. *Id*. at 2118–19.
38.10. Akamai Tech., Inc. v. Limelight Networks, Inc., 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc).
38.11. *Id*. at 1023.
38.12. *See* Medgraph, Inc. v. Medtronic, Inc., 843 F.3d 942, 948 (Fed. Cir. 2016) (affirming grant of summary judgment that Medtronic did not control customer use of its diagnostic equipment in an infringing manner

In *Travel Sentry, Inc. v. Tropp*, the Federal Circuit stressed the importance of properly defining the conditioned activity, the benefits received, and the required third party's conduct.[38.13] The court further underscored that the two-prong test is likely to be met when "a third party hoping to obtain access to certain benefits can only do so if it performs certain steps identified by the defendant, and does so under terms prescribed by the defendant."[38.14]

§ 10:3 Infringement Under the Doctrine of Equivalents

Even if an accused product or process does not literally satisfy each element of a claim, infringement can nevertheless be found under the "doctrine of equivalents." Infringement requires the patent owner to show by a preponderance of the evidence that "the accused product or process contain[s] elements identical or equivalent to each claimed element of the patented invention."[39] The doctrine of equivalents was judicially created to "protect the inventor not only from those who produce devices falling within the literal claims of the patent but also from copyists who 'make unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim, and hence outside the reach of the law.'"[40] However, there is no intent element to infringement under the doctrine of equivalents and one can infringe under the doctrine of equivalents without knowledge of the patent or an attempt to copy the patented invention.[41]

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because it did "not deny users the ability to use [its system] without performance of the claim step of ensuring detachment of the measuring device from the patient after each measurement" and Medtronic "freely permits using [its system] without performing [the claimed] synchronization, and it denies no benefit to such users for their choices to do so"); Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 845 F.3d 1357, 1362–68 (Fed. Cir. 2017) (upholding district court's finding of infringement by physicians who administered vitamin B12 and pemetrexed and guided patients to self-administer folic acid, of claim requiring administration of all three compounds, because the label recites the importance of taking folic acid and states physicians may withhold pemetrexed from patients based on the results of blood tests).

38.13. Travel Sentry, Inc. v. Tropp, 877 F.3d 1370, 1380–81 (Fed. Cir. 2017).

38.14. *Id.* at 1380.

39. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997).

40. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 732–33 (2002) (citation omitted).

41. *Warner-Jenkinson Co.*, 520 U.S. at 36 ("intent plays no role in the application of the doctrine of equivalents").

§ 10:3.1 The "All Elements" Rule

In a determination under the doctrine of equivalents, "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole. It is important to ensure that the application of the doctrine, even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety."[42] As discussed below, the requirement of finding an equivalent for each recited claim element in an accused product or process is an important limitation on the doctrine of equivalents.

However, "[t]he doctrine of equivalents does not require a one-to-one correspondence between components of the accused device and the claimed invention."[43] Accordingly, "[a]n accused device may infringe under the doctrine of equivalents even though a combination of its components performs a function performed by a single element in the patented invention" as long as "[t]he accused device . . . contain[s] *every* limitation or its equivalent."[44] By the same token, "[e]quivalency can also exist when separate claim limitations are combined into a single component of the accused device."[45]

§ 10:3.2 Tests for Equivalence

Infringement by equivalence is an issue of fact.[46] In *Warner-Jenkinson*, the Supreme Court eschewed any particular linguistic formulation of a test for equivalence, stating that its primary concern is "[a] focus on individual elements and a special vigilance against allowing the concept of equivalence to eliminate completely any such elements."[47] The Court discussed two methodologies for determining equivalence. One way is by showing that any differences between the claimed element and the corresponding aspect of the accused product or process are "insubstantial." The other method discussed by the Court focuses on whether the claim element and the corresponding aspect in the accused product or process performs substantially the

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42. *Id*. at 29.
43. Dolly, Inc. v. Spalding & Evenflo Cos., 16 F.3d 394, 398 (Fed. Cir. 1994).
44. *Id*. at 398.
45. *Id*.
46. Interactive Pictures Corp. v. Infinite Pictures, Inc., 274 F.3d 1371, 1376 (Fed. Cir. 2001). As a fact issue, equivalence may be decided by a jury. *Id*. The Court in *Warner-Jenkinson* refused to disturb the Federal Circuit's decision that the doctrine of equivalence is an equitable issue. *Warner-Jenkinson Co.*, 520 U.S. at 38–39.
47. *Warner-Jenkinson Co.*, 520 U.S. at 40.

same function, in substantially the same way, to achieve substantially the same result.[48]

According to the Supreme Court, "the particular linguistic framework used is less important than whether the test is probative of the essential inquiry: Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention?"[49] Accordingly, whichever test is used to determine equivalence is to be applied to each claim element that is not literally satisfied by the accused product or process.

Although in general both tests for equivalence may be used, the "function, way, result" (FWR) test is not always suitable for certain claims.

> Especially when evaluating an equivalents dispute dealing with chemical compositions having many components, chemical compounds with many substituents . . . and those having a medical or biological use, it is often not clear what the "function" or "way" is for each claim limitation. How a particular component of a composition, or a substituent of a compound, functions in a human or animal body, or in what way, may not be known or even knowable.[49.1]

And "[i]n some cases, 'way and 'function' may be synonymous."[49.2] "[T]he substantial differences test may be more suitable than FWR for determining equivalence in the chemical arts."[49.3]

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48. *Id*. The "triple identity" test was discussed in Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950), where the Court stated that "a patentee may invoke this doctrine to proceed against the producer of a device 'if it performs substantially the same function in substantially the same way to obtain the same result'" (citations omitted). Based on the Court's *Warner-Jenkinson* decision, it is apparent that the test for equivalence must be performed for each claim element that is not literally satisfied by the accused product or process. *See also* Pozen Inc. v. Par Pharm., Inc., 696 F.3d 1151 (Fed. Cir. 2012) (claim to pharmaceutical product requiring at least 90% of one active ingredient in a specific layer could be infringed under the doctrine of equivalents by product with layer containing 85% of that active ingredient where that layer performed substantially the same function, in substantially the same way, to achieve substantially the same result).

49. *Warner-Jenkinson Co.*, 520 U.S. at 40.

49.1. Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 867 (Fed. Cir. 2017).

49.2. *Id*. at 868.

49.3. *Id*. at 869. In Amgen Inc. v. Sandoz, Inc., 923 F.3d 1023, 1029 (Fed. Cir. 2019), the court held that the defendant's "one-step, one solution" protein purification process "works in a substantially different way from the claimed three-step, three solution process." In reaching its decision,

§ 10:3.3 Limitations on the Doctrine of Equivalents

The Supreme Court has stated that "[t]here can be no denying that the doctrine of equivalents, when applied broadly, conflicts with the definitional and public-notice functions of the statutory claiming requirement."[50] As discussed below, there are a number of limitations imposed on the application of the doctrine of equivalents.

[A] Prosecution History Estoppel

Actions taken during the pendency of a patent application before the PTO, known as "prosecution history," may serve to limit a patent owner's recourse to the doctrine of equivalents. Prosecution history estoppel can arise when the patentee relinquishes claim coverage during prosecution, either by amendment or argument.[51]

[A][1] Estoppel by a Claim Amendment Made for Substantial Reason Related to Patentability

The Supreme Court, in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*,[52] held that "a narrowing amendment made to satisfy any requirement of the Patent Act may give rise to an estoppel."[53] This includes amendments to avoid prior art and to satisfy the written description and enablement requirements of section 112. When no explanation for a narrowing amendment is given, there is a presumption "that the patent applicant had a substantial reason related to patentability" for making the amendment.[54]

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the original panel decision stated that "[t]he doctrine of equivalents applies only in exceptional cases." *Id*. On a petition for rehearing, the panel deleted this language from its decision but otherwise left its original decision intact. Amgen Inc. v. Sandoz Inc., 776 F. App'x 707 (Fed. Cir. Sept. 3, 2019).

50. *Warner-Jenkinson Co.*, 520 U.S. at 29.
51. Eagle Comtronics, Inc. v. Arrow Commc'n Labs., Inc., 305 F.3d 1303, 1315 (Fed. Cir. 2002).
52. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002).
53. *Id*. at 736. The Supreme Court clarified its earlier decision in *Warner-Jenkinson Co.*, 520 U.S. at 33, which held that estoppel applies to amendments made for "a substantial reason related to patentability," but did not definitively state that a narrowing amendment to overcome a section 112 rejection could give rise to estoppel.
54. *Warner-Jenkinson Co.*, 520 U.S. at 33.

[A][1][a] Presumption of General Disclaimer of Equivalents; Rebutting the Presumption

Once there is a determination that a claim was narrowed for a substantial reason related to patentability, the court must determine whether there has been a surrender of the particular equivalent in question. In *Festo*, the Supreme Court held that "[a] patentee's decision to narrow his claims through amendment may be presumed to be a general disclaimer of the territory between the original claim and the amended claim."[55]

The Supreme Court held that in order to rebut the presumption of surrender of equivalents, "[t]he patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent."[56] In discussing ways in which the presumption could possibly be rebutted, the Court stated the following grounds:

- "The equivalent may have been unforeseeable at the time of the application."[57]
- "[T]he amendment may bear no more than a tangential relation to the equivalent in question."[58]
- "[T]here may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question."[59]

[A][1][a][i] Unforeseeability of Equivalent

Rebuttal of the presumption of prosecution history estoppel based on the "unforeseeability" of the equivalent can be illustrated by two cases involving alleged infringement of the same pharmaceutical formulation patent by two different generic drug companies.

In *Glaxo Wellcome, Inc. v. Impax Laboratories, Inc.*,[60] the Federal Circuit affirmed a grant of summary judgment of non-infringement of a patent claiming a sustained release formulation for the drug bupropion. The application for patent was filed with original claims that recited tablets providing particular plasma concentration levels of bupropion over twenty-four hours and specific bupropion release

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55. *Festo Corp.*, 535 U.S. at 740.
56. *Id*. at 741.
57. *Id*. at 740.
58. *Id*.
59. *Id*. at 740–41.
60. Glaxo Wellcome, Inc. v. Impax Labs., Inc., 356 F.3d 1348 (Fed. Cir. 2004).

rates, but which did not recite a particular release mechanism for the drug.[61] The patent examiner rejected the claims for lack of enablement under 35 U.S.C. § 112 because the specification only disclosed the use of hydroxypropyl methylcellulose (HPMC) to achieve a sustained release of the drug and that the disclosure "could not support a broad generic claim to other sustained release mechanisms."[62] The claims were allowed after they were amended to specifically recite HPMC as the sustained release mechanism. Relying on the Supreme Court's *Festo* decision,[63] the Federal Circuit held that this narrowing amendment created a presumption that the patentee had surrendered the range of equivalence between the original and the amended claims to preclude reliance on the doctrine of equivalents to cover defendant's formulation, which used as a sustained release mechanism hydroxypropyl cellulose (HPC), which was known at the time of the amendment to be equivalent to HPMC.[64]

The Federal Circuit concluded that the presumption under *Festo* that the claim amendment surrendered equivalents to cover HPC was not rebutted because the evidence showed that one skilled in the art at the time of the amendment would have found it foreseeable to use HPC as a suitable sustained release agent for bupropion.[65] In particular, a number of references submitted by applicants during prosecution discussed the use of both HPC and HPMC as hydrogel forming materials that are used in sustained release formulations. The court stated that "[t]hese references suggest that Glaxo was aware of these potential hydrogel equivalents at the time of submitting the '798 patent claims and later amending those claims to recite only HPMC. This court, therefore, discerns from this record that ordinarily skilled artisans at the time would have considered HPC a suitable sustained release agent for bupropion."[66]

In contrast, in *SmithKline Beecham Corp. v. Excel Pharmaceuticals, Inc.*,[67] another case involving the same patent asserted against a different generic drug company's sustained release formulation of bupropion, the Federal Circuit reversed a grant of summary judgment of non-infringement where the excipient polyvinyl alcohol (PVA) was substituted for the claimed HPMC ingredient. Although the court

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61. *Id*. at 1352.
62. *Id*.
63. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002).
64. *Glaxo Wellcome Inc.*, 356 F.3d at 1351–52.
65. *Id*. at 1355–56.
66. *Id*.
67. SmithKline Beecham Corp. v. Excel Pharm., Inc., 356 F.3d 1357 (Fed. Cir. 2004).

concluded that the claim had been narrowed for reasons of patentability, it remanded for a determination as to whether the use of PVA in lieu of the claimed HPMC would have been foreseeable in the sustained release formulation, noting that unforeseeability of the substitution can be used to rebut the presumption precluding recourse to the doctrine of equivalents.[68] In particular, the court stated that if the use of PVA were determined to be a "later-developed technology" (that is, a "technology that was not known in the relevant art"), then "it would not have been foreseeable."[69] The court stated that "the quintessential example of an enforceable equivalent, after-arising technology, would always be unclaimable new matter. In that sense, the doctrine of equivalents compensates for the patentee's inability to claim unforeseeable new matter."[70]

[A][1][a][ii] Amendment Bears "No More than a Tangential Relation" to Equivalent

The presumption that an amendment to a claim results in the surrender of all the territory between the original and amended claim limitation can be overcome by the patentee showing that the amendment was "tangential" to the equivalent. An example of such a tangential amendment (albeit in a non-pharmaceutical case) was found in *Primos, Inc. v. Hunter's Specialties, Inc.*,[71] which involved a patent to a device used by hunters to imitate animal calls. The patent claim at issue had been amended to require that a plate be "differentially spaced" above a membrane. The accused device substituted a dome for the plate, but the dome was differentially spaced above a membrane. The court held that the addition of the "differentially spaced" limitation to the claim did not surrender the range of equivalence to cover defendant's use of a dome (instead of the claimed plate) because the amendment was "merely tangential to the contested element in the accused device."[72] In other words, the amendment which added the "differentially spaced" limitation was tangential to the defendant's substitution of a dome for the plate recited in the claim.

In a pharmaceutical case, the Federal Circuit has held that the tangential exception applied in *Eli Lilly & Co. v. Hospira, Inc.*, which involved a patent for improved methods of administering the antifolate, pemetrexed disodium.[72.1] In determining whether the tangential

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68. *Id*. at 1363–65.
69. *Id*. at 1363.
70. *Id*. at 1364.
71. Primos, Inc. v. Hunter's Specialties, Inc., 451 F.3d 841 (Fed. Cir.), *reh'g denied*, No. 05-1001, 2006 U.S. App. LEXIS 20750 (Fed. Cir. Aug. 2, 2006).
72. *Id*. at 849.
72.1. Eli Lilly & Co. v. Hospira, Inc., 933 F.3d 1320, 1330–34 (Fed. Cir. 2019).

exception to the doctrine of equivalents applied regarding a different antifolate, ditromethamine, the court disagreed with appellant's interpretation of the tangential exception, finding it "in particular, too rigid."[72.2] During prosecution, the patentee had amended the claim at issue to reference "pemetrexed," as opposed to the more general term, "an antifolate."[72.3] Evidence was adduced showing that the patentee had done this to avoid anticipation by a reference that claimed usage of the antifolate, methotrexate.[72.4] The court therefore concluded that "the particular type of salt to which pemetrexed is complexed relates only tenuously to the reason for the narrowing amendment, which was to avoid" the prior art that used methotrexate.[72.5] The court therefore held that the patentee's amendment was "merely tangential to pemetrexed ditromethamine because the prosecution history, in view of the . . . patent itself, strongly indicates that the reason for the amendment was not to cede other, functionally identical, pemetrexed salts."[72.6]

[A][1][a][iii] Some Other Reason

By allowing that "there may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question,"[73] the Supreme Court apparently intended to provide the lower courts with the flexibility to determine other bases for a patentee to rebut the presumption of surrender of equivalents. The Federal Circuit has stated that this category "must be a narrow one."[74] The court further stated that this criterion "may be satisfied when there was some reason, such as the shortcomings of language, why the patentee was prevented from describing the alleged equivalent when it narrowed the claim. When at all possible, determination of the third rebuttal criterion should also be limited to the prosecution history record."[75]

72.2. *Id*. at 1331.
72.3. *See id*. at 1330–31.
72.4. *See id*. at 1331 ("To overcome a clear anticipation, Lilly opted to narrow its original claim 2 and its dependents to more accurately define what it actually invented, an improved method of administering pemetrexed.").
72.5. *Id*.
72.6. *Id*.
73. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 740–41 (2002).
74. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. *(Festo III)*, 344 F.3d 1359, 1370 (Fed. Cir. 2003).
75. *Id*.

[A][2] Estopped by Argument Made During Prosecution

Prosecution history estoppel may be based on arguments made to the PTO during prosecution of a patent application. Thus, the Federal Circuit has held that "[c]lear assertions made during prosecution in support of patentability, whether or not actually required to secure allowance of the claim, may also create an estoppel."[76] However, "[t]o invoke argument-based estoppel, the prosecution history must evince a 'clear and unmistakable surrender of subject matter.'"[77]

[B] Dedication of Described, but Unclaimed Subject Matter: *Johnson & Johnston*

In general, the doctrine of equivalents cannot be used to assert infringement by subject matter that was described, but not claimed, in a patent. Under Federal Circuit authority, disclosed, but unclaimed subject matter is "dedicated" to the public and cannot be later recaptured under the doctrine of equivalents: "[W]hen a patent drafter discloses but declines to claim subject matter . . . this action dedicates that unclaimed subject matter to the public. Application of the doctrine of equivalents to recapture subject matter deliberately left unclaimed would 'conflict with the primacy of the claims in defining the scope of the patentee's exclusive right.'"[78] Whether subject matter is dedicated is viewed from the perspective of one of ordinary skill in the art:

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76. Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1583 (Fed. Cir. 1995).

77. Eagle Comtronics, Inc. v. Arrow Commc'n Labs., Inc., 305 F.3d 1303, 1316 (Fed. Cir. 2002) (citation omitted).

78. Johnson & Johnston Assocs. v. R.E. Serv. Co., 285 F.3d 1046, 1054 (Fed. Cir. 2002) (quoting Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, 1424 (Fed. Cir. 1997)); *see also* Maxwell v. J. Baker, Inc., 86 F.3d 1098, 1107 (Fed. Cir. 1996). In *Maxwell*, the court applied the dedication doctrine, stating:

> A patentee may not narrowly claim his invention and then, in the course of an infringement suit, argue that the doctrine of equivalents should permit a finding of infringement because the specification discloses the equivalents. Such a result would merely encourage a patent applicant to present a broad disclosure in the specification of the application and file narrow claims, avoiding examination of broader claims that the applicant could have filed consistent with the specification.

> [I]f one of ordinary skill in the art can understand the unclaimed disclosed teaching upon reading the written description, the alternative matter disclosed has been dedicated to the public. This 'disclosure-dedication' rule does not mean that any generic reference in a written specification necessarily dedicates all members of that particular genus to the public. The disclosure must be of such specificity that one of ordinary skill in the art could identify the subject matter that had been disclosed and not claimed.[79]

The Federal Circuit's decision in *Johnson & Johnston*[80] demonstrates the application of the dedication doctrine as a limitation on the doctrine of equivalents.[81] The patent in suit was directed to a component for use in the manufacture of printed circuit boards. The specification of the patent described an embodiment that included an aluminum substrate, but also described that in place of aluminum "other metals, such as stainless steel or nickel alloys, may be used."[82] The claims only recited the use of aluminum and the accused product substituted stainless steel for the claimed aluminum. In reversing a judgment of infringement under the doctrine of equivalents, the Federal Circuit held that "[h]aving disclosed without claiming the steel substrates, Johnston cannot now invoke the doctrine of equivalents to extend its aluminum limitation to encompass steel. Thus, Johnston cannot assert the doctrine of equivalents to cover the disclosed but unclaimed steel substrate."[83]

In *Pfizer v. Teva Pharmaceuticals*,[84] the Federal Circuit stated that "the public notice function of patents suggests that before unclaimed subject matter is deemed to have been dedicated to the public, that unclaimed subject matter must have been identified by the patentee as an alternative to a claim limitation."[85] The Federal Circuit held that the patentee did not dedicate the use of the excipient microcrystalline cellulose as an alternative for the claim limitation of a "saccharide." The claimed saccharide element was described as an ingredient that would prevent hydrolysis in a formulation of quinapril, whereas microcrystalline cellulose was only mentioned in the patent as a disintegrating agent and in a description of a prior art, unsuccessful formulation that was outside the scope of the claims.[86] Under

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79. PSC Comput. Prods., Inc. v. Foxconn Int'l, Inc., 355 F.3d 1353, 1360 (Fed. Cir. 2004).
80. *Johnson & Johnston*, 285 F.3d 1046.
81. *Id*. at 1055.
82. *Id*. at 1050.
83. *Id*. at 1055.
84. Pfizer, Inc. v. Teva Pharm. USA, Inc., 429 F.3d 1364 (Fed. Cir. 2005).
85. *Id*. at 1379.
86. *Id*.

these circumstances, the patentee did not dedicate microcrystalline cellulose as an alternative to the saccharide limitation of the claim.

[C] Specific Exclusion: *Dolly v. Spalding*

In *Dolly, Inc. v. Spalding & Evenflo Cos.*,[87] the Federal Circuit has held that "the concept of equivalency cannot embrace a structure that is specifically excluded from the scope of the claims."[88] The Federal Circuit reversed a judgment of infringement under the doctrine of equivalents because the court concluded that the claim at issue excluded the structure of the accused product.[89] The claim covered a child's chair comprising a seat panel, a back panel, two side panels and, as a separate element, a "stable rigid frame" into which the various panels fit. The accused product had four interlocking panels (a seat panel, a back panel, and two side panels) that snapped together to form a child's seat, but lacked the required separate "stable rigid frame." The Federal Circuit held that infringement under the doctrine of equivalents could not be found where the accused product does not have a recited element or an equivalent structure.[90] Thus, in *Dolly*, the claim "excluded" a structure lacking the required separate element of a stable rigid frame, precluding infringement under the doctrine of equivalents.

[D] Vitiation of a Claim Element

"The 'all limitations rule' restricts the doctrine of equivalents by preventing its application when doing so would vitiate a claim limitation."[91] "There is no set formula for determining whether a finding of equivalence would vitiate a claim limitation, and thereby violate the all limitations rule. Rather, courts must consider the totality of the circumstances of each case and determine whether the alleged equivalent can be fairly characterized as an insubstantial change from the claimed subject matter without rendering the pertinent limitation meaningless."[92]

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87. Dolly, Inc. v. Spalding & Evenflo Cos., 16 F.3d 394 (Fed. Cir. 1994).
88. *Id*. at 400.
89. *Id*.
90. *Id*.
91. Primos, Inc. v. Hunter's Specialties, Inc., 451 F.3d 841, 850 (Fed. Cir.), *reh'g denied*, No. 05-1001, 2006 U.S. App. LEXIS 20750 (Fed. Cir. Aug. 2, 2006).
92. Pfizer, Inc. v. Teva Pharm. USA, Inc., 429 F.3d 1364, 1379–80 (Fed. Cir. 2005) (application of doctrine of equivalents found not to vitiate a claim limitation).

In *Pfizer v. Teva Pharmaceuticals*, the patent in suit claimed a formulation of the ACE inhibitor quinapril that recited, among other things, a "saccharide" to inhibit hydrolysis of the active ingredient. In affirming a grant of a preliminary injunction to the patentee, the Federal Circuit agreed with the district court that the defendant's use of microcrystalline cellulose met the "saccharide" limitation literally, and under an alternative claim construction, by equivalence. The Federal Circuit held that if "saccharide" were construed as literally excluding polysaccharides such as microcrystalline cellulose, nevertheless the use of microcrystalline cellulose would be "an insubstantial change from the claimed subject matter without rendering the 'saccharide' limitations meaningless."[93]

[E] The Prior Art

Under Federal Circuit authority, as stated in *Wilson Sporting Goods Co. v. David Geoffrey & Associates*,[94] "there can be no infringement if the asserted scope of equivalency of what is literally claimed would encompass the prior art."[95] The Federal Circuit emphasized that "a patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims. . . . [S]ince prior art always limits what an inventor could have claimed, it limits the range of permissible equivalents of a claim."[96]

The Federal Circuit proposed a test for determining whether recourse to the doctrine of equivalents would impermissibly impinge on the prior art:

> [I]t may be helpful to conceptualize the limitation on the scope of equivalents by visualizing a *hypothetical* patent claim, sufficient in scope to *literally* cover the accused product. The pertinent question then becomes whether that hypothetical claim could have been allowed by the PTO over the prior art. If not, then it would be improper to permit the patentee to obtain that coverage in an infringement suit under the doctrine of equivalents. If the hypothetical claim could have been allowed, then *prior art* is not a bar to infringement under the doctrine of equivalents.[97]

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93. *Id*. at 1380.
94. Wilson Sporting Goods Co. v. David Geoffrey & Assocs., 904 F.2d 677 (Fed. Cir. 1990), *overruled on other grounds by* Cardinal Chem. Co. v. Morton Int'l, Inc., 508 U.S. 83 (1993).
95. *Wilson Sporting Goods*, 904 F.2d at 683.
96. *Id*. at 684.
97. *Id*.

Accordingly, the prior art serves as an independent limitation on the application of the doctrine of equivalents.

The Federal Circuit has further clarified that the doctrine of equivalents will not apply if the patentee is unable to propose an appropriate hypothetical claim that only broadens the claims.[97.1] Accordingly, "a patentee's hypothetical claim may not add any narrowing limitations."[97.2] If a patentee fails "to submit a proper hypothetical claim for consideration," the patentee will be "unable to meet his burden of proving that his doctrine of equivalents theory did not ensnare the prior art."[97.3]

§ 10:4 The "Reverse Doctrine of Equivalents"

If an accused product falls within the literal scope of a claim, the product may not infringe if it is found that the product is "so far changed in principle that it performs the function of the claimed invention in a substantially different way."[98] This doctrine is called the "Reverse Doctrine of Equivalents." However, evidence that an accused product "may be superior to those actually invented . . . would not by itself remove [the accused product] from the scope of [the] claims."[99]

The patent owner bears the initial burden of proving literal infringement by a preponderance of the evidence. The accused infringer may then undertake the burden of coming forward with evidence to show that the accused product is so far changed in principle from what is claimed that it performs the function of the claimed invention in a substantially different way. If the accused infringer comes forward with such evidence, the patentee bears the burden of rebutting this case by a preponderance of the evidence.[100]

The Federal Circuit has called the Reverse Doctrine of Equivalents an "anachronistic exception" to literal infringement, noting that it is "long mentioned but rarely applied."[101]

97.1. *See* Jang v. Bos. Sci. Corp., 872 F.3d 1275, 1286–90 (Fed. Cir. 2017) ("[W]hen utilizing the hypothetical claim tool, that [patentee's] burden starts with proposing a proper hypothetical claim that only broadens the issued asserted claims.").

97.2. *Id*. at 1286.

97.3. *Id*. at 1287.

98. SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1124 (Fed. Cir. 1985).

99. Studiengesellschaft Kohle, m.b.H. v. Dart Indus., 726 F.2d 724, 728 (Fed. Cir. 1984).

100. *SRI Int'l*, 775 F.2d at 1123–24.

101. Tate Access Floors, Inc. v. Interface Architectural Res., Inc., 279 F.3d 1357, 1368 (Fed. Cir. 2002).

§ 10:5 Infringement Defenses

Even assuming that a product or process infringes a patent claim, an accused infringer can raise a number of defenses. The following provides a brief description of certain defenses to a charge of infringement.[102]

§ 10:5.1 Patent Invalidity

An accused infringer can defeat an allegation of patent infringement by proving that the asserted patent claim is invalid for failing to meet any of the statutory requirements of the Patent Laws. Because patents are presumed by statute to be valid,[103] patent invalidity must be proven by clear and convincing evidence.[104]

In its 1969 decision in *Lear v. Adkins*, the Supreme Court abrogated the doctrine of licensee estoppel, which had barred patent licensees from challenging the validity of patents under which they had taken a license.[104.1] In its 2021 decision in *Minerva Surgical, Inc. v. Hologic, Inc.*, the Supreme Court upheld the doctrine of assignor estoppel, which bars the assignor of a patent from challenging the validity of that patent, but clarified that the doctrine applies only where the "assignor's claim of invalidity contradicts explicit or implicit representations he made in assigning the patent."[104.2] The Supreme Court remanded the case to the Federal Circuit to address the question of whether the assignees' new claims were "materially broader" than those of the assigned patent, noting that, where

> the new claims are materially broader than the old claims, the assignor did not warrant to the new claims' validity. And if he made no such representation, then he can challenge the new claims in litigation: Because there is no inconsistency in his positions, there

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102. See 35 U.S.C. § 282, which lists "defenses in any action involving the validity or infringement of a patent" which "shall be pleaded."
103. 35 U.S.C. § 282.
104. Kaufman Co. v. Lantech, Inc., 807 F.2d 970, 973 (Fed. Cir. 1986).
104.1. Lear v. Adkins, 395 U.S. 653, 671 (1969).
104.2. Minerva Surgical, Inc. v. Hologic, Inc., 141 S. Ct. 2298, 2298 (2021). In the underlying decision, the Federal Circuit concluded that assignor estoppel did apply to preclude an assignor from challenging patent validity in district court proceedings but did not apply to preclude an assignor from challenging patent validity in inter partes review proceedings in the PTAB. Hologic, Inc. v. Minerva Surgical, Inc., 957 F.3d 1256 (Fed. Cir. 2020). While the Supreme Court granted certiorari on the Federal Circuit's decision that assignor estoppel applied in district court patent challenges, it denied certiorari on the Federal Circuit's decision that assignor estoppel did not apply to patent challenges in inter partes review proceedings in the PTAB.

> is no estoppel. The limits of the assignor's estoppel go only so far as, and not beyond, what he represented in assigning the patent application.[104.3]

On remand, the Federal Circuit considered (1) whether the assignor warranted the old claim's validity at the time of assignment and (2) whether the new claim is materially broader than the old claim.[104.4] Under the facts of the case, the Federal Circuit held that the assignor had warranted the validity of the old claim despite canceling the claim in response to a restriction requirement prior to assignment because the assignee would have understood that it could later prosecute the canceled claim's subject matter.[104.5] The Federal Circuit then held that the new claim was not materially broader than the old claim because the old claim also covered moisture-impermeable devices, and thus, assignor estoppel applied.[104.6]

§ 10:5.2 Express License

The Patent Laws under section 271(a) provide that certain acts done without authority constitute infringement. Authorization from the patent owner in the form of a license is an affirmative defense to a charge of infringement.[105] If the actions of an accused infringer are covered by a license agreement, the license can be asserted as a defense to a charge of infringement. The scope of the license agreement depends on reading and interpreting its terms and language.

§ 10:5.3 Implied License

Certain conduct on the part of a patent owner may create an implied license to practice a claimed invention notwithstanding the lack of an actual agreement. For example, an implied license to make, use, or sell a patented device or to use a patented process may arise when the patent owner sells a component designed to be used

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104.3. *Minerva Surgical, Inc.*, 141 S. Ct. at 2310.

104.4. Hologic, Inc. v. Minerva Surgical, Inc., 44 F.4th 1358, 1363–64 (Fed. Cir. 2022).

104.5. *Id*. at 1364–65. The court did not address whether a claim canceled for reasons other than to comply with a restriction assignment would be part of an assignment of a pending application. *Id*. at 1365 n.3.

104.6. *Id*. at 1367–69. The court did not define the line between "broader" claim and "materially broader" claims in view of the parties' agreement that the question of material broadness depended on the difference between moisture-permeable and moisture-impermeable devices. *Id*. at 1366 n.4.

105. McCoy v. Mitsuboshi Cutlery, Inc., 67 F.3d 917, 920 (Fed. Cir. 1995) (finding that one who "intentionally creates an express license . . . has an affirmative defense to a claim of patent infringement").

in a patented product or process and that has no substantial noninfringing use.[106]

The grant of a license implied by the sale of nonpatented equipment used to practice a patented invention requires two major elements. First, "the equipment involved must have no noninfringing uses."[109] Second, "the circumstances of the sale must 'plainly indicate that the grant of a license should be inferred.'"[110] The inquiry does not end, however, once it is determined "that a license should be implied." It is necessary to further "look to the circumstances of the sale to determine the scope of the implied license."[111] The burden of proving the establishment of an implied license "falls upon the defendant."[112]

The alleged infringer makes a prima facie showing of implied license when a patent owner sells without restriction a machine useful only in performing the claimed process and in producing the claimed product.[113] The burden of going forward then shifts to the party claiming infringement.[114]

A patent owner may negate an implied license by providing express restrictions or conditions on the sale of products that could otherwise create an implied license.[115]

§ 10:5.4 Exhaustion

In its 2008 decision in *Quanta Computer, Inc. v. LG Electronics, Inc.*,[116] the Supreme Court stated that "[t]he longstanding doctrine of patent exhaustion provides that the initial authorized sale of a patented item terminates all patent rights to that item."[117]

The Supreme Court had previously addressed the exhaustion doctrine in its 1942 decision in *United States v. Univis Lens Co.*[118]

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106. Met-Coil Sys. Corp. v. Korners Unlimited, Inc., 803 F.2d 684, 686–87 (Fed. Cir. 1986) (sale of nonpatented equipment to practice patented invention results in implied license).
107.–108. [Reserved.]
109. *Met-Coil*, 803 F.2d at 686.
110. *Id*. (quoting Bandag, Inc. v. Al Bolser's Tire Stores, Inc., 750 F.2d 903, 925 (Fed. Cir. 1984)); *see also* Monsanto Co. v. Scruggs, 459 F.3d 1328, 1336 (Fed. Cir. 2006); Carborundum Co. v. Molten Metal Equip. Innovations, 72 F.3d 872, 878 (Fed. Cir. 1995).
111. *Carborundum*, 72 F.3d at 878.
112. LG Elecs., Inc. v. Bizcom Elecs., Inc., 453 F.3d 1364, 1369 (Fed. Cir. 2006) (quoting *Bandag*, 750 F.2d at 924).
113. *Met-Coil*, 803 F.2d at 687.
114. *Id*.
115. *Id*. at 686–87.
116. Quanta Comput., Inc. v. LG Elecs., Inc., 128 S. Ct. 2109 (2008).
117. *Id*. at 2115.
118. United States v. Univis Lens Co., 316 U.S. 241 (1942).

In that case, the owner of a patent on multifocal eyeglass lenses granted a license for the manufacture of lens blanks which would then be sold to wholesalers and finishing retailers for grinding into the patented lenses. The Court noted that each lens blank "embodies essential features of the patented device and is without utility until it is ground and polished as the finished lens of the patent."[118.1] The patent owner also granted to the wholesalers and retailers licenses which fixed the prices of the finished lenses.[118.2] The Court held that the patent owner may not control the prices of finishers and retailers because "the authorized sale of an article which is capable of use only in practicing the patent is a relinquishment of the patent monopoly with respect to the article sold."[118.3] Thus, the patentee's sale of an "article embodying the invention . . . exhausts the monopoly in that article and the patentee may not thereafter by virtue of his patent control the use or disposition of the article."[118.4]

In the Supreme Court's *Quanta* decision, a patentee, LGE, licensed its patent portfolio to Intel to "'make, use, sell (directly or indirectly), offer to sell, import or otherwise dispose of' its own products practicing the LGE Patents."[118.5] The LGE agreement with Intel provided that no license was granted to any third party to combine any licensed product with any third-party products.[118.6] The license also stated that it did not alter the rules of patent exhaustion.[118.7] A separate agreement required Intel to provide written notice to purchasers that Intel's license under the patents did not extend to any product a purchaser makes by combining an Intel product with a non-Intel product.[118.8] While the products Intel made pursuant to the license, microprocessors and chipsets, were not themselves within the scope of the licensed patents (which covered combinations of such products with other components and methods using the combinations), their only reasonable and intended use was in practicing the licensed patents.[118.9]

Quanta purchased microprocessors and chipsets from Intel and combined them with non-Intel products in a manner that practiced the LGE patents. LGE sued for patent infringement. The Supreme

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118.1. *Id.* at 249.
118.2. *Id.* at 244–45.
118.3. *Id.* at 249.
118.4. *Id.* at 250.
118.5. *Quanta Comput.*, 128 S. Ct. at 2114.
118.6. *Id.*
118.7. *Id.*
118.8. *Id.*
118.9. *Id.* at 2119.

Court reversed a Federal Circuit holding that exhaustion did not apply to method claims and that exhaustion did not apply because LGE did not license Intel to sell Intel products for use in combination with non-Intel products.[118.10] The Supreme Court held that the exhaustion doctrine applies to method claims as well as product claims because methods may be "embodied" in a product.[118.11] The Court also held that exhaustion applies to the sale of an incomplete article which itself is not covered by the patent if that incomplete article "substantially embodies" or is a "material part of" the patented invention.[118.12] The Court further held that the terms of the license between LGE and Intel did not negate exhaustion. While stating that "[e]xhaustion is triggered only by a sale authorized by the patent holder,"[118.13] the Court concluded that "[n]o conditions limited Intel's authority to sell products substantially embodying the patents."[118.14] The Court held that exhaustion applied even though the LGE-Intel license disclaimed licenses to third parties because "exhaustion turns only on Intel's own license to sell products practicing the LGE Patents."[118.15] In addition, the provision in the separate agreement that Intel provide notice to third parties did not condition Intel's authority to sell products on the provision of such notice.[118.16] In sum, "[b]ecause Intel

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118.10. *Id*. at 2115.

118.11. *Id*. at 2117 ("It is true that a patented method may not be sold in the same way as an article or device, but methods nonetheless may be 'embodied' in a product, the sale of which exhausts patent rights.").

118.12. *Id*. at 2120. The Court cited United States v. Univis Lens Co., 316 U.S. 241 (1942), which held that "exhaustion was triggered by the sale of the lens blanks because their only reasonable and intended use was to practice the patent and because they 'embodie[d] essential features of [the] patented invention.'" *Id*. at 2119.

118.13. *Id*. at 2121.

118.14. *Id*. at 2122. The Court found that LGE's reliance on General Talking Pictures Corp. v. W. Elec. Co., 304 U.S. 175 (1938), *aff'd on reh'g*, 305 U.S. 124 (1938), was misplaced. As related by the *Quanta* Court, in *General Talking Pictures*, "the manufacturer sold patented amplifiers for commercial use, thereby breaching a license agreement that limited the buyer to selling the amplifiers for private and home use. The Court held that exhaustion did not apply because the manufacturer had no authority to sell the amplifiers for commercial use, and the manufacturer 'could not convey to petitioner what both knew it was not authorized to sell.'" *Id*. at 2121. Thus, in *General Talking Pictures*, exhaustion did not apply because the sale of the amplifiers was not authorized, whereas in *Quanta*, exhaustion did apply because the sale of microprocessors and chipsets was authorized.

118.15. *Id*. at 2122.

118.16. *Id*. at 2121–22.

was authorized to sell to Quanta, the doctrine of patent exhaustion prevents LGE from further asserting its patent rights with respect to the patents substantially embodied by those patents."[118.17]

Prior to *Quanta*, the Federal Circuit had held that the "principle of exhaustion of the patent right did not turn a conditional sale into an unconditional sale," indicating that a seller of a patented product could avoid the exhaustion doctrine by imposing conditions on the sale.[118.18] *Quanta*'s impact on the continuing viability of such prior Federal Circuit decisions on the exhaustion doctrine remains to be seen.

In its 2017 decision in *Impression Products, Inc. v. Lexmark International, Inc.*,[119] the Supreme Court stated that, "[i]n sum, patent exhaustion is uniform and automatic. Once a patentee decides to sell—whether on its own or through a licensee—that sale exhausts its patent rights, regardless of any post-sale restrictions the patentee purports to impose, either directly or through a license."[120] The Supreme Court continued by stating that "[a]n authorized sale outside the United States, just as one within the United States, exhausts all rights under the Patent Act."[121]

§ 10:5.5 Laches

The defense of laches previously barred recovery for pre-suit infringement when the patent owner unreasonably delayed filing suit to the prejudice of the accused infringer.

However, in its 2017 decision in *SCA Hygiene Products v. First Quality Baby Products, LLC*, the Supreme Court abrogated the defense of laches in view of the patent statute's six-year damages limitations period in 35 U.S.C. § 286.[133] In deciding to eliminate the defense, the Supreme Court relied heavily on its reasoning in *Petrella v. Metro-Goldwyn-Mayer, Inc.*,[133.1] which held that, in copyright cases, laches could not be asserted as a defense to legal damages for past infringement because, in enacting a three-year statute of limitations for copyright cases, Congress demonstrated its intent that the statute

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118.17. *Id*. at 2122.
118.18. Mallinckrodt, Inc. v. Medipart, Inc., 976 F.2d 700, 706 (Fed. Cir. 1992).
119. Impression Prods., Inc. v. Lexmark Int'l, Inc., 137 S. Ct. 1523 (2017).
120. *Id*. at 1535.
121. *Id*.
122.–132. [Reserved.]
133. SCA Hygiene Prods. v. First Quality Baby Prods., LLC, 137 S. Ct. 954, 961 (2017).
133.1. Petrella v. Metro-Goldwyn-Mayer, Inc., 134 S. Ct. 1962, 1974 (2014).

of limitations alone barred recovery of legal damages for past acts of copyright infringement.[133.2] The Court noted specifically that

> [w]hen Congress enacts a statute of limitations, it speaks directly to the issue of timeliness and provides a rule for determining whether a claim is timely enough to permit relief . . . Therefore, applying laches within a limitations period specified by Congress would give judges a "legislation-overriding" role that is beyond the Judiciary's power.[133.3]

Applying the reasoning in *Petrella*, the Court held that section 286 of the Patent Act "represents a judgment by Congress that a patentee may recover damages for any infringement committed within six years of the filing of the claim."[133.4]

§ 10:5.6 Equitable Estoppel

Equitable estoppel to assert a claim is another defense to a charge of patent infringement. Unlike laches, equitable estoppel "does not require the passage of an unreasonable period of time in filing suit."[134] Its elements are:

(1) a misleading statement or conduct by the patentee,

(2) reasonable reliance by the accused infringer, and

(3) prejudice to the accused infringer.[135]

The usual civil proof burden, preponderance of the evidence, applies fact issues to underlying equitable estoppel.[136] While laches only precludes award for past damages, estoppel may bar all relief, prospective as well as retrospective.[137]

[A] Misleading Statement or Conduct by the Patentee

Silence alone will generally not create equitable estoppel. Nevertheless, silence preceded by a threat of immediate and vigorous

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133.2. *See SCA Hygiene Prods.*, 137 S. Ct. at 961 ("Although the relevant statutory provisions in *Petrella* and this case are worded differently, *Petrella*'s reasoning easily fits the provision at issue here.").

133.3. *Id*. at 960.

133.4. *Id*. at 961.

134. *Id*. at 1041–42.

135. *Id*. at 1042–43.

136. *Id*. at 1045–46.

137. *Id*. at 1041; *see also* Giese v. Pierce Chem. Co., 29 F. Supp. 2d 33, 38 (D. Mass. 1998) ("equitable estoppel . . . may result in the denial of all relief").

enforcement of the patent might be sufficient to trigger equitable estoppel.[138] A mere letter from the patentee inviting the other party to enter into a licensing negotiation followed by silence is not sufficient to create equitable estoppel.[139]

[B] Reasonable Reliance

Reasonable reliance by the accused infringer is an element of the equitable estoppel defense. As stated in *Aukerman*, the infringer typically must have some knowledge of the patent to show reliance:

> An infringer can build a plant being entirely unaware of the patent. As a result of infringement, the infringer may be unable to use the facility. Although harmed, the infringer could not show reliance on the patentee's conduct. To show reliance, the infringer must have had a relationship or communication with the plaintiff which lulls the infringer into a sense of security in going ahead with building the plant.[140]

In a case where the infringer acted in the belief that the patent was invalid or not infringed, the infringer might be precluded from arguing that it relied on the patentee's delay.[141]

§ 10:5.7 Inequitable Conduct

A patent may be held unenforceable due to "inequitable conduct" if there is clear and convincing evidence that "an applicant, with intent to mislead or deceive the examiner, fails to disclose material

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138. ABB Robotics v. GMFanuc Robotics Corp., 52 F.3d 1062, 1064 (Fed. Cir. 1995) (finding estoppel where patentee took no action for a long period of time after the accused infringer denied infringement, even though the patentee never threatened an immediate suit).

139. Meyers v. Brooks Shoe, Inc., 912 F.2d 1459, 1464 (Fed. Cir. 1990) ("[W]e do not believe that a suggestion of infringement coupled with an offer to license followed by silence would suffice to establish equitable estoppel."), *overruled in part by* A.C. Aukerman Co. v. R.L. Chaides Constr. Co., 960 F.2d 1020 (Fed. Cir. 1992); Meyers v. Asics Corp., 974 F.2d 1304, 1308 (Fed. Cir. 1992) ("The fact that Meyers' attempts to negotiate licenses were followed by a period of silence does not, in itself, constitute the necessary misleading conduct.").

140. *A.C. Aukerman Co.*, 960 F.2d at 1043.

141. Hall v. Aqua Queen Mfg., Inc., 93 F.3d 1548, 1558 (Fed. Cir. 1996) (held that the district court's finding of reliance was in error because the defendant "may have acted due to its belief that the patent was invalid rather than due to any belief that Hall would not sue under the patent").

information or submits materially false information to the PTO during prosecution."[142]

§ 10:5.8 Prosecution Laches

Prosecution laches is an equitable defense that, if proven, "may render a patent unenforceable when it has issued only after an unreasonable and unexplained delay in prosecution."[143] The Federal Circuit has cautioned that "the doctrine should be used sparingly" and "applied only in egregious cases of misuse of the statutory patent system."[144] A delay in patent issuance must be unreasonable and "there are no strict time limitations for determining whether continued refiling of patent applications is a legitimate utilization of statutory provisions or an abuse of those provisions."[145]

§ 10:5.9 Patent Misuse

Patent misuse is an affirmative defense to a charge of patent infringement, which, if proven can render the patent unenforceable. A finding of patent misuse "requires that the alleged infringer show that the patentee has impermissibly broadened the 'physical or temporal scope' of the patent grant with anticompetitive effect."[146] A patentee may be accused of misuse when attempting to use the patent to reach activities outside the scope of the patent claims (that is, the "physical" scope of the patent) or to reach activities after a patent has expired (that is, the "temporal" scope of the patent). A finding of misuse does not require that the party asserting the defense has been damaged or adversely impacted by the patent owner's conduct.[147]

Patent misuse focuses on the conduct of a patent owner in licensing or enforcing a patent. A practice may be deemed to be a per se misuse. For example, an agreement by which a patent owner requires

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142. Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 1001 (Fed. Cir. 2006), *reh'g denied*, No. 05-1359, 2006 U.S. App. LEXIS 14354 (Fed. Cir. May 16, 2006). The defense of inequitable conduct is discussed in detail in section 5:9.
143. Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP, 422 F.3d 1378, 1385 (Fed. Cir.), *amended by* 429 F.3d 1051 (Fed. Cir. 2005).
144. *Symbol Techs., Inc.*, 422 F.3d at 1385.
145. *Id*.
146. Windsurfing Int'l, Inc. v. AMF, Inc., 782 F.2d 995, 1001 (Fed. Cir. 1986).
147. Morton Salt Co. v. G.S. Suppiger Co., 314 U.S. 488, 494 (1942) ("It is the adverse effect upon the public interest of a successful infringement suit in conjunction with the patentee's course of conduct which disqualifies him to maintain the suit, regardless of whether the particular defendant has suffered from the misuse of the patent."), *overruled in part by* Ill. Tool Works Inc. v. Indep. Ink, Inc., 547 U.S. 28 (2006).

the payment of royalties after a patent expires has been stated to be a per se misuse.[148]

When a practice is neither per se misuse nor specifically excluded from misuse under section 271(d) of the Patent Act, "a court must determine if that practice is 'reasonably within the patent grant, *i.e.*, that it relates to subject matter within the scope of the patent claims.'"[149] If the practice is within the scope of the patent grant, "the practice does not have the effect of broadening the scope of the patent claims and thus cannot constitute patent misuse."[150] However, if "the practice has the effect of extending the patentee's statutory rights and does so with an anti-competitive effect, that practice must then be analyzed in accordance with the 'rule of reason.'"[151] "Under the rule of reason, 'the finder of fact must decide whether the questioned practice imposes an unreasonable restraint on competition, taking into account a variety of factors, including specific information about the relevant business, its condition before and after the restraint was imposed, and the restraint's history, nature and effect.'"[152]

A practice that constitutes patent misuse may not render a patent permanently unenforceable. The Supreme Court in *Morton Salt Co. v. G.S. Suppiger Co.*[153] stated that the patent should be rendered unenforceable "at least until it is made to appear that the improper practice has been abandoned and that the consequences of the misuse of the patent have been dissipated."[154] This would indicate that a patent owner may be able to take curative action to purge the misuse and

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148. *See* Va. Panel Corp. v. Mac Panel Co., 133 F.3d 860, 869 (Fed. Cir. 1997) (stating that it is a per se misuse when "a patentee effectively extends the term of its patent by requiring post-expiration royalties") (citing Brulotte v. Thys Co., 379 U.S. 29, 33 (1964) (holding unenforceable an agreement requiring licensees of patented machine to pay royalties beyond the expiration of the patents)). The *Brulotte* decision was reaffirmed in Kimble v. Marvel Enters., Inc., 135 S. Ct. 2401, 2405 (2015): the Supreme Court declined to overrule *Brulotte* and reaffirmed the principle that "a patent holder cannot charge royalties for the use of his invention after its patent term has expired." It should be noted that in holding unenforceable licenses requiring the payment of post patent expiration royalties, neither *Brulotte* nor *Kimble* dealt with the enforceability of the underlying patent.
149. *Va. Panel*, 133 F.3d at 869 (quoting Mallinckrodt, Inc. v. Medipart, Inc., 976 F.2d 700, 708 (Fed. Cir. 1992)).
150. *Id*.
151. *Id*.
152. *Id*. (citation omitted).
153. Morton Salt Co. v. G.S. Suppiger Co., 314 U.S. 488 (1942), *overruled in part by* Ill. Tool Works Inc. v. Indep. Ink, Inc., 547 U.S. 28 (2006).
154. *Id*. at 493.

argue that any anti-competitive effects have "dissipated," rendering the patent enforceable once again.[155]

§ 10:5.10 35 U.S.C. § 271(e)(1)

Congress enacted section 271(e)(1) to provide a defense to infringement for activities "solely for uses reasonably related to the development and submission of information under Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."[156]

§ 10:5.11 Experimental Use

Courts have recognized a limited "experimental" use defense to patent infringement where the use is "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry."[157] This exception does not apply when the use has "'definite, cognizable, and not insubstantial commercial purposes.'"[157.1]

§ 10:5.12 Defense of Prior Commercial Use

The America Invents Act (AIA), enacted September 16, 2011, amended 35 U.S.C. § 273 to expand the noninfringement defense based on prior commercial use beyond "business method" patents to patents on any subject matter.[157.2] Effective for any patent issued on or after September 16, 2011, it will be a defense to a claim of patent infringement if (a) the defendant, acting in good faith, used the claimed subject matter in the United States in connection with an internal commercial use, an actual arm's-length sale, or other arm's-length commercial transfer of a useful end result of such commercial use, and (b) such commercial use occurred at least one year before the earlier of either (i) the effective filing date of the claimed invention, or (ii) the date on which the invention was disclosed to the public in a manner that qualified for the exception from prior art under section 102(b).[158]

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155. *See* Sylvania Indus. Corp. v. Vicking Corp., 132 F.2d 947, 959 (4th Cir. 1943).
156. See *supra* section 8:1.8 for a detailed discussion of section 271(e)(1).
157. Embrex, Inc. v. Serv. Eng'g Corp., 216 F.3d 1343, 1349 (Fed. Cir. 2000).
157.1. *Id*. at 1359 (quoting Roche Prods., Inc. v. Bolar Pharm. Co., 733 F.2d 858, 863 (Fed. Cir. 1984)). *See also* Madey v. Duke Univ., 307 F.3d 1351, 1363 (Fed. Cir. 2002) ("so long as the act is in furtherance of the alleged infringer's legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense").
157.2. Pub. L. No. 112-29, § 5 (2011).
158. 35 U.S.C. § 273(a).

The defense of prior commercial use must be proven by clear and convincing evidence,[159] and a finding of an unreasonable assertion of the defense will result in an award of attorney fees to the patent owner under 35 U.S.C. § 285.[160] The defense is not available if the commercial use was derived from the inventor.[161] The right to assert the defense is not transferrable except as part of a transfer of the entire line of business to which the defense applies and in such cases can only be asserted for uses at sites where the subject matter was in use before the later of the filing date of the claimed invention or the transfer of the line of business.[162] The sale or other disposition of a useful end result by a person entitled to assert the defense in connection with a patent exhausts the patent owner's rights under the patent to the extent that such rights would have been exhausted if the sale or other disposition of the useful end result had been made by the patentee.[162.1] If the commercial use is abandoned, activities performed before the date of abandonment cannot be relied upon in establishing a defense for actions on or after the date of abandonment. The defense cannot be asserted with respect to an invention made by an institution of higher education unless the invention was made using funds provided by the federal government.[163] Finally, the successful assertion of the defense alone does not invalidate the patent.[164]

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159. 35 U.S.C. § 273(b).
160. 35 U.S.C. § 273(f).
161. 35 U.S.C. § 273(d)(2).
162. 35 U.S.C. § 273(e)(1).
162.1. 35 U.S.C. § 273(d).
163. 35 U.S.C. § 273(e)(5).
164. 35 U.S.C. § 273(g).

Chapter 12. Government Funded Research: Bayh-Dole and Other Acts

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Chapter 12

Government Funded Research: Bayh-Dole and Other Acts

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§ 12:1 Policy Behind Enactment of Bayh-Dole

Congress enacted the Bayh-Dole Act in 1980.[1] Bayh-Dole made into law a new free-market approach to government funded inventions that had been taking root in federal regulations and policy sometime before. The Bayh-Dole Act grew out of a recognition that the federal government was not adept at commercializing inventions and bringing new technology to the public. The statute sought to make government funded technology more widely available by putting the ownership rights into the hands of entrepreneurs who had the profit motive and skills to turn inventions into products.

1. 35 U.S.C. § 200.

§ 12:1.1 Ownership of Government Funded Inventions Prior to Bayh-Dole

The government policy in place prior to the Bayh-Dole Act was embodied in a 1971 presidential policy memorandum.[2] The policy required that federal contracts award ownership rights to inventions made in the course of the contract work to the federal government whenever the principal purpose of the contract was to create products or was "for exploration into fields which directly concern the public health, public safety or public welfare" or where the work related to a field where there had been little significant work outside the government.[3]

The 1971 policy statement provided that, among other things, "the Government shall normally acquire or reserve the right to acquire the principal or exclusive rights throughout the world in and to any inventions made in the course of or under the contract."[4] If a federal contract intended a private contractor to build on knowledge or technology in which the contractor had acquired competence and a commercial position, then the private contractor was permitted to acquire exclusive rights to an invention resulting from the work. The government, however, retained a non-exclusive license to make, or have made, the invention for its own use.

§ 12:1.2 The Motive for Change

As the congressional reports on the Bayh-Dole Act noted, the policy of government ownership of inventions did little to promote the improvement of technology available to the public, and also did little to benefit the government.[5] Although government licensing provided a potential way to exploit its intellectual property, that rarely happened. In essence, taxpayers were paying for inventions from which they would often never see benefit because nobody had the incentive to commercialize their inventions.

The Bayh-Dole Act sought to remedy this waste of assets by allowing small businesses and non-profit organizations to acquire rights to inventions arising out of federal funding or contracts.[6] Underlying the Act is the expectation that the private sector would

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2. Presidential Memorandum on Government Patent Policy, 36 Fed. Reg. 16,887 (Aug. 26, 1971).
3. *Id.* at 16,889.
4. *Id.* at 16,890.
5. *See* General Accounting Office, Report to Congressional Committee, Technology Transfer—Agencies' Rights To Federally Sponsored Biomedical Inventions, GAO-03-536, at 3 (July 2003), *available at* www.gao.gov/highlights/d03536high.pdf (last visited Aug. 3, 2005).
6. 35 U.S.C. § 200.

be motivated to commercialize worthwhile inventions. In fact, the Act has resulted in the development of a multiplicity of useful pharmaceuticals by private parties cooperating with a federal agency.[7]

§ 12:1.3 Reagan Policy Extension of Bayh-Dole to All Contracting Parties

In 1983, President Reagan issued a new policy memorandum that extended the policy embodied in the Bayh-Dole Act to all contracting entities, large or small, profit or non-profit. The policy statement provides:

> To the extent permitted by law, agency policy with respect to the disposition of any invention made in the performance of a federally-funded research and development contract, grant or cooperative agreement award shall be the same or substantially the same as applied to small business firms and non-profit organizations under Chapter 38 of Title 35 of the United States Code.[8]

The policy statement effectively eliminated the distinction between small and large businesses for the purpose of determining ownership of federal inventions. Because large, for-profit corporations are particularly adept at exploiting important inventions and commercializing technology, the 1983 policy statement extending the Act to all government contractors better achieves the goal of utilizing government funded intellectual property more efficiently.

§ 12:2 Overview of the Bayh-Dole Act

The Bayh-Dole Act operates by defining the terms that federal contracts should contain concerning ownership of intellectual property created in the course of work pursuant to federal contracts or grants. The provisions of the Act are implemented through the terms of actual agreements that the federal government enters into with other parties.

§ 12:2.1 "Funding Agreements"

The Bayh-Dole Act terms operate to define the contract terms concerning invention ownership in "Funding Agreements." A Funding Agreement is broadly defined in section 201(b) of the statute:

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7. *See* Office of Technology Transfer, Nat'l Institute of Health, U.S. Department of HHS, *available at* www.ott.od.nih.gov/pdfs/therapeutics.pdf (last visited Aug. 2, 2005).
8. Memorandum to the Heads of Executive Departments and Agencies: Government Patent Policy, Pub. Papers 248 (Feb. 18, 1983).

> The term 'funding agreement' means any contract, grant, or cooperative agreement entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor for the performance of experimental, developmental, or research work funded in whole or part by the Federal government. This term includes any assignment, substitution of parties, or subcontract of any type entered into for the performance of experimental, developmental, or research work under a funding agreement as herein defined.[9]

The definition of Funding Agreements encompasses virtually any means by which research is "funded in whole or part by the Federal government" directly, or where research is undertaken as part of the performance of a federal contract.[10]

The requirements for the Funding Agreement are found in the Department of Commerce's regulations.[11] The requirements, which apply to all government agencies, include standard mandatory language.[12]

§ 12:2.2 Potential Requirement for Written Agreement

The Bayh-Dole Act appears to assume the existence of a written agreement between the government agency and the company receiving the funds. Nearly all of the respective rights and obligations of the government and the contracting party under the Act are specified as terms that must be included in a Funding Agreement. For example, the Act directs that the Funding Agreement include provisions that the contractor must elect to retain rights in the invention within a reasonable time after disclosure.[13] The Act describes the terms that each Funding Agreement must contain, and does not contain any statement of obligations independent of an agreement.[14]

Currently, there is no written court opinion deciding how rights to an invention are allocated if the mandatory terms of the Funding Agreement were not included in a contract with the federal

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9. The regulations of the Department of Commerce define Funding Agreement in similar terms. *See* 37 C.F.R. § 401.2(a).
10. *See* Trinity Indus. v. Rd. Sys., Inc., 235 F. Supp. 2d 536, 539–40 (E.D. Tex. 2002).
11. *See* 37 C.F.R. § 401 *et seq.*
12. *See* 37 C.F.R. §§ 401.3(a), 401.14(a). The standard clauses provide suggested contractual language for, inter alia, definitions, allocation of principal rights, disclosure, and conditions when the government may obtain title.
13. The period is typically within two years after disclosure. *See* 35 U.S.C. § 202(c)(2) (stating "Each funding agreement . . . shall . . . effectuate the following: . . . (2) That the contractor make a written election within two years after disclosure to the Federal agency . . . .").
14. *See* 35 U.S.C. § 202(c).

government to which the Act applies. The Act appears to require the execution of a Funding Agreement before Bayh-Dole rights and obligations come into existence. Otherwise, the Act would have dispensed with the need for mandatory Funding Agreement terms, and merely set forth the respective rights of the government and parties who accept government resources. On the other hand, the Act does not explicitly require a written agreement to trigger Bayh-Dole rights.[15]

Although the term "Funding Agreement" is defined broadly,[16] there are circumstances when the federal government may provide assistance to private researchers who do not qualify for a "Funding Agreement." For example, the government may allow use of laboratory facilities for a particular experiment.[17] The National Institutes of Health (NIH), which is the agency that is regularly involved in providing government funding for pharmaceutical research, often provides biological materials and samples to researchers without requiring a formal agreement. The Secretary of Health and Human Services (HHS) has authority to:

> [M]ake available to individuals and entities, for biomedical and behavioral research, substances and living organisms. Such substances and organisms shall be made available under such terms and conditions (including payment for them) as the Secretary determines appropriate.[18]

§ 12:2.3 Private Party Right to Acquire Inventions Made Under Funding Agreement

The Act gives the private party to a Funding Agreement the right to acquire ownership of inventions made under the terms of the Funding Agreement, subject to certain rights reserved to the federal government.[19] A Funding Agreement, however, need not grant rights to the private party in the following circumstances:

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15. 35 U.S.C. § 201(b).
16. *Id.* (stating "The term 'funding agreement' means any contract, grant, or cooperative agreement entered into between any Federal agency . . . funded in whole or in part by the Federal Government.").
17. *See* 42 U.S.C. § 241(a)(2).
18. 42 U.S.C. § 241.
19. *See* 35 U.S.C. § 202(a) (subject to certain exceptions "[e]ach nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention").

> ex-U.S.: "(i) when the contractor is not located in the United States or does not have a place of business located in the United States or is subject to the control of a foreign government"
>
> exceptional circumstances: "(ii) in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter"
>
> intelligence activities: "(iii) when it is determined by a Government authority which is authorized by statute or Executive order to conduct foreign intelligence or counter-intelligence activities that the restriction or elimination of the right to retain title to any subject invention is necessary to protect the security of such activities" or
>
> weapons: "(iv) contracts related to nuclear propulsion or weapons under DOE."[20]

The statute encourages restraint when considering the possibility of the government retaining rights under one of these exceptions. Except in cases that involve foreign intelligence activities, an agency retaining rights to an invention must file a statement with the Department of Commerce explaining its retention of the ownership rights.[21] Furthermore, the Administrator of the Office of Federal Procurement Policy is authorized to issue regulations if it finds that the government is abusing its right to retain ownership of inventions contrary to the purpose of the Act.[22]

§ 12:2.4 Requirements for Acquiring Private Ownership of an Invention Pursuant to Funding Agreement

The rights of the contracting party to an invention made under a Funding Agreement do not vest automatically in the contractor. The contractor must provide timely notice of invention and make a timely election to acquire the patent rights or they will revert to the government.[23]

[A] Notice of the Invention

[A][1] Timing

The contractor must disclose each invention to the federal agency within a "reasonable time" after the invention becomes known to the contractor's personnel responsible for the administration of patent

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20. *See* 35 U.S.C. § 202(a).
21. *See* 35 U.S.C. § 202(b)(1).
22. *See* 35 U.S.C. § 202(b)(2).
23. *See* 35 U.S.C. § 202(c); 37 C.F.R. § 401.14.

matters.[24] The federal government may receive title to any invention not so disclosed.[25] While the Act requires disclosure within a "reasonable time," the regulations require the disclosure to be within "two months."[26]

The notice requirement is triggered when the contractor's personnel responsible for patent matters learns of the invention, not when the inventor employed by the contractor makes an invention.[27] This provision in the Act protects the contractor whose employee may have made an invention, but never identified it to management. The statute also protects the contractor if the inventor delayed identifying the invention because they were unaware of the obligations to disclose or if the inventor did not consider the development to be a patentable invention. Once the invention is disclosed to the person whose job it is to manage patents, the government must be notified within two months, that is, the Department of Commerce's interpretation of the statute's term, a "reasonable time."

[A][2] Scope of Disclosure

The regulation governing reporting of the invention to the federal agency requires significant detail about the invention, including written disclosures about sales and publications, or planned publications describing the invention.[28]

A contractor preparing a notice of invention to the federal agency should do so carefully, with the understanding that the written notice may not be protected from disclosure in later patent infringement litigation.[29] Furthermore, a description of the invention that is

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24. *See* 35 U.S.C. § 202(c)(1).
25. *See id.*
26. 37 C.F.R. § 401.14(c)(1); *see also* 37 C.F.R. § 401.1(b) (implements the Bayh-Dole Act sections 202 through 204 and applies to all federal agencies).
27. *See* 35 U.S.C. § 202(c)(1).
28. *See* 37 C.F.R. § 401.14.
29. Generally, in the absence of a common interest, disclosure to another party waives privilege. *See, e.g., In re* Horowitz, 482 F.2d 72, 81 (2d Cir. 1973). Depending on the jurisdiction, the "common interest" exception applies only when the party asserting it carries the burden of establishing that both parties have "an identical legal interest." Shamis v. Ambassador Factors Corp., 34 F. Supp. 2d 879, 893 (S.D.N.Y. 1999) ("The key consideration is that the nature of the interest be identical, not similar, and be legal, not solely commercial.").

    Federal agencies generally receive a nonexclusive license to patents subject to the Bayh-Dole Act. *See* 35 U.S.C. § 202(c)(4). This interest may not give the government an identical legal interest sufficient to support a "common interest" exception to waiver of the privilege. *See* Research Inst. for Med. & Chem., Inc. v. Wis. Alumni Research Found., 114 F.R.D. 672, 677–78

incomplete, too narrow, or inaccurate could be used as an admission in later patent litigation on issues such as the date of complete conception, the identity of inventors, or other matters that may be asserted in the disclosure. Accordingly, parties litigating against patents that were based on inventions funded by the federal government would do well to seek such notice documents in discovery.

For the same reason, it would not be wise to simply forward to the government the inventor's written disclosure of the invention originally addressed to the in-house patent attorney. An invention disclosure form that inventors within the organization are required to prepare should go directly to counsel, preserving the attorney-client privilege of the communication seeking legal advice and assistance in preparing the appropriate patent applications.

[A][3] Good Practices

The required notice of invention sent to the government should be a separate document from the inventor's disclosures to counsel. This document should be prepared by the party responsible for the administration of government contracts after consulting with the patent attorney investigating the scope of the invention, and collecting the required detailed information. The notice of invention to the government should then be drafted with care, ensuring that the invention's entire scope is disclosed. If the invention's scope of notice does not cover all the inventions later claimed in the patent, the propriety of the notice may be disputed at a later date. As a result, the rights to the inventions not included in the notice may be jeopardized.[30]

[B] Election to Retain Rights to the Invention

In addition to disclosing the invention, the contractor must make a written election to retain title within two years after the disclosure.[31] Where a sale or publication triggers the one year grace period,[32] the election to retain rights may be shortened to a period that expires sixty days prior to the end of the grace period. This acceleration of the

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(W.D. Wis. 1987) (patentee and its nonexclusive licensee do not have "common and identical legal interests in the validity of the patents" because the license only grants the licensee "the right to be free from claims of patent infringement by" the patentee).

30. For example, the notice of invention of a chemical compound might not be notice of a method of treatment for a disease using that compound if the method of treatment was not apparent.
31. 35 U.S.C. § 202(c)(2).
32. A person is entitled to a patent unless, inter alia, the invention was described in a printed publication more than one year prior to the date of the application for patent in the United States. *See* 35 U.S.C. § 102(b).

election provision protects the right of the government to seek patent protection if the contractor elects not to retain the invention rights. Therefore, the contractor must be cognizant of potential triggers to the section 102(b) grace period to ensure that timely election to retain rights is given.

[C] Consequences of Failure to Provide Timely or Sufficient Notice or Election

A failure to provide timely disclosure to the government of the invention or timely election of the invention can be fatal to the contractor's rights. The federal government has the right to claim title to the invention for which timely disclosure has not been made.[33] The form language for Funding Agreements set forth in the regulations requires the contractor to convey title to the federal government for any invention not properly disclosed or elected, provided the government requests the conveyance within sixty days after learning of the failure to give timely disclosure or election.[34]

[C][1] Insufficient Disclosure: Campbell Plastics

The Federal Circuit, in *Campbell Plastics Engineering & Manufacturing, Inc. v. Brownlee*,[35] held that a contractor's failure to comply with Bayh-Dole Act notice requirements incorporated into the contract resulted in forfeiture of the patent. The agreement between the contractor and the Department of Defense (DOD) required the contractor to disclose any subject invention to the agency in the form of a written report, and specified the content that needed to be included in this report. Although the contractor submitted "various progress reports and drawings" that were arguably sufficient to allow the government to gain an understanding of the invention, the court held that the contractor's submissions had been insufficient.[36] The court further held that the Bayh-Dole Act as well as implementing regulations[37] vested discretion in the government to invoke forfeiture even without a showing that the government had been harmed by the contractor's failure to disclose.[38]

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33. 35 U.S.C. § 202(c)(1).
34. 37 C.F.R. § 401.14(d).
35. Campbell Plastics Eng'g & Mfg., Inc. v. Brownlee, 389 F.3d 1243 (Fed. Cir. 2004).
36. *Id.* at 1249.
37. *See* Federal Acquisition Regulation, 48 C.F.R. § 52.227-11(d).
38. *Id.*; *see also* T.M. Patents v. Int'l Bus. Mach. Corp., 121 F. Supp. 2d 349 (S.D.N.Y. 2000) (dismissing plaintiff's patent infringement action because patentee had failed to comply with the Bayh-Dole Act notice requirements and therefore never owned the patent).

In *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, Inc.*,[39] the patent-in-suit resulted from Bayh-Dole funded research at the University of California (U.C.). During the patent prosecution, U.C. notified NIH that it was no longer interested in the patent. The individual inventor then requested that NIH waive its rights to the patent and allow the individual inventor to pursue the patent in his own right. NIH agreed and granted the waiver on the condition that the inventor sign the statutorily required non-exclusive license to the government. During the infringement litigation, the inventor admitted that he never signed the license agreement. Defendant argued that the failure to execute the license resulted in a forfeiture of the inventors title. The Federal Circuit held that the title was not automatically void, but was voidable upon action by the government. Because the NIH had taken no action, the court held the title remained valid in the inventor for purposes of the infringement action.

[C][2] Failure to Comply with Bayh-Dole Act As a Defense: T.M. Patents

In *T.M. Patents v. International Business Machine Corp.*,[40] it was the defendant to a patent infringement suit, not the government, who made use of a failure to comply with the Act to defeat the plaintiff's title to the invention. The plaintiff sought patent infringement damages against IBM on a government-funded invention plaintiff had purchased from the inventor. IBM defended by arguing that plaintiff lacked standing to bring suit because it never held title to the invention. The court agreed that plaintiff lacked standing. The inventor made the invention under a government-funded agreement while he was employed at MIT, but MIT decided to waive its ownership rights in the invention to the government. Although the government was willing to let the inventor retain the rights to the invention, the inventor never completed the necessary forms as requested by the government. The court held the inventor therefore had no right to retain title, and could not assign to plaintiff a title he did not own.

Thus, infringement actions brought on a government-funded invention are vulnerable to a lack of standing defense when the assignee's title to the patent can be attacked for failure to comply with the Bayh-Dole Act and Funding Agreement requirements.[41]

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39. Cent. Admixture Pharmacy Servs., Inc. v. Advanced Cardiac Sols., Inc., 482 F.3d 1347 (Fed. Cir. 2007).
40. T.M. Patents v. Int'l Bus. Mach. Corp., 121 F. Supp. 2d 349 (S.D.N.Y. 2000).
41. *Id.* at 371.

[C][3] Good Practices

For companies that may acquire patent rights subject to the Bayh-Dole Act, it is important for contract administration officers and patent departments to have a method of identifying all government-funded projects so that notice and election of rights provisions are not overlooked. One method for monitoring possible government rights to inventions is to create an internal invention disclosure form that asks the inventors to identify all sources of funding of their research, including funding for their staff and equipment, so that government funding sources can be identified. Moreover, the possibility of government involvement in the invention through cooperation agreements, where no government funding is provided, must also be investigated.[42]

During litigation involving Bayh-Dole Act patents, a defendant must seek appropriate discovery and both parties must evaluate compliance with the Funding Agreement to determine whether there exists a lack of standing defense based on not having proper title to the patent.

[D] Filing Patent Applications

A contractor electing to retain invention rights must file a patent application in the United States within any time allowed by a statutory bar provision (such as a year-on-sale bar), and in foreign countries where the contractor elects to retain rights. The federal government may obtain title to inventions in territories where the contractor has not filed patent applications. Regulations require the inventor file foreign applications within ten months of the initial application, or within six months of the date on which the Commissioner of Patents grants permission to file in foreign countries.[43]

A patent application relating to a Bayh-Dole Act funded agreement must contain a notice that will be printed on the face of the patent.[44] The regulations require the following language:

> This invention was made with government support under (identify the contract) awarded by (identify the federal agency). The government has certain rights in the invention.[45]

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42. *See infra* section 12:3.2[D].
43. 37 C.F.R. § 401.14(c)(3).
44. 35 U.S.C. § 202(c)(6).
45. 37 C.F.R. § 401.14(f)(4).

§ 12:2.5 Special Funding Agreement Requirements for Non-Profit Corporations

Funding agreements with non-profit corporations have some additional requirements.[46] These include:

(1) A prohibition on assignment of the invention without approval of the federal agency (assignment to intellectual property management organizations is permitted).

(2) A requirement that the contractor share royalties with the inventor. This provision, however, does not specify a specific percentage, nor does it give a private right of action to the inventor to claim royalty payments.[47]

(3) A requirement that net royalties or income be used for further research or education (except for government-owned, contractor-operator facilities).[48] Government-owned, contractor-operator facilities must use royalties or income up to 5% of their annual budget for research, development, and education. Any amount exceeding 5% of the annual budget is divided, with 75% going to the U.S. Treasury and 25% going to research and education.

(4) A requirement, where feasible, that, when granting licenses, preference be given to small business firms.

§ 12:3 Retained Government Rights in Inventions Funded Under a Bayh-Dole Agreement

The contractor's ownership rights in inventions obtained under the Bayh-Dole Act are not unlimited. The government retains (1) a non-exclusive license to make or have made for it the invention, and (2) "march-in" rights permitting the government to require the patent owner to grant to a responsible third party a non-exclusive, partially exclusive, or exclusive license in any field of use upon terms that are reasonable in the circumstances. The march-in rights may be exercised only when one of four conditions specified in the statute is found to exist.[49] The government rights, in theory, could have a great impact on the rights to any pharmaceutical patent, but thus far they have not

46. 35 U.S.C. § 202(c)(7).
47. Platzer v. Sloan-Kettering Inst., 787 F. Supp. 360 (S.D.N.Y. 1992).
48. 35 U.S.C. § 207(c).
49. *See infra* section 12:3.2[A].

been used to diminish the value of any pharmaceutical patent owner's rights.[50]

§ 12:3.1 Non-Exclusive Government License

[A] Statutory Provision

The Bayh-Dole Act provides that the government will retain a royalty-free, non-exclusive license to the invention:

> With respect to any invention in which the contractor elects rights, the Federal Agency shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world.[51]

The statute also states that the Funding Agreement could give the government greater rights, including the right to assign or have assigned foreign patent rights necessary for meeting international treaty or military agreements. Funding Agreements, however, should not contain provisions allowing the government to require licensing to third parties of inventions that are not subject to the Bayh-Dole Act unless such provision has been approved by the agency head.[52]

[B] Potential Impact on Patented Drugs

The federal government now pays for a large percentage of prescription drugs under Medicare, Medicaid, and veterans programs. If providing drugs to patients covered by such federal programs were deemed to be a use for the government included in the Bayh-Dole non-exclusive license, and if the government elected to use such rights to supply drugs to patients in federal programs, the government would have a large impact on the value of a drug covered by patents under Bayh-Dole.

The government has never tried to use its license to have a third-party contractor make a drug for government use, nor has it ever tried to practice an invention of a pharmaceutical itself to supply government medical needs.[53] There may be little financial incentive for it to do so.

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50. The government's use of "march-in" rights, if used extensively, could seriously undermine the value of a patent to the contractor-patentee because the government could grant a license to a third party under the patent.
51. 37 U.S.C. § 202(c)(4).
52. 35 U.S.C. § 202(f); 37 C.F.R. § 401.2.
53. *See* General Accounting Office, Report to Congressional Committee, Technology Transfer—Agencies' Rights to Federally Sponsored Biomedical Inventions, GAO-03-536, at 3 (July 2003), *available at* www.gao.gov/highlights/d03536high.pdf (last visited Aug. 3, 2005).

First, the federal government's license rights to major pharmaceuticals have been reported as not being very significant. The government had license rights to only six of the top one hundred brand-name drugs procured by the U.S. Department of Veterans Affairs in fiscal 2001, and only four of the top one hundred brand-name drugs procured by the Department of Defense.[54]

Second, the federal government can already extract extremely favorable prices for drugs. To be listed on the Federal Supply Schedule, a branded drug must be sold at a 24% discount from the average non-federal price, and some national contracts entered by the federal government have negotiated even deeper discounts.[55]

If the government stays committed to the goals of the Bayh-Dole Act, it would not likely use its license rights to undercut the patent rights on pharmaceuticals by having third parties manufacture under license for the government. Government use of its license rights may provide it with some short-term benefit for the few existing drugs under patent protection and subject to the Bayh-Dole Act, but that benefit would soon dry up. No pharmaceutical company would likely thereafter make the enormous investment required to bring a drug subject to Bayh-Dole rights to market if there was a substantial risk that its exclusive rights to the drug would be undercut by government licensing. Pharmaceutical inventions subject to Bayh-Dole Act licenses would not likely be able to attract the necessary capital to fund the extensive safety and efficacy trials and still make them available in the marketplace. Similarly, universities and small start-up research companies might not accept federal funds concerning pharmaceutical research in such an environment, because universities and non-profit research organizations also depend on private pharmaceutical investment to develop drugs and get them to market.[56]

§ 12:3.2 *March-In Rights: Federal Power to Use Privately Owned Bayh-Dole Act Patents to Make Inventions Publicly Available*

[A] Statutory Provision

Another set of rights retained by the government under the Bayh-Dole Act are the so-called march-in rights.[57] March-in rights refer to

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54. *Id.* at 18, 21.
55. *Id.* at 12.
56. The expense of the full development process may be as high as $800 million. *See* Joseph DiMasi, Ronald Hansen, Henry Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166 (2003).
57. 35 U.S.C. § 203.

the government's ability to make an invention available to the public when the contractor has not sufficiently done so.

The government can issue additional licenses under these march-in rights:

(1) if no reasonable steps have been taken to achieve practical application of the invention;[58]

(2) where the public health or safety requires the invention, and the assignee or its licensees are not reasonably satisfying the public's need for the invention;

(3) where it is necessary to satisfy a public use requirement under Federal Regulations;[59] and

(4) when the invention is not being made in the United States in breach of section 204 of the Act.[60]

March-in rights may be exercised only after a contractor has been given opportunity to respond. If there exists a genuine dispute over material facts, the Agency must engage in fact finding and allow hearings.[61]

[B] Failure to Satisfy U.S. Manufacturing Requirements Could Trigger Use of March-In Rights

Section 204 of the Bayh-Dole Act requires an exclusive licensee of a government funded invention with rights to sell in the United States to substantially manufacture the invention in the United States.[62] The government, however, may waive this provision.[63] The penalty for a

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58. The funding agreement may require reports on the utilization or efforts to obtain utilization of the invention. 35 U.S.C. § 202(c)(5).
59. It is not at all clear what Congress had in mind by a public use requirement under federal regulations. One case, Rose v. Associated Univs. Inc., 1994 WL 167974 (S.D.N.Y. Apr. 29, 1994), interpreted this clause to imply that even subsequent to execution of a Funding Agreement, the federal government could issue federal regulations that would effectively terminate any exclusive license arrangement.
60. Rose v. Associated Univs. Inc., 1994 WL 167974 (S.D.N.Y. Apr. 29, 1994).
61. *See* 37 C.F.R. § 401.6.
62. *See* 35 U.S.C. § 204 (no rights "unless such person agrees that any products embodying the subject invention or product though the use of the subject invention will be manufactured substantially in the United States").
63. *See id.* ("the requirements for such an agreement may be waived by the Federal agency . . . upon a showing . . . that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible").

failure to comply with or request a waiver is the government's possible exercise of march-in-rights.[64] With a pharmaceutical invention, there is no clear authority whether manufacturing the active ingredient in a foreign country and formulating the tablet in the United States meets this requirement. The requirement that the invention be "substantially" manufactured in the United States clearly implies that it need not be entirely manufactured in the United States. "Substantially" is a term that leaves room for dispute with the agency.

[C] Petitions to Exercise March-In Rights

A broad reading of the statute might suggest that the government can use march-in rights to allow competing drugs or medical devices to enter the market if it is not satisfied with the patent holder's pace of commercialization. The Agency could argue that the inventor is either "not satisfying the public's need for the invention," "no reasonable steps have been taken to achieve practical application of the invention," or both.[65]

Efforts by petitioners to trigger march-in rights to allow an infringing product on the market when the patent owner had not received FDA approval and to allow lower price sellers on the market have been rejected based on the foregoing arguments.

[C][1] Product Still in Trials: In re CellPro

In *In re CellPro*,[66] the underlying product was an antibody useful in bone marrow transplantation for cancer patients, which was partly developed with federal funds at Johns Hopkins University.

The licensee of the product developed by Johns Hopkins sued CellPro, the developer of a similar antibody, for patent infringement, and was successful in obtaining an injunction against CellPro.

CellPro then petitioned the NIH to assert its march-in rights. CellPro's main assertion was that because CellPro's product had been approved for use by the FDA while the Johns Hopkins product was still in clinical trials, there existed a health and safety need that was not reasonably being satisfied by Johns Hopkins and its licensee.

Apparently seeing some merit in this position, Johns Hopkins and its licensee wisely granted CellPro a stay of the injunction and allowed it to continue its sales pending FDA approval of the Johns Hopkins product.

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64. 35 U.S.C. § 203(a)(4).
65. *See* 37 C.F.R. § 401.6.
66. *In re* CellPro, Nat'l Inst. of Health, Determination letter from Office of the Director (Aug. 1, 1997), *available at* www.nih.gov/icd/od/foia/cellpro/pdfs/foia_cellpro39.pdf (last visited Aug. 5, 2005).

In those circumstances, the NIH determined that none of the four factors forming the basis for march-in rights were present, and therefore declined assertion of those march-in rights.

[C][2] High Prices: In re Norvir® *and* In re Xalatan®

The Act allows for the government to use march-in rights if the agency determines "action is necessary to alleviate health or safety needs . . . not reasonably satisfied by the contractor, assignee, or their licensees."[67] A concern to a pharmaceutical manufacturer who may have relied on a Bayh-Dole Act patent in developing a new drug is that the government might use the march-in rights in an aggressive way to lower prices to "reasonably satisfy the public's need" for the invention.[68] Petitions seeking to have the government engage in such price regulation, however, have been rejected on two occasions.

In re Novir,[69] involved an AIDS antiviral drug (Norvir®), and *In re Xalatan*,[70] involved a treatment for glaucoma (Xalatan®). In these two cases, a group known as "Essential Inventions" petitioned the HHS to assert its march-in rights against the makers of two drugs. The petitions argued that the drug manufacturers were charging an unreasonably high price. The maker of Norvir® had increased the price of its drug more than 400%; the maker of Xalatan® sold the drug in the United States for two to five times the price in other developed, high-income countries.

The petitioners asked the government for an open 5% royalty license, with a requirement that each licensee establish a fund for further research and development.

NIH rejected both petitions. It found that price was irrelevant in determining whether the contractor had reasonably satisfied the health and safety needs of the public and had taken effective steps to achieve practical application of the drug. Because the drug was readily available to the public, NIH decided that march-in rights were not appropriate. NIH also decided that "march-in" petitions could not be used as a method to control prices, and that such action would best be left to Congress. NIH expressed the view that its role is not to try to lower prices of a drug that is adequately available in the marketplace by using march-in rights.

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67. *See* 35 U.S.C. § 203(a)(2).
68. *See* 37 C.F.R. § 401.6.
69. *In re* Norvir, Nat'l Inst. of Health, Determination letter from Office of the Director, July 29, 2004, *available at* http://ott.od.nih.gov/Reports/March-In-Norvir.pdf (last visited Aug. 5, 2005).
70. *In re* Xalatan, Nat'l Inst. of Health, Determination letter from Office of the Director, Sept. 17, 2004, *available at* http://ott.od.nih.gov/Reports/March-in-xalatan.pdf (last visited Aug. 5, 2005).

[D] Failure of Prior Government Efforts to Support Research As a Means to Regulate Drug Prices

The determination letters described in the preceding section noted that prior efforts to regulate drug prices through licenses failed. From 1990 to 1995, the NIH inserted a "Reasonable Pricing" clause in its model Cooperative Research and Development Agreements (CRADAs).[71] NIH would not grant a license to any invention made under such agreement unless there was a "reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public."[72] Many companies objected to the clause and declined to enter into cooperative agreements with the NIH because of this price restriction. Accordingly, the growth rate of these specialized agreements slowed between 1990 and 1994, and rebounded in 1995 after the director of the NIH rescinded the policy that required the "reasonable pricing" clause.[73]

[E] Federal Abuse of March-in Rights Would Defeat Policy Behind Act

Any shift in the policy against using march-in rights as a means of causing lower drug prices on patented drug products might, like aggressive use of the government's non-exclusive license rights, defeat the purpose of the Bayh-Dole Act to commercialize inventions. The first time march-in rights are used to reduce a pharmaceutical price to generic drug levels will likely mark the end of rational pharmaceutical companies' willingness to make the enormous investment required to bring a drug covered by a Bayh-Dole patent to market.

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71. *See* Federal Technology and Transfer Act, discussed *infra* section 12:9. CRADAs are agreements between a federal laboratory and one or more non-federal parties, which confer intellectual property rights on federal inventions. These are agreements under which the federal laboratory provides personnel, services, facilities, equipment, or other resources with or without reimbursement (but not funds to non-federal parties), while the non-federal party provides funds, personnel, services, facilities, equipment, or other resources toward research consistent with the federal laboratory. *See* Public Health Service CRADA Policy, United States Public Health Service Technology Transfer, *available at* http://ott.od.nih.gov/crada_policy.html (last visited on Aug. 1, 2005).
72. *See* General Accounting Office, Report to Hon. Ron Wyden, U.S. Senate, Technology Transfer—NIH-Private Sector Partnership in the Development of Taxol, GAO-03-829, at 8 (June 2003).
73. *See* NIH 2001 Report.

§ 12:3.3 Additional Contractually Imposed Restrictions

Because the rights conferred by the Bayh-Dole Act operate through the means of contract, the government in a particular Funding Agreement may reserve more rights than the Act presumptively provides for the government.[74] Accordingly, a company licensing a patent subject to the Bayh-Dole Act must examine the particular Funding Agreement involved to be certain of what rights are available. The company cannot rely merely on the default terms of the statute.

§ 12:4 Federal Employee Inventions

Inventions made solely by government employees are generally owned by the government,[75] subject to discretionary powers of the relevant agency to allow the inventor to retain certain rights to the invention.[76] Disposition of government rights based on government employee inventions are governed by the Bayh-Dole Act and the Federal Technology Transfer Act (FTTA),[77] as applicable.

The FTTA permits the individual federal employee inventor to obtain a share of royalties paid to the federal government of 15%, up to $150,000 per year.[78] The statute, however, does not give the government employee any right to control the licensing of the patent, nor to object to the terms that the license or conveyance provides.[79]

§ 12:5 Ownership of Private Party-Government Employee Co-Inventions

A federal agency, in the case of a joint invention with a contractor subject to the Bayh-Dole Act, may jointly own the invention.[80] Alternatively, if the government agency "finds that it would expedite the development of the invention,"[81] it has two more options. First, it may "license or assign whatever rights it may acquire in the subject invention to the [private party]."[82] Second, it may also "acquire any rights in the subject invention from the [private party]" if it

74. 35 U.S.C. § 202(a).
75. *See* 37 C.F.R. § 501.6(a)(1), (3)(ii), (iv).
76. *See* 37 C.F.R. § 501.6(a)(2).
77. See *infra* section 12:9 for further discussion.
78. *See* 15 U.S.C. § 3710c(a)(1)(A)(i).
79. *See* S. REP. NO. 283, 99th Cong. 2d Sess. 10 (1986), *reprinted in* 1986 U.S.C.C.A.N. 3442, 3452.
80. *See* 35 U.S.C. § 202(e).
81. *Id.*
82. *Id.*

"voluntarily enters into the transaction and no other transaction under this chapter is conditioned on such acquisition."[83]

Section 202(e) of the Act may be applicable to a joint invention involving federal and private employees where there is no Funding Agreement in place. Otherwise, it might be viewed as inconsistent with the more general terms of section 202(a) of the Act, which gives the right to acquire the invention to the private party but does not limit that right to the situation where the inventor is a non-federal employee. Section 202(e), giving the federal agency the option to assign or license, should logically refer to situations where the Funding Agreement does not already grant the private party the rights to the invention.

Section 202(e) can be quite important to the development of any patented invention. Each joint inventor has the right to practice, license, or assign the rights to a patent without accounting to the other co-inventors. Accordingly, a split in ownership of a pharmaceutical patent between a private party and the federal government could pose an obstacle to development of the patented pharmaceutical.[84] The existence of joint ownership rights that could be freely licensed or assigned to others would undermine the incentive of either owner to make the large investment required to develop the drug. Section 202(e), by allowing the government to consolidate ownership of the patent rights, protects the value of the patent so that it can be used to secure the required development capital for the invention.

§ 12:6 Bayh-Dole Act Does Not Change the Substance of the Patent or Antitrust Laws

The Federal Circuit rejected an argument that the Bayh-Dole Act reflected a policy of easing the standards for obtaining patents on basic research by a university.[85] The court stated:

> The Bayh-Dole Act was intended to enable universities to profit from their federally-funded research. It was not intended to relax the statutory requirements for patentability. As pointed out by amicus Eli Lilly, 'no connection exists between the Bayh-Dole Act and the legal standards that courts employ to assess patentability.' Furthermore, none of the eight policy objectives of the Bayh-Dole Act encourages or condones less stringent application of the patent laws to universities than to other entities.[86]

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83. *Id.*
84. See *supra* section 4:5.1[C] on inventorship in the absence of a contractual obligation.
85. *See* Univ. of Rochester v. G. Searle & Co., 358 F.3d 915 (Fed. Cir. 2004).
86. *See* 35 U.S.C. § 200 (2000).

Furthermore, the statute provides that it shall not "be deemed . . . to create any defenses to actions, under any antitrust law."[87]

§ 12:7 Licensing Federally Owned Inventions

Section 208 grants the Secretary of Commerce the authority to promulgate regulations specifying the terms and conditions on which federally owned inventions (other than those owned by the Tennessee Valley Authority) may be licensed on a non-exclusive, partially exclusive or exclusive basis. The Secretary of Commerce promulgated regulations pursuant to this authority.[88]

The Act contains mandatory restrictions on "exclusive and partially exclusive" licenses. The exclusive or partially exclusive license may be granted "only if," among other requirements:

(1) the license is necessary to call forth needed capital investment;[89]

(2) the Federal Agency finds that the public will be served by the license as evidenced by the licensee's plans and ability to bring the invention to practical application;[90]

(3) the proposed scope of exclusivity is not greater than reasonably necessary;[91] and

(4) the licensee commits to achieve practical application in a reasonable time.[92]

An exclusive or partially exclusive license may be granted only after public notice and comment, except for inventions made under cooperative agreements under section 3710a of title 15.[93] The regulations generally require three months' notice in the Federal Register.[94]

For *any* license under section 207(a)(2), which includes non-exclusive and exclusive licenses, section 209(b) "normally" requires U.S. manufacture of the invention by the licensee. The term "normally" implies there may be exceptions to this requirement, but no criteria are established for exception.

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87. *See* 35 U.S.C. § 211.
88. *See* 37 C.F.R. § 404 *et seq*.
89. 35 U.S.C. § 209(a)(1)(A).
90. 35 U.S.C. § 209(a)(2).
91. *Id.*
92. 35 U.S.C. § 209(a)(3).
93. 35 U.S.C. § 209(e).
94. 37 C.F.R. § 404.7.

Small businesses are given a preference for any licenses.[95] No license may be granted unless the licensee supplies a plan for development of the invention.[96]

Government licenses—apparently even those that are exclusive, "shall include provisions—

> (1) retaining a nontransferable, irrevocable, paid-up license for any Federal agency to practice the invention or have the invention practiced throughout the world by or on behalf of the United States."[97]

This reservation of government rights appears consistently in all provisions concerning inventions made or funded by the government. It reflects a fear that the government might be blocked from use of an invention to which it has some connection, but it is not clear that it does more good than harm to the government. The government does not appear to aggressively use such rights, yet the reservation of the rights may reduce the compensation in royalties that the government might otherwise be able to obtain.

The Act further provides that the granting agency include further terms, at its discretion, to protect the interests of the federal government and the public.[98] Such provisions include:

(1) periodic reporting on the utilization progress made by licensee;[99] and

(2) the right of the agency to terminate the license if it determines the licensee is not making adequate progress towards utilization or violates any of the requirements of initially receiving the license.[100]

The list of restrictions and the injection of competing policies into the licensing considerations suggest that Congress did not quite trust a free-market approach in developing government-owned intellectual property. If licensing operations were placed in capable hands, there should be no reason why the government could not negotiate its best licensing deal on a case-by-case basis, just as any commercial party could. Courts in the past have recognized the critical role that

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95. 35 U.S.C. § 209(c).
96. 35 U.S.C. § 209(f); 37 C.F.R. § 404.5.
97. 35 U.S.C. § 209(d)(1).
98. 35 U.S.C. § 209(f).
99. 35 U.S.C. § 209(f)(1).
100. 35 U.S.C. § 209(f).

investors and the need for patent protection play in bringing inventions to the public.[101]

§ 12:8 Government Sale of Patent Rights

The Bayh-Dole Act addresses "licensing of government-owned inventions," but not sale or assignment. Article IV, section 3, clause 2 of the U.S. Constitution requires congressional authorization for the government to dispose of property.[102] Surprisingly, there is no generally applicable statutory authority for the government to sell or assign, rather than license, any patent it owns.[103]

§ 12:9 The Federal Technology Transfer Act

The FTTA has a purpose similar to the Bayh-Dole Act: stimulating the development and use of technology and encouraging exchange of information.[104] Recall that the Bayh-Dole Act's purpose is to promote commercialization of inventions by vesting title in the private party receiving government funding. Similarly, the FTTA covers situations where the government is seeking to transfer or share intellectual property already owned by the government to a private party. The FTTA states that it is the federal government's policy to ensure the nation's full use of its research investment. To achieve this end, the government shall, where appropriate, transfer technology to the state and local governments, and to private parties.[105]

The FTTA creates offices in the Department of Commerce to manage technology policy, with a long list of duties.[106] The FTTA also establishes cooperative research centers.[107]

Of interest to industry are the statutory provisions for cooperative research and development agreements.[108] Those provisions authorize each federal agency to enter into agreements with private parties or state and local governments concerning cooperative research. These CRADAs[109] allocate rights when the federal agency provides

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101. *See* SCM Corp. v. Xerox Corp., 645 F.2d 1195, 1206 n.9 (2d Cir. 1991).
102. *See* United States v. Steinmety, 763 F. Supp. 1291 (D.N.J. 1991), *aff'd*, 973 F.2d 212 (3d Cir. 1992).
103. In 1924, then Attorney General, Harlan Fiske Stone, opined that a patent owned by the United States could not be assigned, although it could be licensed, absent Congressional authority. 34 Op. Att'y Gen. 320 (1924).
104. *See* 15 U.S.C. § 3701 *et seq.*
105. *Id.*
106. *See* 15 U.S.C. § 3703.
107. *See* 15 U.S.C. § 3705.
108. *See* 15 U.S.C. § 3710a.
109. *See supra* section 12:3.2[D].

resources, but not actual funding, for co-operative research with a private party.

Under the FTTA, the government may agree to give a collaborating party a license or assignment of an invention made in whole or in part by the federal employee.[110] It further requires the laboratory:[111] "[s]hall ensure . . . that the collaborating party has the option to choose an exclusive license for a pre-negotiated field of use for any such invention."[112] In return, the government obtains (1) a royalty-free, non-exclusive license to the invention, and (2) rights to license or compel a license to third parties in "exceptional circumstances."[113]

If the invention is made entirely by employees of the collaborating private party during the cooperative agreement, the collaborating party may retain ownership of the invention subject only to the government's non-exclusive license.[114] The FTTA provides the private party with rights to inventions specified when they enter a collaboration agreement, regardless of whether the invention was made jointly, by both private and government employees, solely by government employees, or solely by the private company's own employees.[115] While the FTTA assures the private party of rights to inventions arising from the cooperative research without regard to who the inventors are, the party may have fewer rights than it would have in the absence of a CRADA.[116] There is a trade-off of complete rights to inventions made by the private party's own employees, for the greater certainty of ownership of rights coming out of any collaborative project, regardless of the inventorship.

The acquisition of an invention developed as part of a CRADA raises issues similar to those that arise from a Funding Agreement under the Bayh-Dole Act: the risk to pharmaceutical inventions from the non-exclusive license to the government and the potential for march-in rights.

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110. *See* 15 U.S.C. § 3710a(b)(1).
111. Defined as a federally owned facility where substantial research is conducted. *See* 15 U.S.C. § 3703(6).
112. 15 U.S.C. § 3710a(b)(1).
113. *See* 15 U.S.C. § 3710(a), (b)(1)(B), (b)(1)(C) (2000). These are analogous to march-in rights, the term used in the Bayh-Dole Act.
114. *See* 15 U.S.C. § 3710a(b)(1)(A).
115. *See* 15 U.S.C. § 3710(a).
116. For example, if the private party's own employee makes the invention during the collaboration, it must give the government a non-exclusive license.

Chapter 13. Biologic and Biosimilar Drug Products

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Chapter 13

Biologic and Biosimilar Drug Products

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§ 13:1 Introduction

Biologic drug products are generally derived from living materials originating from humans, animals, or microorganisms and are generally more complex and difficult to characterize and manufacture than small molecules that can be chemically synthesized. For example, biologic drug products may be manufactured using recombinant DNA technologies that use the cellular machinery of microorganisms or other host cells to manufacture complex proteins, such as insulin, human growth hormone, and erythropoietin, and also therapeutic antibodies used to treat disease conditions, such as cancer and rheumatoid arthritis.

As the FDA has explained with regard to biologic products based on complex proteins,

> [u]nlike small molecule drugs, whose structures can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in protein structure can arise. Because even minor structural differences (including certain changes in glycosylation patterns) can

> significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences.[1]

Biologic drug products are in general approved by a different regulatory pathway from the one used for drug products containing small molecules as active ingredients. Thus, while most drugs based on small molecules are regulated under section 505 of the Federal Food Drug and Cosmetic Act (FFDCA),[2] biologic drug products are generally regulated under section 351 of the Public Health Service Act (PHSA).[3]

Significantly, in 1984, the Hatch-Waxman Act was enacted to provide an accelerated pathway for the approval of generic versions of previously approved small molecule drugs.[4] However, it was not until the passage in 2010 of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) that an accelerated pathway became available for the approval of follow-on or "biosimilar" versions of previously approved biologic drugs.[5]

The BPCIA provides for periods of exclusivity for reference biological products and for the first biosimilar product that is determined to be "interchangeable" with a reference product. The BPCIA also provides for a procedural mechanism for resolving patent disputes between a reference product sponsor (RPS) and a biosimilar applicant. These exclusivity periods and patent dispute procedures are different from those provided for in the Hatch-Waxman Act with respect to holders of approved New Drug Applications (NDAs) and to the filer of the first Abbreviated New Drug Application (ANDA) with a "paragraph IV" certification which challenges the validity, enforceability, or infringement of an Orange Book–listed patent for a reference drug.[6]

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1. Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 5 (Apr. 2015).
2. Codified at 21 U.S.C. § 355.
3. Codified at 42 U.S.C. § 262.
4. The Drug Price Competition and Patent Term Restoration Act of 1984. Pub. L. No. 98-417, 98 Stat. 1585 (1984). The Hatch-Waxman Act was amended in 2003 by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Pub. L. No. 108-173, 117 Stat. 2066 (2003). See *supra* chapter 8 for a detailed discussion of the Hatch-Waxman Act.
5. The BPCIA was enacted as Title VII of the Patient Protection and Affordable Care Act. Pub. L. No. 111–148, 124 Stat. 119.
6. The "Orange Book" is the commonly used name for an FDA publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*. The Orange Book can be accessed on the FDA's website at www.fda.gov.

§ 13:2 Biological Drug Product Defined

By statute, a "biological product" is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."[7] Biologic products marketed pursuant to FDA approval have included monoclonal antibodies, chimeric and humanized antibodies, recombinantly produced proteins, blood products, and vaccines.

Like other drugs, biologic drugs first undergo initial testing in laboratories and in animals to support the filing of an Investigative New Drug Application (IND) to demonstrate that the drug is reasonably safe to be studied in clinical trials on human patients. However, whereas new drugs are approved through the filing of an NDA, new biologic drugs are approved through the filing of a Biologics License Application (BLA). The approval of a BLA results in a biologics license that permits the marketing of a biologic drug product.[8]

§ 13:3 FDA Approval of "Follow-On Biologics" Before the BPCIA

Prior to the enactment of the BPCIA, the FDA did not have a specific statutory provision under the PHSA for approving a follow-on biologic product that it deemed safe and effective based in part on the prior approval of a reference product that had undergone full safety and efficacy testing. However, certain drug products which are biological in nature, such as certain recombinantly produced human growth hormone drug products, had been approved under the FFDCA.

On May 30, 2006, the FDA approved under section 505(b)(2) of the FFDCA the biosimilar product Omnitrope, a recombinant human growth hormone product, pursuant to a "paper NDA" filed by Sandoz which referenced Pfizer's NDA for Genotropin. Genotropin had been approved under section 505(b)(1) of the FFDCA. At the time, the FDA stated that Omnitrope was approved under section 505(b)(2) because it "is highly similar to Genotropin physiochemically, pharmacokinetically, pharmacodynamically, biologically and clinically."[9] The FDA also stated, however, that the

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7. 42 U.S.C. § 262(c)(i)(1).
8. *See generally* Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product, at 2 (Apr. 2015).
9. Letter from FDA denying citizen petition in Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355, at 52 (May 30, 2006).

> approval of Omnitrope does not signal that the Agency has concluded that—regardless of the nature and complexity of the active ingredient and indications for use—every protein product approved under section 505 of the Act is an appropriate candidate for reference by an applicant seeking approval of a follow-on protein product through an abbreviated pathway. Further, this decision does not address the distinct legal and regulatory issues related to approving follow-on versions of products licensed under the PHSA or the scientific challenges that may be posed by more complex and less well-understood licensed biological products.[10]

It was not until the passage of the BPCIA that Congress addressed the approval of follow-on versions of biological drug products approved under the PHSA.

§ 13:4 The BPCIA

On March 23, 2010, the BPCIA was enacted to create a regulatory pathway for the abbreviated approval of biological products that meet certain criteria relative to a previously approved biological drug product that had been licensed under a BLA, defined as the "reference product."[11] In particular, the new law set forth a pathway for the approval of two new categories of biologic drug products that are determined to be either "biosimilar" to, or "interchangeable" with, a previously approved reference product.

The BPCIA provides for periods of both marketing and data exclusivity for reference biologic products and for marketing exclusivity for the first follow-on product that is "interchangeable" with a reference biologic product.

The BPCIA also established a complex procedure for the RPS and the party submitting an application for approval of a biosimilar version of the reference product (applicant) for litigating patents applicable to the biosimilar product. In this connection, the BPCIA also amended 35 U.S.C. § 271 (in the Patent Act) to address patent infringement actions between the RPS and the applicant and remedies available should the RPS prevail.

§ 13:4.1 "Biosimilar" Drug Products

The BPCIA sets forth the criteria for follow-on biologic drug products to be approved as "biosimilar" to a reference biological drug product that has been approved by a BLA. In order for a biologic drug product to be "biosimilar" relative to a reference drug product, it

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10. *Id.*
11. 42 U.S.C. § 262(i)(4).

must be shown "(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[12]

An application for approval of a biologic drug as biosimilar to a reference product must include data supporting biosimilarity demonstrating that:

> (I) The biological product is derived from—(aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (bb) animal studies (including the assessment of toxicity); and (cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product;
>
> (II) The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;
>
> (III) The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;
>
> (IV) The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and
>
> (V) The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.[13]

§ 13:4.2 "Interchangeable" Biosimilar Drug Products

The BPCIA also provides for the approval of a subset of biosimilar drug products that further meet the criteria to be categorized as "interchangeable" with a reference biologic product. In order for a biologic drug product to be "interchangeable" relative to a reference biologic product, it must, in addition to the above standards for a biosimilar

12. 42 U.S.C. § 262(i)(2).
13. 42 U.S.C. § 262(k)(2)(A)(i).

drug product, be shown that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[14]

An application supporting the interchangeability of a proposed biosimilar product with a reference product must demonstrate that:

> (A) the biological product (i) is biosimilar to the reference product; and (ii) can be expected to produce the same clinical result as the reference product in any given patient; and (B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[15]

Accordingly, a determination that a biosimilar drug product is "interchangeable" with a reference product will generally provide that the interchangeable biologic product may be substituted for the reference product, similar to the substitutability of an AB-rated generic drug demonstrated to be bioequivalent to a corresponding reference listed drug product.[16]

§ 13:4.3 FDA Guidances on Biosimilar Drugs

The FDA has published final or draft guidances on a number of topics relating to the evaluation of applications for biosimilar products. As of August 2020, the FDA has issued a Final "Guidance for Industry" on each of the following topics: "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," "Quality Considerations in Demonstrating Biosimilarity to a Reference Product," "Questions and Answers on Biosimilar Development and the BPCI," "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants," "Labeling for Biosimilar Products," and "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." Pending as of the same date are the following Draft Guidances: "Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS," "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act," "Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry," and "Development of

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14. 42 U.S.C. § 262(i)(3).
15. 42 U.S.C. § 262(k)(4).
16. Therapeutic equivalence codes for approved drug products can be found in the FDA's Orange Book.

Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations."[17]

The FDA's guidances are intended to facilitate the biosimilar pathway. However, FDA states in the introduction to each guidance that "FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited."

§ 13:4.4 BPCIA Exclusivity Provisions

The BPCIA provides for periods of exclusivity for a reference product relative to biosimilar products and for the first interchangeable biosimilar product relative to subsequent applicants for interchangeable versions of the same reference product.

[A] Reference Product Exclusivity

The BPCIA provides the reference biologic product with a period of marketing exclusivity such that an application for a biosimilar product may not be approved until twelve years after the date that the reference product was first licensed.[18] The BPCIA also provides the reference biologic product with a period of "data" exclusivity such that an applicant for a biosimilar version of a reference biologic product cannot be filed with the FDA until four years after the date that the reference product was first licensed.[19]

These exclusivity periods do not apply to a license for approval of a supplement for the reference product or a subsequent application filed by the same sponsor or manufacturer of the reference product for (a) a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or (b) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.[20]

In comparison, under the Hatch-Waxman Act, an NDA for a new chemical entity (NCE) that has not previously been approved is entitled to a period of five years of exclusivity before an ANDA can be

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17. The final and draft guidances and other information on biosimilars can be found on the FDA's biosimilars page on its website. *See* www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm.
18. 42 U.S.C. § 262(k)(7)(A).
19. 42 U.S.C. § 262(k)(7)(B).
20. 42 U.S.C. § 262(k)(7)(C).

filed, unless an ANDA is filed with a paragraph IV certification, in which case the ANDA can be filed four years after NDA approval.[21] In addition, an NDA for an active ingredient that has been previously approved which contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant" is entitled to a period of three years during which an ANDA may not be approved.[22]

[A][1] Pediatric Exclusivity

If either prior to or after the approval of a reference biologic product, the FDA determines that studies directed to the use of the biologic product in pediatric populations would be beneficial and the FDA makes a written request for such studies, and if the RPS conducts such studies in the specified time, the period of data exclusivity will be extended to four years and six months and the period of marketing exclusivity is extended to twelve years and six months, and the period of orphan drug exclusivity will be extended to seven years and six months.[23]

In comparison, under the Hatch-Waxman Act, an NDA approved drug meeting the requirements for pediatric exclusivity is entitled to a six-month extension of applicable data and patent exclusivities.[24]

[A][2] Orphan Drug Exclusivity

As passed, the BPCIA provides that for reference biologic products meeting the criteria for orphan drugs under 21 U.S.C. § 360bb, a biosimilar or interchangeable drug product cannot be approved by the FDA until the later of the expiration of the seven-year period of orphan drug exclusivity or the twelve-year period of marketing exclusivity under the BPCIA, with the two periods running concurrently.[25]

In comparison, under the Hatch-Waxman Act, an NDA approved drug meeting the requirements for orphan drug exclusivity is entitled to a seven-year period of marketing exclusivity.[26]

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21. 21 U.S.C. § 355(c)(3)(E)(ii) and (j)(5)(F)(ii).
22. 21 U.S.C. § 355(j)(5)(F)(iii). The same exclusivity applies if the new clinical investigation is included in a supplement to an NDA. § 355(j)(5)(F)(iv).
23. 42 U.S.C. § 262(m). However, under section 262(m)(4), these extensions shall not apply if the FDA's determination under 21 U.S.C. § 355a(d)(3) that the studies fairly respond to the FDA's written request is made later than nine months prior to the expiration of the applicable period.
24. 21 U.S.C. § 355a.
25. Pub. L. No. 111-148, § 7002(h), 124 Stat. 821 (2010).
26. 21 U.S.C. §§ 360aa–360cc.

[B] Exclusivity for the First Interchangeable Biological Product

The BPCIA provides for a period of marketing exclusivity for the applicant whose biosimilar product is first to be approved as an interchangeable product for a reference biologic product relative to other interchangeable products. Under section 262(k)(6), after a determination that a biosimilar product is interchangeable with a reference product, the FDA shall not make a determination that a second biosimilar product is interchangeable until the earlier of:

(A) one year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;

(B) eighteen months after (i) a final court decision on all patents in suit in an infringement action under the Act against the first applicant for the first approved interchangeable product; or (ii) the dismissal with or without prejudice of an action against the first applicant; or

(C) forty-two months after approval of the first interchangeable biologic if the first applicant has been sued for patent infringement, or eighteen months after approval of the first interchangeable biologic if the first applicant has not been sued.[27]

For the purposes of this provision, a "final court decision" means "a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken."[28]

The above should be compared and contrasted with the Hatch-Waxman Act's award of 180 days of marketing exclusivity to the first ANDA filer with a paragraph IV certification challenging the validity, enforceability, or infringement of an Orange Book listed patent relative to a subsequent ANDA filer for the same reference listed drug product.[29]

§ 13:4.5 The "Purple Book"

On September 9, 2014, the FDA published the first edition of the "Purple Book," which lists biological products, including any biosimilar and interchangeable products licensed by the FDA. The Purple Book comprises two lists: (1) products approved by the Center for

27. 42 U.S.C. § 262(k)(6).
28. *Id*.
29. 21 U.S.C. § 355(j)(5)(B)(iv).

Drug Evaluation and Research (CDER), and (2) products approved by the Center for Biologics Evaluation and Research (CBER). Approved biosimilar and interchangeable products are listed under the applicable reference product.

The Purple Book lists include: (a) the date a biological product was licensed under section 351(a) of the Public Health Service Act (42 U.S.C. § 262(a)); (b) whether the FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) (42 U.S.C. § 262(k)(7)); (c) whether a biological product licensed under section 351(k) has been determined to be biosimilar to or interchangeable with a reference biological products; and (d) biosimilarity or interchangeability evaluations. If the FDA has determined that a biological product is protected by a period of reference product exclusivity, the Purple Book will identify the date the product was first licensed and the date that reference product exclusivity, including any pediatric exclusivity, will expire. The Purple Book will not list orphan drug exclusivity, as such information will be available on a separate searchable database.[29.1] The Purple Book does not include a list of the reference product sponsor's patents applicable to the reference product.

§ 13:4.6 BPCIA's Patent Dispute Resolution Provisions

The BPCIA establishes a complex framework within which the sponsors of reference biologic products and those applying for approval of biosimilar versions of reference products can resolve patent disputes and amended the Patent Act to specify the circumstances under which the filing of a biosimilar application is an act of infringement and to govern the causes of action and remedies for infringement.

The patent dispute provisions differ in significant ways from the provisions established in the Hatch-Waxman Act regarding the filing of ANDAs.

[A] Confidential Access to the Biosimilar Application and Manufacturing Information

The BPCIA establishes a procedure by which the biosimilar applicant provides the RPS with confidential access to its application and "other information" relating to the manufacture of the biosimilar product. Thus, within twenty days after the FDA notifies the biosimilar applicant that its application has been accepted for review, the

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29.1. Information about the Purple Book can be accessed at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm.

statute provides that the applicant "shall" provide the RPS with a copy of its biosimilar application and "other information" that describes the manufacturing process for the biologic product.[30] The applicant may also provide additional information requested by or on behalf of the RPS.[31]

The BPCIA further provides procedures that, unless otherwise agreed by the parties, will apply to maintain the confidentiality of the biosimilar application. Under these default procedures, the biosimilar application may be provided to (1) outside counsel for the reference product sponsor, provided that such outside attorneys "do not engage, formally or informally, in patent prosecution relevant or related to the reference product," and (2) one attorney who is an employee of the reference product sponsor, provided that such attorney "does not engage, formally or informally, in patent prosecution relevant or related to the reference product."[32]

A representative of the owner of a patent exclusively licensed to a reference product sponsor with respect to the reference product and who has retained the right to enforce the patent may also receive access to the biosimilar application if the representative of the patent owner agrees to abide by the same confidentiality provisions that apply to the reference sponsor owner.[33]

Under the BPCIA, persons receiving confidential information from the biosimilar applicant must not disclose such information to others, including outside scientific consultants, without the prior written consent of the biosimilar applicant, although such consent must not be unreasonably withheld.[34] The BPCIA requires that confidential information provided by the biosimilar applicant pursuant to this provision be used solely for determining whether patents owned by or exclusively licensed to the RPS can be reasonably asserted if the biosimilar applicant engaged in the manufacture, use, sale, offer for sale, or importation into the United States of the subject biologic drug product.[35]

The BPCIA specifies that the use of confidential information provided by the biosimilar applicant will be governed by these provisions until a protective order is entered by a court if a patent action is filed by the RPS.[36] Furthermore, no confidential information is to be included in a publicly filed complaint or other pleading. If a patent

30. 42 U.S.C. § 262(*l*)(2)(A).
31. 42 U.S.C. § 262(*l*)(2)(B).
32. 42 U.S.C. § 262(*l*)(1)(B)(ii).
33. 42 U.S.C. § 262(*l*)(1)(B)(iii).
34. 42 U.S.C. § 262(*l*)(1)(C).
35. 42 U.S.C. § 262(*l*)(1)(D).
36. 42 U.S.C. § 262(*l*)(1)(F).

action is not brought by the time specified by 42 U.S.C. § 262(*l*)(6), the RPS shall return or destroy the confidential information provided by the biosimilar applicant.[37]

The disclosure of a biosimilar applicant's confidential information in violation of the confidentiality provisions of the BPCIA "shall be deemed to cause the [biosimilar] applicant to suffer irreparable harm for which there is no adequate legal remedy and the court shall consider immediate injunctive relief to be an appropriate and necessary remedy for any violation or threatened violation of this paragraph."[38]

It should be noted that the Hatch-Waxman Act provides that an ANDA filer may provide an offer of confidential access to its ANDA for the purpose of permitting the patent owner to determine whether to bring an infringement action.[39] This offer of confidential access is required if the ANDA applicant based its paragraph IV certification on noninfringement and the ANDA applicant wishes to bring a declaratory judgment action after the expiration of the forty-five-day period provided for a patent owner to file an infringement suit after receiving notice from the ANDA filer.[40]

[B] Patent Lists Relating to the Reference Product

The BPCIA provides for an intricate series of steps intended to lead the parties to an identification of specific patents to be asserted by the RPS against the biosimilar applicant.

Within sixty days of the receipt of the biosimilar application, the RPS is required to provide the biosimilar applicant with a list of patents as to which the RPS "believes a claim of patent infringement could be reasonably asserted" by the RPS or its exclusive licensor against the proposed biosimilar product, and an identification of any patents on the list the RPS sponsor would be prepared to license to the biosimilar applicant.[41] Based on this provision, it appears that the RPS can include on its list, not only composition and method-of-use patents, but also method-of-making patents that it believes will be infringed by the manufacture of the biosimilar product.

If an RPS does not timely include a patent on its list, under 35 U.S.C. § 271(e)(6)(C), the patent owner "may not bring an action under this section for infringement of the patent with respect to the biological product."[42]

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37. *Id*.
38. 42 U.S.C. § 262(*l*)(1)(H).
39. 21 U.S.C. § 355(j)(5)(C)(i)(III).
40. 21 U.S.C. § 355(j)(5)(C)(i)(I).
41. 42 U.S.C. § 262(*l*)(3)(A).
42. 35 U.S.C. § 271(e)(6)(C).

In turn, within sixty days after the RPS provides the above list of patents, the biosimilar applicant may provide its own list of patents with respect to which it believes that a reasonable claim of patent infringement could be asserted by the RPS with regard to the proposed biosimilar product. In that same time period, the biosimilar applicant is required to provide for any patents on either the list provided by the RPS or its own list, a detailed statement on a claim-by-claim basis of the factual and legal basis of an opinion of the biosimilar applicant that any such patent is invalid, unenforceable, or would not be infringed by the commercial marketing of the proposed biosimilar product or a statement that the biosimilar applicant does not intend to begin commercial marketing of the proposed biosimilar product before the expiration of the listed patent.[43]

Within sixty days of receipt of the list and statement provided by the biosimilar applicant, the RPS is required to provide the biosimilar applicant with a detailed statement that, for those patents the biosimilar applicant is asserting are invalid, unenforceable, or not infringed, describes on a claim-by-claim basis the factual and legal basis of the opinion that the proposed biosimilar product would infringe any such claim, and a response to the biosimilar applicant's positions on invalidity and unenforceability.[44]

The BPCIA thus provides for a private process under which the RPS and biosimilar applicant identify patents that may be litigated with respect to the biosimilar application and obligates both parties to provide detailed infringement and validity contentions and responses before a patent infringement suit is initiated. This is in contrast to the Hatch-Waxman Act, which requires the NDA holder to publicly list certain patents in the FDA's Orange Book and which only requires the filer of an ANDA that certifies as to the invalidity, unenforceability, or noninfringement of a listed patent to provide a detailed basis for such a position.[45]

[C] Patent Resolution Negotiations

Following receipt of the RPS's detailed statement, the RPS and the biosimilar applicant are required to engage in good faith negotiations in an effort to reach agreement on which of the patents they have listed will be the subject of a patent infringement action brought by the RPS against the proposed biosimilar product.[46]

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43. 42 U.S.C. § 262(*l*)(3)(B).
44. *Id*.
45. 21 U.S.C. § 355(b)(1); § 355(j)(2)(B)(i); § 355(j)(2)(B)(iv)(II).
46. 42 U.S.C. § 262(*l*)(3)(C).

If within fifteen days of beginning negotiations the parties fail to agree on a final list of patents to be litigated, the biosimilar applicant is required to provide the RPS with the number of patents to be litigated (but not the identity of the patents) that it will provide on a list to the RPS.[47] Then on an agreed date (but in no event later than five days after the biosimilar applicant notifies the RPS of the number of patents to be litigated), the parties are required to simultaneously exchange their respective lists of patents that each believes should be litigated.[48] The number of patents listed by the RPS may not exceed the number of patents identified by the biosimilar applicant, unless the biosimilar applicant does not list any patents, in which case the RPS may list one patent.[49]

[D] Patent Infringement Actions Based on Filing of a Biosimilar Application

Under 35 U.S.C. § 271(e)(2)(C), the submission of the biosimilar application is an "act of infringement . . . with respect to a patent that is identified in the list of patents described in section 351(*l*)(3)" of the PHSA (including newly issued or licensed patents under section 351(*l*)(7)), if the purpose of the submission is to "engage in the commercial manufacture, use, or sale of a . . . biological product claimed in a patent or the use of which is claimed in a patent before the expiration of one of such patent."

Moreover, if the biosimilar applicant fails to provide its application and other required information to the RPS under section 351(*l*)(2)(A) of the PHSA, the filing of the application is deemed to be an act of infringement "for a patent that could be identified pursuant to Section 351(*l*)(3)(A)(i)" of the PHSA, if the purpose of the submission is to "engage in the commercial manufacture, use, or sale of a . . . biological product claimed in a patent or the use of which is claimed in a patent before the expiration of one of such patent."[50] Thus, if the biosimilar applicant does not provide its application and other required information to the RPS, the RPS apparently has a wide degree of latitude in its choice of patents as to which it can bring suit.[51]

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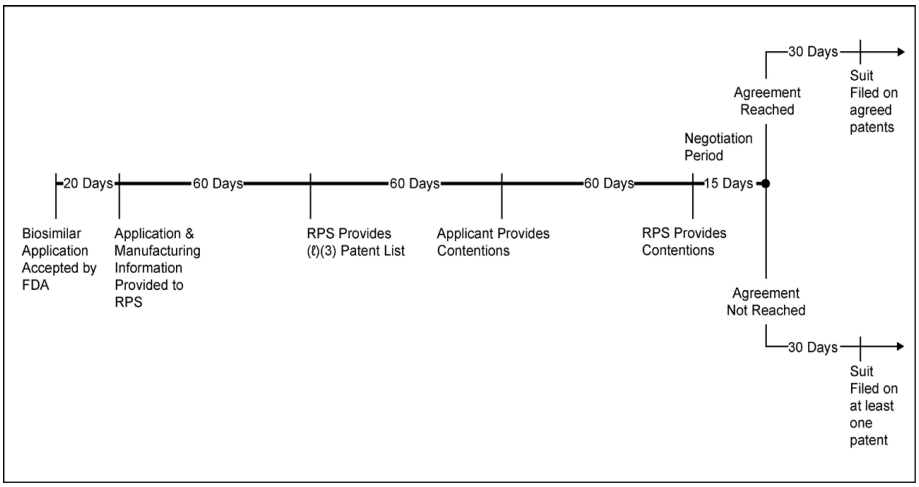
47. 42 U.S.C. § 262(*l*)(5)(A).
48. 42 U.S.C. § 262(*l*)(5)(B).
49. 42 U.S.C. § 262(*l*)(5)(B)(ii)(I) & (II).
50. 35 U.S.C. § 271(e)(2)(C)(ii).
51. One potential ambiguity in 35 U.S.C. § 271(e)(2)(C) is that, while that section provides that the "act of infringement" extends broadly to "a patent that is identified in the list described in section 351(*l*)(3)" or "a patent that could be identified pursuant to section 351(*l*)(3)(A)(i)," and such lists

If the biosimilar applicant and the RPS reach agreement on the patents to be litigated, the RPS is required to bring an action within thirty days after the agreement is reached as to each such patent.[52] If no agreement is reached, the RPS is required to bring an action for patent infringement with respect to each patent included on the exchanged lists of patents specified in section 262(*l*)(5) within thirty days of the exchange of patent lists.[53] See Figure 13-1 below.

Fig. 13-1

BPCIA Dispute Resolution Timeline (Phase I)



may include patents "for which the reference product sponsor believes a claim of patent infringement could reasonably be asserted . . . if a person not licensed by the reference product sponsor engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the subsection (k) application," the "act of infringement" may also arguably be limited by the concluding language "if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a . . . biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." Thus, while a method of manufacture patent is one that an RPS may conclude will be infringed by the biosimilar applicant and include on its patent list, a method of manufacture patent generally does not claim the "biological product" or a "use" of the "biological product." Whether Congress intended that the concluding "purpose" language of 35 U.S.C. § 271(e)(2) imposes a limitation on the types of patents that could be asserted in a biosimilar patent infringement action that is different in scope from the patent lists in 42 U.S.C. § 262(*l*)(3), (5), and (7), may have to be resolved in the future.

52. 42 U.S.C. § 262(*l*)(6)(A).

53. 42 U.S.C. § 262(*l*)(6)(B).

Within thirty days after an applicant is served with a complaint for patent infringement by an RPS, the applicant is required to provide the FDA with notice and a copy of the complaint. The FDA is required to publish a notice of the complaint in the *Federal Register*.[54]

The BPCIA does not provide for a litigation stay of FDA approval of a biosimilar application as does the Hatch-Waxman Act, which provides that if a patent owner files suit within forty-five days of receiving notice that an ANDA has been filed with a paragraph IV certification, the FDA may generally not approve the ANDA for thirty months, beginning on the date of receipt of the ANDA filer's notice, unless a court earlier enters a judgment of invalidity, unenforceability, or noninfringement.[55]

[E] Remedies for Infringement

35 U.S.C. § 271(e)(4) sets forth the remedies available to the RPS for patent infringement by a biosimilar applicant: First, "the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed."[56] Second, "injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product."[57] Third, "damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product."[58] Fourth,

> the court shall order a permanent injunction prohibiting any infringement of the patent by the biological product involved in the infringement until a date which is not earlier than the date of the expiration of the patent that has been infringed under paragraph (2)(C), provided the patent is the subject of a final court decision, as defined in section 351(k)(6) of the Public Health Service Act, in an action for infringement of the patent under section 351(*l*)(6) of such Act, and the biological product has not yet been approved because of section 351(k)(7) of such Act.[59]

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54. 42 U.S.C. § 262(*l*)(6)(C).
55. 21 U.S.C. § 355(j)(5)(B)(iii).
56. 35 U.S.C. § 271(e)(4)(A).
57. 35 U.S.C. § 271(e)(4)(B).
58. 35 U.S.C. § 271(e)(4)(C).
59. 35 U.S.C. § 271(e)(4)(D).

While the first three of these remedy provisions apply as well to Hatch-Waxman cases, the last is unique to actions against a biosimilar applicant. It should be noted that this last provision, section 271(e)(4)(D), specifies that (1) the permanent injunction is contingent on the patent being "the subject of a final court decision, as defined in section 351(k)(6)," which means a Federal Circuit decision, and (2) the permanent injunction is contingent on the biosimilar product not having been approved because exclusivity remains for the reference product. Accordingly, the injunctive remedy of section 271(e)(4)(D) is apparently available under a more limited set of circumstances than the relief that can be provided under sections 271(e)(4)(A) and (B).

Under 35 U.S.C. § 271(e)(6), if the RPS fails to bring suit within the required thirty days with respect to a patent that was included in the lists of 42 U.S.C. § 262(*l*)(4) or (5), then the "sole and exclusive remedy" available to the RPS is the award of a reasonable royalty,[60] meaning that the RPS forgoes the right to obtain an injunction or lost profits. The same penalty is imposed on an RPS that files a timely action if that action was dismissed without prejudice or was not prosecuted to judgment in good faith.[61]

Furthermore, the owner of a patent that should have been included in the section 262(*l*)(3)(A) list is barred from bringing an infringement action as to the patent against the proposed biosimilar product.[62]

[F] Later Issued or Exclusively Licensed Patents

The statute also provides that if after the date that the RPS provided its list of patents under section 262(*l*)(3)(A), the RPS is issued or exclusively licenses a patent as to which a claim of patent infringement could reasonably be asserted by the RPS against the proposed biosimilar product, the RPS may supplement its list of patents within thirty days of the issuance or exclusive licensing of the patent. The biosimilar applicant then has thirty days to provide a statement with regard to patent invalidity, unenforceability, or noninfringement or a statement that it does not intend to commercially market the product until after the patent expires.[63] The added patent is then subject to the preliminary injunction provisions of section 262(*l*)(8), discussed below.[64]

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60. 35 U.S.C. § 271(e)(6)(B).
61. *Id*.
62. 35 U.S.C. § 271(e)(6)(C).
63. 42 U.S.C. § 262(*l*)(7).
64. *Id*.

[G] Notice of Commercial Marketing and Preliminary Injunction Motions

The BPCIA requires that the biosimilar applicant provide notice to the RPS at least 180 days before it first markets a product pursuant to its application.[65] After receiving this notice and before the date of first commercial marketing by the biosimilar applicant, the RPS may seek a preliminary injunction against such commercial marketing with respect to any patent included on the lists specified in paragraph (*l*)(3)(A) or (B), but which was not included on the lists specified in paragraphs (*l*)(4) or (*l*)(5).[66] In other words, the RPS may seek a preliminary injunction as to a patent that was on its initial list in paragraph (*l*)(3), but which was not on the final list of patents that were litigated under either paragraphs (*l*)(3) or (*l*)(4). The parties are required to "reasonably cooperate to expedite" any further discovery needed in connection with such a preliminary injunction motion.[67]

The BPCIA's provision for notice of commercial marketing and motion for preliminary litigation sets the stage for two phases of patent litigation that may be separated by several years. First, the parties may litigate a subset of the RPS's patents in a first stage of litigation commenced, based on the timing provisions of the statute, somewhat more than seven months after the biosimilar applicant provides its application to the RPS. As discussed above, the biosimilar applicant can control the number of patents litigated in this first stage by deciding not to reach agreement with the RPS[68] and designating only a limited number of patents to litigate.[69] Second, the biosimilar applicant is required to provide notice to the RPS 180 days before it commercially launches its product, permitting the RPS to bring suit and a motion for a preliminary injunction on patents on the RPS's initial list, but which the biosimilar applicant did not agree to litigate.[70] See Figure 13-2 below.

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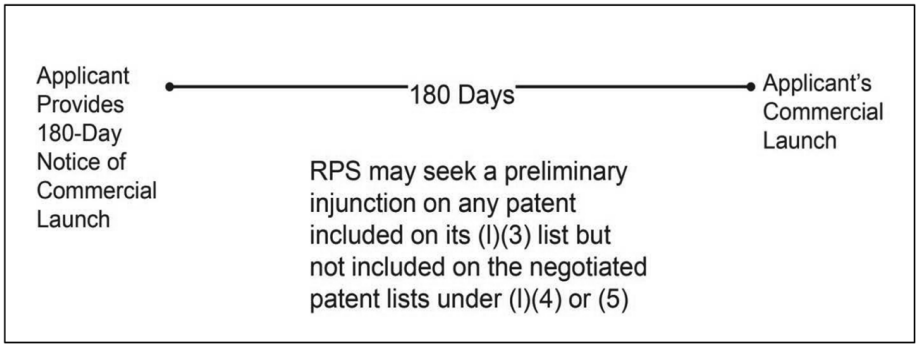
65. 42 U.S.C. § 262(*l*)(9). As noted above, unlike the Hatch-Waxman Act which provides for a thirty-month litigation stay of FDA approval of an ANDA, there is no comparable litigation stay of FDA approval of a biosimilar application.
66. 42 U.S.C. § 262(*l*)(8)(A) & (B).
67. 42 U.S.C. § 262(*l*)(8)(C).
68. 42 U.S.C. § 262(*l*)(4).
69. 42 U.S.C. § 262(*l*)(5)(A) & (B).
70. 42 U.S.C. § 262(*l*)(8).

Fig. 13-2

BPCIA Dispute Resolution Timeline (Phase II)



[H] Limitation on Declaratory Judgment Actions

If a biosimilar applicant provides its application and other information as required under paragraph (2)(A), neither party may, prior to the date notice of commercial marketing is received under paragraph (8)(A), bring a declaratory judgment action regarding the infringement, validity, or enforceability of any patent included in the lists described in paragraph (8)(B)(i) and (ii).[71] In other words, prior to the notice of commercial marketing, patent litigation is limited to those patents listed under section 262(*l*)(4) or (*l*)(5)(B).

However, if the biosimilar applicant fails to complete an action required of it under paragraphs (*l*)(3)(B)(ii), (*l*)(5), (*l*)(6)(C)(i), (*l*)(7), or (*l*)(8)(A), the RPS, but not the biosimilar applicant, may bring a declaratory judgment action with regard to the infringement, validity, or enforceability of any patent in the RPS's paragraph (*l*)(3)(A) list, including as provided under paragraph (*l*)(7).[72]

Furthermore, if the biosimilar applicant fails to provide its application and other information required under paragraph (*l*)(2)(A), the RPS, but not the biosimilar applicant, may bring a declaratory judgment action for the infringement, validity, or enforceability of any patent "that claims the biological product or a use of the biological product."[73] By specifying patents that "claim the biological product or a use of the biological product," this provision apparently excludes from its scope patents directed to the method of manufacturing the product and patents that may claim an intermediate used to make the product.[74]

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71. 42 U.S.C. § 262(*l*)(9)(A).
72. 42 U.S.C. § 262(*l*)(9)(B).
73. 42 U.S.C. § 262(*l*)(9)(C).
74. By limiting, in this particular instance, the scope of patents to those either claiming the biological product or the use of the biological product,

§ 13:5 Litigation Under the BPCIA

There have been relatively few reported decisions under the BPCIA. These decisions, however, have addressed important issues relating to biosimilar drug products, including subject matter jurisdiction over patent challenges raised by those seeking to make biosimilar drugs and whether a biosimilar applicant is required under the BPCIA to provide its application to the innovator company.

§ 13:5.1 Sandoz v. Amgen (*Enbrel®*)

In *Sandoz Inc. v. Amgen Inc.*,[75] the Federal Circuit affirmed, on subject matter jurisdiction grounds, the dismissal of Sandoz's declaratory judgment complaint seeking to invalidate two patents owned by Hoffman-LaRoche exclusively licensed to Amgen, and alleged to cover Amgen's biologic drug product Enbrel® (entracept), indicated for the treatment of rheumatoid arthritis.

At the time Sandoz filed its declaratory judgment action, it had begun a large-scale clinical trial for its contemplated entracept product.[76] The clinical trial was to be completed before Sandoz would file a biosimilar application for FDA approval.[77] The district court dismissed Sandoz's declaratory judgment complaint on two grounds.

First, the district court concluded that Sandoz's declaratory judgment action was not permitted under the BPCIA because Sandoz, by not having yet filed a biosimilar application with the FDA, had not complied with BPCIA procedures under section 262(*l*)(2)–(6).[78] The district court also disagreed with Sandoz's argument that it was permitted to file a declaratory judgment action because it had given notice of commercial marketing.[79] The district court reasoned that under section 262(*l*)(8)(A), a notice of commercial marketing can only be given if the biosimilar product was "licensed under subsection (k)," and Sandoz's biosimilar product was not yet licensed.[80] Also, the district court concluded that a biosimilar applicant could not file a declaratory judgment action "until, at a minimum, it has complied with its obligations under § 262(*l*)(2)(A)."[81]

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this provision apparently indicates that a broader scope of patents, including method of manufacture patents, may be listed by the parties and litigated under other provisions of the statute.

75. Sandoz Inc. v. Amgen Inc., 773 F.3d 1274 (Fed. Cir. 2014).
76. *Id*. at 1276.
77. *Id*.
78. Sandoz Inc. v. Amgen Inc., 2013 WL 6000069, at *2 (N.D. Cal. Nov. 12, 2013).
79. *Id*.
80. *Id*.
81. *Id*.

Second, the district court concluded, as a separate matter, that there was no case or controversy supporting declaratory judgment jurisdiction because Sandoz had only alleged an intent to file a biosimilar application with the FDA at some time in the future. The district court found that this was insufficient to establish a "case or controversy" sufficient to support subject matter jurisdiction.[82]

On appeal, the Federal Circuit affirmed the dismissal of Sandoz's declaratory judgment complaint, but only on subject matter jurisdiction grounds. In particular, the Federal Circuit concluded that under the circumstances in which Sandoz had not yet filed an application with the FDA for approval of its biosimilar product, the case did not meet the "immediacy" and "reality" requirements for subject matter jurisdiction under the declaratory judgment action.[83] The court noted that the product undergoing clinical testing may be modified, which could change or eliminate the patent dispute.[84] Moreover, the court noted that the clinical testing being undertaken did not create liability for patent infringement as it was protected by the safe harbor of 35 U.S.C. § 271(e)(1).[85]

Thus, the Federal Circuit concluded that, under the circumstances presented, the filing of an application for FDA approval was needed for justiciability: "We have found no justiciability where a declaratory-judgment plaintiff had not filed an application for the FDA approval required to engage in the arguably infringing activity."[86] Moreover, in reviewing the statutory provisions of both the Hatch-Waxman Act and the BPCIA, the court concluded that "Congress has not specifically provided for suits where the potential infringer has not filed an FDA application for the approval required before it can undertake the activity that might expose it to liability."[87] However, the Federal Circuit did "not address Sandoz's ability to seek a declaratory judgment if and when it files an FDA application under the BPCIA."[88]

Because the Federal Circuit affirmed on case or controversy grounds, it did not address the district court's holding that the BPCIA precluded Sandoz's declaratory judgment action.[89]

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82. *Id.* at *3.
83. *Sandoz Inc.*, 773 F.3d at 1279.
84. *Id.* at 1280.
85. *Id.* at 1279 & n.3.
86. *Id.* at 1281.
87. *Id.*
88. *Id.* at 1278.
89. *Id.* at 1282.

§ 13:5.2 Celltrion v. Kennedy Trust *and* Hospira v. Janssen *(Remicade®)*

In a pair of related cases, *Celltrion Healthcare Co. v. Kennedy Trust for Rheumatology Research*[90] and *Hospira, Inc. v. Janssen Biotech, Inc.*,[91] the Southern District of New York dismissed two declaratory judgment actions seeking to invalidate patents directed to Janssen's Remicade® biologic drug product because, at the time of suit, an application for a biosimilar version of Remicade® had not yet been filed with the FDA.

In *Celltrion*, Celltrion had not filed its biosimilar application at the time it filed its declaratory judgment complaint seeking to invalidate three patents owned by Kennedy that were licensed to Janssen. In *Hospira*, Hospira, which had entered into an agreement with Celltrion to co-exclusively market the biosimilar product, sought to invalidate two Janssen patents as well as the three Kennedy patents at issue in *Celltrion* by filing a declaratory judgment action before Celltrion's biosimilar application had been filed. In both cases, the district court found that subject matter jurisdiction was lacking because the application for the biosimilar product had not been filed with the FDA at the time of filing of the action and because the declaratory judgment defendants had not taken adverse positions against the plaintiffs. Moreover, in both decisions, the court concluded that even if the requirements for justiciability had been met, the court would exercise its discretion to decline jurisdiction in view of Congress' purpose in enacting the BPCIA and its patent dispute resolution procedures.[92] In this connection, the court rejected Celltrion's argument that the

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90. Celltrion Healthcare Co. v. Kennedy Tr. for Rheumatology Research, 2014 WL 6765996 (S.D.N.Y. Dec. 1, 2014).

91. Hospira, Inc. v. Janssen Biotech, Inc., 113 U.S.P.Q.2d (BNA) 1260 (S.D.N.Y. 2014).

92. *See Celltrion*, 2014 WL 6765996, at *4 ("In enacting the BPCIA, Congress provided a dispute resolution mechanism specifically for disputes arising out of the manufacture and marketing of biosimilars. The BPCIA seeks to promptly and efficiently resolve patent disputes in order to ensure that approved biosimilars may be sold in the U.S. as soon as they are ready for market. There is no reason to believe, and Celltrion has failed to demonstrate or even allege, that the dispute resolution procedure established by the BPCIA would be insufficient to resolve any patent disputes here."); *Hospira*, at 1262 ("The BPCIA purposefully ties the dispute resolution process to events throughout the biosimilar approval process, ensuring that full information exchange occurs at relevant and crucial periods during the approval process. As defendants argue, adjudicating this case would enable any biosimilar developer to partner with another distributor and thereby skirt the dispute resolution procedures Congress purposefully enacted for use in such situations.").

BPCIA provisions did not apply because Kennedy was not the reference product sponsor,[93] and Hospira's argument that the BPCIA procedures did not apply because Hospira is not the biosimilar applicant.[94] In both cases, the court concluded that the BPCIA applied to the patent disputes raised by the plaintiffs.

§ 13:5.3 Amgen v. Sandoz (*Neupogen®*)

Amgen Inc. v. Sandoz Inc.[95] addressed (a) whether a biosimilar applicant can, under the BPCIA, decline to provide the reference product sponsor (RPS) with its biosimilar application and manufacturing information under 42 U.S.C. § 262(*l*)(2) and further whether it may decline to participate in the patent information and exchange process set forth in the BPCIA under section (*l*)(3)–(7), and (b) whether FDA approval is a prerequisite for a biosimilar applicant to provide 180-days' notice of commercial marketing under section 262(*l*)(8). The case marked the first time that either the Federal Circuit or the Supreme Court construed provisions of the BPCIA.

The facts are set forth in the district court opinion. On July 7, 2014, Sandoz received notice that the FDA had accepted for review its application for a biosimilar version of Amgen's Neupogen® (filgrastim) biologic drug product.[96] The next day, Sandoz wrote Amgen (i) offering to provide a copy of its application under the protection of an Offer of Confidential Access, (ii) notifying Amgen that it believed that it would receive FDA approval in the first or second quarters of 2015, and (iii) stating its intent to market immediately after receiving approval.[97] Sandoz sent Amgen a second letter on July 25, 2014, again offering access to its application under a confidential access agreement and stating that it was entitled under the BPCIA to opt out of the patent information exchange procedures of subsection (*l*), and that Amgen could procure the information through discovery by filing an infringement action.[98]

Amgen filed suit on October 24, 2014, asserting (1) an unfair competition claim under California statutory law based on Sandoz's alleged noncompliance with the BPCIA, (2) conversion, and (3) infringement of an Amgen patent. Sandoz counterclaimed seeking

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93. *Celltrion*, 2014 WL 6765996, at *5.
94. *Hospira*, at 1262.
95. Amgen Inc. v. Sandoz Inc., No. 14-cv-04741-RS, 2015 WL 1264756 (N.D. Cal. Mar. 19, 2015), *aff'd in part, vacated in part*, 794 F.3d 1347 (Fed. Cir. 2015).
96. *Amgen*, 2015 WL 1264756, at *3.
97. *Id*.
98. *Id*.

declaratory judgments that (1) its interpretation of the BPCIA was correct, (2) that the BPCIA renders remedies under the California unfair competition statute unlawful and/or preempted, and (3) for noninfringement and invalidity of the asserted Amgen patent.[99]

Both parties cross-moved for partial judgment on the pleadings, or in the alternative for partial summary judgment, based on their interpretations of the BPCIA provisions, and Amgen further moved for a preliminary injunction against Sandoz's marketing of its biosimilar product until a decision on the merits was rendered.

Amgen's claims were predicated on its assertion that Sandoz's decision not to provide its biosimilar application and manufacturing information, or engage in subsection (*l*)'s patent disclosure procedures, was "unlawful" because the word "shall" is used in the BPCIA to describe the obligations of the biosimilar applicant and reference product sponsor.[100] Sandoz countered by arguing that subparagraphs (*l*)(9)(B) and (C) permit the reference product sponsor to bring a declaratory judgment action if the biosimilar applicant decides not to engage in the procedures of subparagraph (*l*).[101]

While the case was pending in the district court, on March 6, 2015, the FDA approved Sandoz's aBLA and Sandoz, while maintaining "that it gave an operative notice of commercial marketing in July 2014 . . . nevertheless gave a 'further notice of commercial marketing' to Amgen on the date of FDA approval."[102]

[A] The District Court Decision

The district court agreed with Sandoz regarding its interpretation of the BPCIA provisions as issue. The court noted that the BPCIA provided certain advantages, including a temporary safe harbor from declaratory judgment suits, to those who chose to follow the procedures.[103] With regard to the use of the word "shall" in subsection (*l*), the court stated "that an action 'shall' be taken does not imply it is mandatory in all contexts. It is fair to read subsection (*l*) to demand that, if both parties wish to take advantage of its disclosure procedures, then they 'shall' follow the prescribed procedures; in other words, these procedures are 'required' where the parties elect to take advantage of their benefits, and may be taken away when parties 'fail.'"[104] Moreover, the court concluded that the BPCIA presented biosimilar

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99. *Id*. at *4.
100. *Id*. at *5.
101. *Id*. at *6.
102. *Amgen*, 794 F.3d at 1353.
103. *Amgen*, 2015 WL 1264756, at *6.
104. *Id*.

applicants with the choice of whether to follow the procedures of subsection (*l*) and obtain its procedural benefits, or to proceed outside its provisions and risk an early suit by the reference product sponsor: "It is therefore evident that Congress intended merely to encourage use of the statute's dispute resolution process in favor of litigation, where practicable, with the carrot of a safe harbor for applicants who otherwise would remain vulnerable to suit."[105]

Separately, Amgen asserted that Sandoz could not provide 180 days' notice of its first commercial marketing until the FDA had approved Sandoz's biosimilar application. Subsection (*l*)(8) provides that an applicant "shall provide notice to the reference product sponsor no later than 180 days before the date of first commercial marketing of the biological product licensed under subsection (k)." Upon receipt of such notice, the reference product sponsor may seek a preliminary injunction against the marketing of the biosimilar product.

Amgen argued that the word "licensed" in subsection (*l*)(8) was in the past tense, meaning that the biosimilar applicant could not give the 180-day marketing notice until after the FDA had approved its application.[106] The district court disagreed, finding that the term "licensed" only refers to the fact that the product has to be licensed before it can be marketed and does not refer to the appropriate time for notice.[107] The district court noted that because the BPCIA provides twelve years of marketing exclusivity to the reference product, under Amgen's reading, the reference product sponsor would obtain an additional six months of marketing exclusivity if notice could not be provided until the biosimilar receives FDA approval.[108] The district court noted that Congress had not provided for this additional six months of reference product exclusivity.[109] Accordingly, the district court decided that Sandoz was not wrongful in providing notice

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105. *Id*.

106. *Id*. at *7.

107. *Id*. at *8. The district court concluded that its prior decision in Sandoz Inc. v. Amgen Inc., 2013 WL 6000069, at *2 (N.D. Cal. Nov. 12, 2013), relating to Enbrel® (discussed above), has "little persuasive authority over the present dispute" because, although it stated that notice of commercial marketing could not be provided when the biosimilar product is not "licensed under subsection (k)," the dismissal of the declaratory judgment action was based on Article III standing and it was "merely in passing" that the court noted that a declaratory judgment could not be obtained under the BPCIA prior to filing of a biosimilar application. Moreover, the Federal Circuit had affirmed only on standing grounds, and had expressly declined to address the BPCIA ground for dismissing the declaratory judgment action.

108. *Id*.

109. *Id*.

prior to first commercial marketing in advance of receiving FDA approval.[110]

In its decision, the district court denied Amgen's motion for partial summary judgment and dismissed its California state unfair competition and conversion claims with prejudice. In addition, the district court denied Amgen's motion for preliminary injunction against Sandoz's marketing of its biosimilar product.[111]

On April 15, 2015, the district court denied Amgen's motion for an injunction against Sandoz's marketing its biosimilar product pending appeal.[112] However, on May 5, 2015, the Federal Circuit granted the injunction until Amgen's appeal could be decided. The appeal was argued on June 3, 2015, and on July 21, 2015, the Federal Circuit issued its decision.

[B] The Federal Circuit Decision

In a divided panel opinion, the Federal Circuit affirmed in part, vacated in part, and remanded to the district court for consideration of the patent infringement claims. Judge Lourie wrote the majority opinion, while Judges Newman and Chen both concurred in part and dissented in part with regard to different aspects of the majority opinion.

The majority opinion affirmed the district court's determination that a biosimilar applicant does not violate the BPCIA by not disclosing its (k) application, or "aBLA," and its manufacturing information to the Reference Product Sponsor under 42 U.S.C. § 262(*l*)(2)(A).[113] The majority concluded that although the statute uses the word "shall" in (*l*)(2)(A) with regard to providing the aBLA and manufacturing information, the "'shall' provision cannot be read

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110. *Id*.

111. *Id*. at *8–10.

112. Amgen Inc. v. Sandoz Inc., No. 14-cv-04741-RS (N.D. Cal. Apr. 15, 2015), Order Denying Motion for Injunction Pending Appeal. The district court noted in footnote 1 of its Order, that Sandoz had agreed to refrain from marketing until the earlier of May 11, 2015, or a decision by the Federal Circuit on Amgen's application for injunction pending appeal. Sandoz's biosimilar product had been approved by the FDA on March 6, 2015. *See* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm.

113. *Amgen*, 794 F.3d at 1351. The majority opinion began by dropping the following footnote commenting on the BPCIA: "Winston Churchill once described Russia as 'a riddle wrapped in a mystery inside an enigma.' . . . . That is this statute. In these opinions, we do our best to unravel the riddle, solve the mystery, and comprehend the enigma." 794 F.3d at 1351 n.1 (citation omitted).

in isolation."[114] The majority looked to two provisions that provided recourse to the RPS in the event that the (k) applicant did not provide its aBLA and manufacturing information under (*l*)(2)(A). First, section 262(*l*)(9)(C) provides that "If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the reference product sponsor, but not the applicant, may bring an action under section 2201 of Title 28, for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product." Second, 35 U.S.C. § 271(e)(2)(C)(ii), as amended by the BPCIA, provides that "It shall be an act of infringement to submit . . . if the applicant for the application fails to provide the application and information required under section 351(*l*)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(*l*)(3)(A)(i) of such Act . . . ."[115] The majority thus found that the BPCIA "explicitly contemplates" that a biosimilar applicant might fail to provide its aBLA and manufacturing information and "specifically sets forth the consequence for such failure: the RPS may bring an infringement action under 42 U.S.C. § 262(*l*)(9)(C) and 35U.S.C. § 271(e)(2)(C)(ii). Those latter provisions indicate that 'shall' in (*l*)(2)(A) does not mean 'must.'"[116] The majority stated that "mandating compliance with paragraph (*l*)(2)(A) in all circumstances would render paragraph (*l*)(9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii) superfluous," and further pointed out that "35 U.S.C. § 271(e)(4) provides 'the *only* remedies which may be granted by a court for an act of infringement described in paragraph (2)'" and that "filing a subsection (k) application and failing to provide the required information under paragraph (*l*)(2)(A) is such an act of infringement."[117]

However, the majority disagreed with the district court and held that the district court had erred in holding that "a notice of commercial marketing under paragraph (*l*)(8)(A) may be effectively given before the biological product is 'licensed.' The majority held that "under paragraph (*l*)(8)(A), a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product."[118] In reaching its decision, the majority concluded that the language used in paragraph (*l*)(8)(A), "the biological product licensed under subsection (k)," means that the aBLA has to be approved before the notice of commercial marketing can be given. The majority found

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114. *Id*. at 1356.
115. *Id*. at 1354.
116. *Id*.
117. *Id*. at 1356.
118. *Id*. at 1358.

support for its conclusion because, "[i]n other provisions of subsection (*l*), the statute refers to the product as 'the biological product that is the subject of' the application, even when discussing commercial marketing."[119] The majority rejected the argument that requiring FDA licensure before notice of commercial marketing would provide the RPS with an additional six months of exclusivity and therefore conflict with the twelve-year exclusivity provision of section 262(k)(7)(A). The majority stated that while true in this particular case, "because Sandoz only filed its aBLA 23 years after Amgen received FDA approval of its Neupogen product . . . , [t]hat extra 180 days will not likely be the usual case, as aBLAs will often be filed during the 12-year exclusivity period for other products."[120]

Finally, the majority considered whether the "shall" provision in (*l*)(8)(A) is "mandatory" and concluded that it is. While the majority had concluded that "the BPCIA explicitly contemplates that a subsection (k) applicant might fail to comply with the requirement of paragraph (*l*)(2)(A) and further specifies the consequence for such failure in 42 U.S.C. § 262(*l*)(9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii)," it found that "[i]n contrast, with respect to paragraph (*l*)(8)(A), we do not find any provision in the BPCIA that contemplates, or specifies the consequence for, noncompliance with paragraph (*l*)(8)(A) here, which would be the case if Sandoz attempts to launch in disregard of the requirement of paragraph (*l*)(8)(A), as we have interpreted it."[121] The majority rejected the argument that paragraph (*l*)(9)(B) provides a consequence for a failure to give 180-day notice of commercial marketing because, "[w]hile it is true that paragraph (*l*)(9)(B) specifies the consequence for a subsequent failure to comply with paragraph (*l*)(8)(A) *after the applicant has complied* with paragraph (*l*)(2)(A), it does not apply in this case, where Sandoz did not comply with paragraph (*l*)(2)(A) to begin with."[122] The majority stated that "Paragraph (*l*)(8)(A) is a standalone provision in subsection (*l*). . . . Unlike the actions described in paragraphs (*l*)(3) through (*l*)(7), which all depend on, or are triggered by, the disclosure under paragraph (*l*)(2)(A), nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (*l*). Moreover, nothing in subsection (*l*) excuses the applicant from its obligation to give notice of commercial marketing to the RPS after it has chosen not to comply with paragraph (*l*)(2)(A). The purpose of paragraph (*l*)(8)(A) is clear: requiring notice of

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119. *Id*. at 1357 (citing 42 U.S.C. § 262(*l*)(3)(B)(ii)(I), (*l*)(3)(C); § 262(*l*)(1)(D), (*l*)(2)(A), (*l*)(3)(A)(i), (*l*)(3)(B)(i), (*l*)(7)(B)).
120. *Id*. at 1358.
121. *Id*. at 1359.
122. *Id*.

commercial marketing be given to allow the RPS a period of time to assess and act upon its patent rights."[123]

The majority therefore concluded that, "where, as here, a subsection (k) applicant completely fails to provide its aBLA and the required manufacturing information to the RPS by the statutory deadline, the requirement of paragraph (*l*)(8)(A) is mandatory. Sandoz therefore may not market Zarxio before 180 days from March 6, 2015, *i.e.*, September 2, 2015."[124]

Based on its interpretations of the BPCIA provisions at issue in the case, the majority opinion affirmed the dismissal of Amgen's state law claims.[125]

Judge Newman concurred in part and dissented in part. Judge Newman concurred in the majority's decision that "notice of issuance of the FDA license is mandatory, and that this notice starts the 180-day stay of commercial marketing, in accordance with 42 U.S.C. § 262(*l*)(8)(A)."[126]

Judge Newman, however, dissented from the majority's decision that providing the (k) application and information exchanges under 42 U.S.C. § 262(*l*)(2)(A) was not mandatory. Judge Newman viewed the "shall" provision of section 262(*l*)(2)(A) as mandatory and disagreed with the majority that subsection (*l*)(9)(C) provides a remedy for the RPS if the (k) applicant does not provide its aBLA and manufacturing information because "[s]ubsection (*l*)(9)(C) provides declaratory jurisdiction only for product or use claims" and "does not include manufacturing process claims."[127] In disagreeing with the majority, Judge Newman also concluded that "35 U.S.C. § 271(e)(2)(C)(ii) similarly states that it shall be an act of infringement if the applicant fails to provide the information required under paragraph (*l*)(2)(A). However, this does not diminish the obligation set by section (*l*)(1)(B)(i) that the subsection (k) applicant 'shall provide . . . confidential access to the information required to be produced pursuant to paragraph (2).' Such obligation is mandatory."[128]

Judge Chen also concurred in part and dissented in part, but on different aspects of the majority's opinion than Judge Newman. Judge Chen agreed with the majority that providing the aBLA and manufacturing information was not mandatory under the BPCIA: "I agree that a subsection (k) applicant's failure to supply the information

123. *Id*. at 1359–60.
124. *Id*. at 1360.
125. *Id*. at 1361.
126. *Id*. at 1362.
127. *Id*. at 1364.
128. *Id*. at 1366.

described in (*l*)(2) to the reference product sponsor (RPS) is not a violation of the BPCIA, because the BPCIA itself, in (*l*)(9) and § 271(e)(2)(C)(ii), provides the RPS the remedial course of action in such circumstances."[129]

However, Judge Chen disagreed with the majority that providing 180 days' notice of commercial marketing is mandatory when the (k) applicant decides not to provide its aBLA and manufacturing information because "when, as here, the (k) applicant fails to comply with (*l*)(2), the provisions in (*l*)(3)–(*l*)(8) cease to matter. In such a situation, as recognized by the majority opinion, the RPS's course of action is clearly defined in (*l*)(9) and § 271(e)(2)(C)(ii): the unfettered right to immediately pursue patent infringement litigation unconstrained by any of the timing controls or limits on the number of patents it may assert that would result from the (*l*)(2)–(*l*)(8) process."[130] Moreover, Judge Chen disagreed with the majority that (*l*)(8)(A) is "a 'standalone' provision that provides, implicitly, the RPS a 180-day injunction beyond the express twelve-year statutory exclusivity period."[131] Judge Chen stated that "[t]he most persuasive reading of subsection (*l*) as a whole is that Congress provided two paths to resolve patent disputes: (1) the intricate route expressed in (*l*)(2)–(*l*)(8); and (2) the immediate, more flexible route provided in (*l*)(9), should the (k) applicant falter on any of its obligations recited in (*l*)(2)–(*l*)(8)."[132] In particular, Judge Chen views 42 U.S.C. § (*l*)(9)(C) as providing the RPS with a remedy when the (k) applicant fails to provide its aBLA and information under paragraph (*l*)(2), the ability to file an immediate declaratory judgment action: "Contrary to the majority's conclusion, however, the absence of such a remedial provision in (*l*)(9)(B) *confirms* that Congress deemed any additional remedy to be unnecessary. Congress created the fallback provision of (*l*)(9)(C) for just these circumstances. An RPS does not need the remedy in (*l*)(9)(B) because (*l*)(9)(C) and § 271(e)(2)(C)(ii) already grant the right to file, immediately, an unrestricted patent infringement action when the (k) applicant fails to comply with (*l*)(2). At this point, the RPS possesses the statutory right to seek a preliminary injunction for any of its patents that 'could be identified pursuant to section [262](*l*)(3)(A)(i).' 35 U.S.C. § 271(e)(2)(C)(ii)."[133]

Following issuance of the Federal Circuit's divided panel decision, both Amgen and Sandoz filed petitions for writs of certiorari, which

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129. *Id*. at 1367.
130. *Id*.
131. *Id*.
132. *Id*. at 1370.
133. *Id*.

were granted. The Supreme Court heard argument on April 26, 2017, and issued its unanimous decision on June 12, 2017.

[C] The Supreme Court Decision

On June 12, 2017, the U.S. Supreme Court issued a unanimous opinion, written by Justice Thomas, in *Sandoz, Inc. v. Amgen, Inc.*,[133.1] marking the Court's first decision construing the BPCIA.

The Court addressed two key provisions under the BPCIA. The first provision, section 262(*l*)(2)(A), provides that a biosimilar applicant "shall provide" to the reference product sponsor its biosimilar application and its manufacturing information within twenty days after the Food and Drug Administration (FDA) accepts the application. On this issue, the Court held that the provision is not enforceable by injunctive relief under federal law, but remanded for a determination as to whether injunctive relief is available under state law. The second provision, section 262(*l*)(8)(A), provides that a biosimilar applicant "shall provide" to the reference product sponsor notice at least 180 days "before the date of the first commercial marketing of the biological product licensed under subsection (k) [the subsection directed to biosimilar applications]." On this issue, the Court held that a biosimilar applicant may provide notice of commercial marketing before FDA approval of the biosimilar application.

In the case, Sandoz had filed an application with the FDA for Amgen's reference product, Neulasta® (filgrastim), under the brand name Zarxio®. Although Sandoz had notified Amgen of the filing of its biosimilar application, it declined to provide its application and manufacturing information under section 262(*l*)(2)(A) and informed Amgen that it intended to market its biosimilar product immediately upon receiving FDA approval. Sandoz further informed Amgen that Amgen could sue for patent infringement immediately under section 262(*l*)(9)(C), which provides that a reference product sponsor can bring a declaratory judgment action against a biosimilar applicant which "fails to provide the application and information required under paragraph (2)(A)."

Amgen sued Sandoz in the U.S. District Court for the Northern District of California for patent infringement and also asserted two claims under California state unfair competition law. Amgen alleged that Sandoz engaged in "unlawful" conduct when it failed to provide its biosimilar application and manufacturing information under section 262(*l*)(2)(A), and also when it provided its notice of commercial marketing under section 262(*l*)(8)(A) before, rather than after,

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133.1. Sandoz, Inc. v. Amgen, Inc., No. 15-1039, 582 U.S. ___, 137 S. Ct. 1664 (June 12, 2017).

its biosimilar application was approved by the FDA. Amgen sought injunctive relief to enforce both provisions of the BPCIA that it accused Sandoz of violating. Sandoz counterclaimed for declaratory judgment that the asserted patent was invalid and not infringed, and that it had not violated the BPCIA.

The district court granted Sandoz partial summary judgment on the BPCIA claims and dismissed Amgen's state law unfair competition claims. Thereafter, a divided Court of Appeals for the Federal Circuit[133.2] held that an injunction under federal law was not available to enforce section 262(*l*)(2)(A) where the biosimilar applicant does not provide the reference product sponsor with its biosimilar application or manufacturing information, but that the 180-day notice of commercial marketing under section 262(*l*)(8)(A) could not be provided until after the biosimilar application is approved and that the provision could be enforced by injunctive relief.

After the FDA licensed Sandoz's biosimilar application while the action was pending, Sandoz gave Amgen a second notice of commercial marketing. The Federal Circuit enjoined Sandoz from marketing its approved biosimilar product until 180 days after it provided its second notice of commercial marketing.

The Supreme Court affirmed the Federal Circuit's decision that section 262(*l*)(2)(A)'s requirement that the biosimilar applicant provide its biosimilar application and manufacturing information was not enforceable under federal law by injunctive relief. In reaching this decision, the Supreme Court concluded that section 262(*l*)(9)(C) authorizes the reference product sponsor to bring an immediate declaratory judgment action when the biosimilar applicant fails to provide the required information[133.3] and that "[t]he remedy provided by § 262(*l*)(9)(C) excludes all other federal remedies, including injunctive relief."[133.4] However, the Supreme Court remanded the issue

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133.2. Amgen Inc. v. Sandoz Inc., 794 F.3d 1347 (Fed. Cir. 2015). *See* discussion *supra* in section 13:5.3[B].

133.3. The Supreme Court disagreed with the Federal Circuit's alternative holding that 35 U.S.C. § 271(e)(2)(C)(ii) precluded enforcing section 262(*l*)(2)(A) by federal injunction. The Supreme Court noted that section 271(e)(2)(C)(ii), which made the filing of a biosimilar application an act of patent infringement, did not also make an act of infringement, as the Federal Circuit had concluded, the failure to provide the biosimilar application and manufacturing information. Accordingly, the Supreme Court concluded that only section 262(*l*)(9)(C), and not section 271(e)(2)(C)(ii), provided a remedy for a biosimilar applicant failing to provide its application and manufacturing information. *Sandoz*, slip op. at 11–12.

133.4. *Id*. at 12. In a footnote, the Supreme Court stated that "we express no view on whether a district court could take into account an applicant's

of whether injunctive relief was available under state law. The Supreme Court reasoned that whether the disclosure requirement of section 262(*l*)(2)(A) is mandatory or conditional is an issue of state law, and if mandatory, a violation of the provision could be "unlawful" under state law. The Supreme Court further stated that if on remand the Federal Circuit determines that noncompliance with section 262(*l*)(2)(A) is unlawful under California law, the Federal Circuit should proceed to determine whether the BPCIA preempts any additional remedy available under state law. The Supreme Court added that the Federal Circuit "is also of course free to address the pre-emption question first by assuming that a remedy under state law exists."[133.5]

In reversing the Federal Circuit's decision that section 262(*l*)(8)(A)'s 180-day notice of commercial manufacturing could be provided only after the FDA approved the biosimilar application, the Supreme Court rejected the Federal Circuit's construction based on the use of the term "licensed" in the provision. Whereas the Federal Circuit had concluded that the term "licensed" meant that the FDA had to have licensed the biosimilar product before the 180-day notice under section 262(*l*)(8)(A) could be given, the Supreme Court concluded that "[t]he statute's use of the word 'licensed' merely reflects the fact that, on the 'date of the first commercial marketing,' the product must be licensed."[133.6] The Supreme Court therefore held that Sandoz had "fully complied with § 262(*l*)(8)(A) when it first gave notice (before licensure)" and that "the Federal Circuit erred in issuing a federal injunction prohibiting Sandoz from marketing Zarxio until 180 days after licensure."[133.7] Furthermore, because Amgen's state law claims were predicated on its argument that the BPCIA forbids prelicensure notice, the state law claims also failed.

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violation of § 262(*l*)(2)(A) (or any other BPCIA procedural requirement) in deciding whether to grant a preliminary injunction under 35 U.S.C. § 271(e)(4)(B) or § 283 against marketing the biosimilar," citing case authority on a court's consideration of the "balance of equities" in deciding whether to grant a preliminary injunction. *Id*. at 13 n.2.

133.5. *Id*. at 15.

133.6. *Id*. at 16. The Supreme Court noted that section 262(*l*)(8)(A) had only one timing requirement (that the biosimilar applicant had to provide notice at least 180 days prior to commercial marketing), whereas the Federal Circuit had interpreted the provision as having two timing requirements (the biosimilar applicant must provide notice after licensing and at least 180 days before commercial marketing). The Supreme Court pointed to another to another provision, section 262(*l*)(8)(B), which did have two timing requirements as support for its interpretation that Congress only intended a single timing requirement for section 262(*l*)(8)(A).

133.7. *Id*. at 16.

Justice Breyer, in a concurring opinion, stated that "Congress implicitly delegated to the Food and Drug Administration authority to interpret [the] same terms" that the Supreme Court interpreted in its opinion, and set forth his understanding that the FDA "may well have the authority to depart from, or to modify, today's interpretation" of the BPC.

In *Amgen Inc. v. Sandoz Inc.*,[134] the Federal Circuit, on remand from the Supreme Court, held that Sandoz had not waived its defense that Amgen's state law claims were preempted by the BPCIA, because Sandoz had pleaded the defense in its answer, notwithstanding that the issue was not argued in the district court. The Federal Circuit further held that the BPCIA did preempt Amgen's state law claims under both field and conflict preemption principles. In particular, the Federal Circuit stated that "the preemption analysis here demonstrates that Amgen's state law claims conflict with the BPCIA and intrude upon a field, biosimilar patent litigation, that Congress reserved for the federal government."[135]

§ 13:5.4 Amgen v. Sandoz *(Neulasta®)*

In *Amgen v. Sandoz*,[140] relating to Sandoz's biosimilar application for Amgen's Neulasta® (pegfilgrastim) biologic drug product, the District of New Jersey dismissed Amgen's complaint seeking declaratory relief requiring Sandoz to comply with the patent litigation provisions of the BPCIA because post-complaint, the parties had reached agreement on meeting those patent litigation provisions, thus mooting the case. In fact, shortly after reaching agreement, Amgen had sued Sandoz for infringement of two patents in the Northern District of California.[141] The New Jersey District Court found that a live case or controversy no longer existed and dismissed the complaint for lack of case or controversy. By continuing to press its complaint, Amgen was seeking to obtain an improper advisory opinion on a case that had been rendered moot.

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134. Amgen Inc. v. Sandoz Inc., 877 F.3d 1315 (Fed. Cir. 2017).
135. *Id*. at 1330.
136.–139. [Reserved.]
140. Amgen Inc. v. Sandoz Inc., No. 16-1276 (SRC)(CLW) (D.N.J. July 22, 2016) (slip op.).
141. Amgen Inc. v. Sandoz Inc., No. 3:16-cv-2581-RS (N.D. Cal. May 12, 2016).

§ 13:5.5 Amgen v. Hospira (*Epogen®*)

In *Amgen v. Hospira*,[142] relating to Hospira's biosimilar application for Amgen's Epogen® (epoetin alfa) biologic drug product, the Federal Circuit rejected Amgen's appeal and petition for a writ of mandamus regarding the District of Delaware's denial of a motion to compel discovery from Hospira regarding information relating to the cell-culture medium used in the manufacture of Hospira's biosimilar. The Federal Circuit noted that although the parties proceeded under the BPCIA to identify patents that would be subject to litigation, Amgen "never identified a cell-culture patent as part of its own BPCIA disclosures."[143] The district court denied the requested discovery because the requested cell-culture information had "'essentially, no relevance to the patents that are asserted.'"[144]

First, the Federal Circuit held that it did not have jurisdiction over the appeal of the order denying discovery because it did not satisfy the requirements of the collateral order doctrine such that an immediate appeal would be available.[145] Second, the Federal Circuit denied Amgen's mandamus petition, essentially because Amgen never asserted the cell-culture patents that would have made the cell-culture information relevant. The Federal Circuit rejected Amgen's argument that it needed the information before it could have listed the cell-culture patents during the BPCIA patent information exchange process, agreeing with Hospira that "Amgen could have validly listed its cell-culture patents under paragraph (*l*)(3)(A) and that Hospira would have been obligated to respond with 'detailed statement[s]' under paragraph (*l*)(3)(B)."[146] In this way, the Federal Circuit concluded, "Amgen would have had an opportunity to assess the reasonableness of its litigation position long before filing suit."[147] Accordingly, "Amgen has not established a clear and indisputable right to discovery of the information it seeks" and "therefore has not established the prerequisites" for a writ of mandamus.[148]

§ 13:5.6 Amgen v. Sandoz (*Neulasta®*)

In *Amgen Inc. v. Sandoz Inc.*,[149] the Federal Circuit affirmed a district court's award of summary judgment of no literal infringement

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142. Amgen Inc. v. Hospira, Inc., 866 F.3d 1355, 2017 WL 3427716 (Fed. Cir. Aug. 10, 2017).
143. *Id.*, 2017 WL 3427716, at *2.
144. *Id.*
145. *Id.* at *4.
146. *Id.* at *6.
147. *Id.*
148. *Id.*
149. Amgen Inc. v. Sandoz Inc., 923 F.3d 1023 (Fed. Cir. 2019).

and no infringement under the doctrine of equivalents with respect to patents that Amgen asserted against Sandoz's biosimilar version of Amgen's Neulasta® (pegfilgrastim) biologic product.

§ 13:5.7 Amgen v. Coherus *(Neulasta®)*

In *Amgen Inc. v. Coherus Biosciences Inc.*,[150] the Federal Circuit affirmed the district court's dismissal of Amgen's complaint against Coherus for failure to state a claim, concluding that prosecution history estoppel precluded Amgen's claim that Coherus's biosimilar of Amgen's Neulasta® product infringed under the doctrine of equivalents. The claim at issue was directed to a protein purification process that specified the use of one of three salt combinations. Coherus's process did not use any of those three recited salt combinations. The Federal Circuit agreed with the district court that other salt combinations, including the one used by Coherus, had been surrendered during prosecution, and thus affirmed dismissal of Amgen's doctrine of equivalents infringement claim: "We agree with the district court that, during prosecution of the '707 patent, Amgen clearly and unmistakably surrendered salt combinations other than the particular combinations recited in the claims. Prosecution history estoppel thus bars Amgen from succeeding on its infringement claim under the doctrine of equivalents."[151]

§ 13:5.8 Amgen v. Hospira *(Epogen®)*

In *Amgen Inc. v. Hospira, Inc.*,[152] the Federal Circuit affirmed the denial of Hospira's motion for judgment as a matter of law (JMOL) and alternative new trial motion and thereby let stand a jury verdict that one of two Amgen patents-in-suit was infringed and not invalid, that fourteen batches of Hospira's biosimilar version of Amgen's Epogen® (erythropoietin) product were not covered by the Safe Harbor of 35 U.S.C. § 271(e)(1) because they were not related to developing information for the FDA, and that Amgen was entitled to $70 million in damages. The Federal Circuit also affirmed the denial of Amgen's JMOL motion and alternative new trial motion, upholding the jury's verdict of non-infringement of Amgen's second patent-in-suit.

The Federal Circuit concluded that the district court's jury instruction on the Safe Harbor defense was proper and that the jury's finding that fourteen of twenty-one Hospira batches at issue were not subject to the Safe Harbor was supported by substantial

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150. Amgen Inc. v. Coherus Biosciences Inc., 931 F.3d 1154 (Fed. Cir. 2019).
151. *Id*. at 1159.
152. Amgen Inc. v. Hospira, Inc., 944 F.3d 1327 (Fed. Cir. 2019).

evidence. The Federal Circuit also concluded that substantial evidence supported the jury's other findings, including damages.

§ 13:5.9 Immunex v. Sandoz (*Enbrel®*)

In *Immunex Corp. v. Sandoz, Inc.*,[153] the Federal Circuit affirmed a district court judgment in favor of Immunex, the developer of the biologic drug product Enbrel®, its exclusive licensee Amgen Manufacturing, and patent owner Roche against Sandoz, which had filed an application with the FDA seeking approval for its biosimilar version of Enbrel®, Erelzi®. In the litigation, Immunex asserted two patents directed to the fusion protein etanercept and methods of making etanercept, the active ingredient in Enbrel®. Prior to trial, Sandoz stipulated to infringement of the asserted claims of the two patents. Following a bench trial, the district court rejected Sandoz's invalidity defenses of obviousness-type double patenting, written description, and obviousness, and entered judgment in favor of plaintiffs.

On appeal, the Federal Circuit affirmed in a 2–1 decision, with Judges O'Malley and Chen in the majority and Judge Reyna dissenting. The Federal Circuit rejected Sandoz's obviousness-type double patenting defense because it concluded that Roche, the patentee, did not transfer all substantial rights in those patents to Immunex, therefore precluding a finding that the Roche patents were commonly owned with the asserted reference patents owned by Immunex. Because common ownership of the challenged patents and the reference patents was a predicate to obviousness-type double patenting, the defense failed. The Federal Circuit also agreed with the district court that the priority application for the patents-in-suit adequately described the claimed fusion protein. Finally, the Federal Circuit also agreed with the district court's rejection of the obviousness defense, concluding that motivation to combine the asserted prior art references had not been established and agreed with the district court's weighing of the objective indicia of non-obviousness. Judge Reyna's dissent was directed to the obviousness-type double patenting defense and his view that the rights retained by Roche in the licensed patents were "illusory" and therefore common ownership existed.

§ 13:5.10 Genentech v. Immunex (*Avastin®*)

In *Genentech, Inc. v. Immunex Rhode Island Corp.*,[154] the district court denied Genentech's motions for a temporary restraining

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153. Immunex Corp. v. Sandoz, Inc., 964 F.3d 1049 (Fed. Cir. 2020).

154. Genentech, Inc. v. Immunex R.I. Corp., 395 F. Supp. 3d (D. Del. 2019), *aff'd*, 964 F.3d 1109 (Fed. Cir. 2020).

order to prevent the defendants from marketing Mvasi®, a biosimilar version of Genentech's Avastin (bevacizumab) product. The district court rejected Genentech's argument that the filing of supplements to Amgen's aBLA rendered ineffective Amgen's prior notice of commercial marketing under section 262(l)(8)(A) and required Amgen to provide a new notice.

On appeal, the Federal Circuit affirmed, agreeing with the district court that Amgen's notice of commercial marketing was effective and that it did not have to provide new notices following the filing of supplements to its aBLA. The Federal Circuit concluded that

> Amgen notified Genentech of its intent to commercially market its biological product, Mvasi®, on October 6, 2017. Despite its later supplements to its applications adding a manufacturing facility and changing its drug product label, Amgen's biological product, Mvasi®, did not change. Genentech, therefore, had notice of Amgen's intent to commercially market Mvasi as required under Section 262(*l*)(8)(A) as early as October 6, 2017.[155]

In interpreting the BPCIA, the Federal Circuit concluded that "[a] biosimilar applicant that has already provided Section 262(*l*)(8)(A) notice regarding its biological product need not provide another notice for each supplemental application concerning the same biological product."[156]

§ 13:5.11 Janssen v. Celltrion (*Remicade®*)

In *Janssen Biotech, Inc. v. Celltrion Healthcare Co. Ltd.*, the Federal Circuit affirmed in a per curiam decision the district court's grant of summary judgment that Celltrion's Inflectra® biosimilar version of Janssen's Remicade® biologic product did not infringe a formulation patent under the doctrine of equivalents.[157] Previously, the Federal Circuit had affirmed the decision of the Patent Trademark and Appeal Board in an ex parte reexamination that another Janssen patent on the antibody contained in Remicade was invalid for obviousness-type double patenting.[158]

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155. *Immunex*, 964 F.3d at 1111.
156. *Id.* at 1112.
157. Janssen Biotech, Inc. v. Celltrion Healthcare Co., 2018 WL 10910845 (D. Mass. July 30, 2018), *aff'd per curiam*, 796 F. App'x 741 (Fed. Cir. Mar. 5, 2020).
158. *In re* Janssen Biotech, Inc., 880 F.3d 1315 (Fed. Cir. 2018). In a series of decisions, the district court had granted summary judgment that Janssen's patents directed to the antibody contained in Remicade® were invalid for obviousness-type double patenting. Janssen Biotech, Inc. v. Celltrion Healthcare Co., 210 F. Supp. 3d 244 (D. Mass. 2016), 210 F.

§ 13:5.12 Genentech v. Amgen (*Herceptin®*)

In *Genentech, Inc. v. Amgen Inc.*,[159] the district court denied Genentech's motion for a temporary restraining order and a preliminary injunction to prevent Amgen's marketing of Kanjinit®, its biosimilar version of Genentech's Avastin® biologic product. The district court found that Genentech had failed to make the required showing of irreparable harm where it received Amgen's notice of commercial marketing on May 15, 2018, and Kanjinit® was approved on June 13, 2019, but Genentech did not file its motions for temporary restraining order and preliminary injunction until July 10, 2019. The district court concluded that Genentech's "undue delay" warranted denial of its motions. In addition, the district court found that Genentech had granted licenses to certain of its patents that would allow other applicants for biosimilar versions of Avastin® to enter the market, which also supported a failure to show irreparable harm. The Federal Circuit affirmed the district court in a per curiam decision. The case was voluntarily dismissed by stipulation of the parties on July 7, 2020.

§ 13:5.13 AbbVie Inc. v. Alvotech hf. (*Humira®*)

In 2021, AbbVie filed a pair of related cases involving Alvotech's AVT02, a biosimilar version of AbbVie's Humira® product: one to adjudicate Alvotech's infringement of four patents selected by Alvotech for immediate litigation under the first phase of BPCIA litigation and one to adjudicate sixty other patents relating to Humira® triggered by Alvotech's notice of commerical marketing under the second phase of BPCIA litigation.[160] Alvotech moved to dismiss AbbVie's infringement claims in the second-phase litigation action, arguing that the second phase was limited to declaratory judgment and preliminary injunctive relief.[161] Alvotech's argument was based, in part, on the differences in the statutory language in section 262(l)(6) and sections 262(l)(8)–(9), which govern the first and second phases, respectively.[162]

Supp. 3d 278 (D. Mass. 2016), and 211 F. Supp. 3d (D. Mass. 2016). Janssen's appeal of the district court's decision was dismissed by the Federal Circuit as moot in light of the Federal Circuit's affirmance of the PTAB's decision of obviousness-type double patenting. 2018 WL 2072723 (Fed. Cir. Jan. 23, 2018).

159. Genentech, Inc. v. Amgen Inc., 2019 WL 3290167 (D. Del. July 18, 2019), *aff'd per curiam*, 796 F. App'x 726 (Fed. Cir. Mar. 6, 2020).

160. AbbVie Inc. v. Alvotech hf., No. 21 C 2238, ECF No. 1; AbbVie Inc. Alvotech hf., No. 21 C 2899, ECF Nos. 1, 77.

161. AbbVie Inc. v. Alvotech hf., 582 F. Supp. 3d 584, 590 (N.D. Ill. 2022).

162. *Id*. at 591–92.

Specifically, Alvotech noted that sections 262(l)(8)–(9) lack the phrase "an action for patent infringement" present in section 262(l)(6), while section 262(l)(9)(A) further describes second-phase litigations as actions "for a declaration of infringement, validity, or enforceability."[163] In denying Alvotech's motion to dismiss, the district court concluded that

> Indeed, it is more natural to read the BPCIA as first creating an artificial act of infringement with respect to all patents (both those in phase one and phase two), § 271(e)(2)(C); focusing the parties (and the trial court) on the most relevant patents in phase one . . . ; then encouraging the parties to litigate any remaining relevant patents in phase two, where the RPS can seek declaratory relief as to those patents, as well as remedies provided by § 271(e)(4).[164]

§ 13:5.14 Regeneron v. Mylan *(Eylea®)*

On August 2, 2022, Regeneron filed a BPCIA action against Mylan in the Northern District of West Virginia, asserting twenty-four patents based on Mylan's filing of an aBLA directed to a biosimilar of Regeneron's Eylea® biologic product.[165] Shortly after filing the complaint, Regeneron filed a motion requesting an expedited status conference to put in place a case schedule that would enable it to obtain a statutory permanent injunction under 35 U.S.C. § 271(e)(4)(D), which "requires resolving the parties' disputes through final judgment and appeal *before* the date on which FDA may approve the biosimilar product for marketing."[166] Mylan opposed the motion, arguing that (1) no substantive rights would be lost under a longer case schedule in view of the May 2024 expiration of regulatory exclusivity and availability of a preliminary injunction and (2) such schedule would deprive it of its statutory right to control the timing and scope of litigation from its participation in the patent dance.[167] The district court entered a scheduling order setting trial for June 12, 2023, for the subset of asserted patents as to which Regeneron sought injunctive relief, approximately ten months after filing, consistent with Regeneron's request.[168]

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163. *Id*. at 591.
164. *Id*. at 592.
165. Regeneron Pharm., Inc. v. Mylan Pharm. Inc., No. 1:22-cv-00061-TSK (N.D. W. Va. Aug. 5, 2022), ECF No. 1.
166. Regeneron Pharm., Inc. v. Mylan Pharm. Inc., No. 1:22-cv-00061-TSK (N.D. W. Va. Aug. 5, 2022), ECF No. 7.
167. Regeneron Pharm., Inc. v. Mylan Pharm. Inc., No. 1:22-cv-00061-TSK (N.D. W. Va. Aug. 19, 2022), ECF No. 26.
168. Regeneron Pharm., Inc. v. Mylan Pharm. Inc., No. 1:22-cv-00061-TSK (N.D. W. Va. Oct. 25, 2022), ECF No. 87.

§ 13:5.15 Genentech v. Dr. Reddy's Laboratories *(Rituximab)*

On November 17, 2023, Genentech, Hoffmann-La Roche, and Biogen jointly filed a complaint in the federal district court for the District of New Jersey against Dr. Reddy's Laboratories and Fresenius Kabi based on the filing of an abbreviated new drug application for a biosimilar version of plaintiffs' Rituxan® (rituximab) biologic product. Plaintiffs alleged that defendants had failed to provide necessary manufacturing information required by the BPCIA, despite having received a request. The patent dance proceedings resulted in plaintiffs asserting fifteen patents against defendants. Defendants provided a 180-day Notice of Commercial Marketing on November 16, 2023, the day before the action was filed. The complaint seeks a declaration of infringement and patent validity, damages, and an injunction against sales of defendants' biosimilar product.[169]

§ 13:6 Conclusion

The BPCIA provides a pathway for the accelerated approval of biosimilar drug products. As described above, the provisions governing the procedures by which a reference product sponsor and a biosimilar applicant will litigate patent issues prior to FDA approval or commercial launch of the biosimilar product are complex and may be subject to differing interpretations. The patent litigation procedures of the BPCIA have been tested in the courts as the number of biosimilar applications and resulting patent litigations have increased since the BPCIA's enactment.

Just as the jurisprudence for the Hatch-Waxman Act has evolved over many years, and indeed continues to evolve, the body of case law relating to the BPCIA is also evolving. As the number of biologic drugs approved by the FDA continues to grow, and with it the number of patent challenges by biosimilar applicants, litigation under the BPCIA should mature much in the same way as Hatch-Waxman litigation. Thus, it is expected that the parties and the courts will develop and adopt practices and procedures to facilitate the conduct and resolution of BPCIA litigation.

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169. Genentech, Inc. v. Dr. Reddy's Labs., Inc., No. 2:23-cv-22485 (D.N.J. 2023).

Chapter 14. Patent Issues Confronting Cell and Gene Therapy Products

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Chapter 14

Patent Issues Confronting Cell and Gene Therapy Products

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§ 14:1 Overview of Cell and Gene Therapy Products

§ 14:1.1 Introduction

Cell and gene therapies are two relatively new treatment modalities that have emerged as promising approaches in the treatment or prevention of disease and, in particular, the treatment of rare and often life-threatening or debilitating diseases. Cell and gene therapies are directed to manipulating and modifying a patient's cells to achieve a therapeutic effect. These therapies can provide the ability to tailor and target therapies specific for a particular patient and achieve results previously unavailable to clinicians.

Cell and gene therapies are generally directed to the treatment of small patient populations for whom standard therapies have been ineffective. As such, those developing these products will seek to protect their investments through patents. Because cell and gene therapies operate at the cellular level and involve the transformation of a patient's cells, the patent landscape for such therapies is complex and covers a wide range of aspects.

Although academic research institutions and biotech startups have primarily conducted initial research and development related to cell and gene therapies, growth opportunities have attracted increased research and investment more broadly, including the largest pharmaceutical companies. This chapter provides insight into some of the opportunities, challenges, and uncertainties surrounding patent protection of cell and gene therapy products, including an overview of the patent landscape and recent U.S. patent law developments.

§ 14:1.2 Cell and Gene Therapy Products Defined

While closely related and to a certain extent overlapping, cell and gene therapies can be differentiated by their intended purposes. Cell therapies generally involve the manipulation of a cell to alter its function to provide a therapeutic effect, whereas gene therapies generally involve the replacement, inactivation, or introduction of genes into cells, including to restore function when a patient's gene is missing or defective.

The U.S. Food and Drug Administration (FDA) provides a global definition of "gene therapy" that encompasses both cell and gene therapies:

> Human gene therapy seeks to modify or manipulate the expression of a gene or alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples

> of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings.[1]

The American Society of Cell and Gene Therapy provides the following descriptions of cell and gene therapies:

> **Cell Therapy** is the transfer of cells into a patient with the goal of improving a disease. Some cell therapies are routine, like blood transfusions. One approach is gene-modified cell therapy, which removes the cells from the patient's body, then a new gene can be introduced or a faulty gene can be corrected. The modified cells are then put back into the body. An example of this approach is CAR-T cell therapy.
>
> **Gene Therapy** is the use of genetic material in the treatment or prevention of disease. Typically, genetic material, such as a working copy of a gene, is delivered to cells using a vector. A vector is often derived from a virus. For safety, all viral genes are removed and the vector is modified to only deliver therapeutic genes into the cells. Once in the cell, a working copy of the gene will help make proteins despite the presence of a faulty gene. Achieving the normal expression and function of proteins makes a big impact on our overall health.[2]

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1. U.S. FOOD & DRUG ADMIN., FDA Guidance: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (Sept. 2021), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interpreting-sameness-gene-therapy-products-under-orphan-drug-regulations.
2. AM. SOC. OF GENE CELL THERAPY, *Different Approaches*, https://patienteducation.asgct.org/gene-therapy-101/different-approaches (last updated Nov. 5, 2021). *See also* Wuyuan Zhou & Xiang Wang, *Human gene therapy: a patent analysis*, 803 GENE 145889 (Nov. 30, 2021) ("Gene therapy is an emerging experimental treatment that delivers functional genes into the human body to counter or replace malfunctioning genes, thus curing diseases without pharmacological intervention, radiotherapy, or surgery.").

§ 14:1.3 The U.S. Regulatory Pathway for Cell and Gene Therapy Products

Cell and gene therapy products are regulated as biologic drug products in the United States and are therefore governed under section 351 of the Public Health Service Act.[3] Biologic drugs are reviewed by the FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER). The Biologics Price Competition and Innovation Act of 2009 (BPCIA) provides regulatory exclusivities for approved biologic products and an accelerated pathway for the approval of "biosimilar" versions of innovator biologic products. The BPCIA also provides procedures for innovator companies to assert patents against applicants seeking to market biosimilar versions of the innovator's approved products.[4]

§ 14:1.4 FDA-Approved Cell and Gene Therapy Products

In 2017, the FDA approved the first cell therapy product in the United States, Kymriah®, and the first gene therapy product, Luxturna©. Subsequently, five additional oncolytic and gene therapy products have been approved. The twenty-five cell and gene therapy products approved by the FDA to date are summarized in the chart below.[5]

Product Name	Manufacturer	Original Approval Date	Approved Indications
ABECMA	Celgene Corp.	March 26, 2021	Relapsed or refractory multiple myeloma after four or more prior lines of therapy

3. 42 U.S.C. § 262.
4. Biologic drug products and the BPCIA regime providing for regulatory and patent exclusivities for innovators and the pathway for biosimilar approval are covered more fully in chapter 13, *supra*.
5. *See* U.S. FOOD & DRUG ADMIN., Approved Cellular and Gene Therapy Products, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products (last updated Sept. 19, 2022). Note that products approved prior to 2017 do not involve gene manipulation. Asterisks (*) indicate indications approved under accelerated approval.

Product Name	Manufacturer	Original Approval Date	Approved Indications
ADSTILADRIN	Ferring Pharmaceuticals	December 16, 2022	For the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors
ALLOCORD (HPC, Cord Blood)	SSM Cardinal Glennon Children's Medical Center	May 30, 2013	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
AMTAGVI	Iovance Biotherapeutics, Inc.	February 16, 2024	Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without an MEK inhibitor
BREYANZI	Juno Therapeutics, Inc.	February 5, 2021	Relapsed or refractory large B-cell lymphoma
CARVYKTI	Janssen Biotech, Inc.	February 28, 2022	Relapsed or refractory multiple myeloma after four or more prior lines of therapy
CLEVECORD (HPC, Cord Blood)	Cleveland Cord Blood Center	September 1, 2016	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment

Product Name	Manufacturer	Original Approval Date	Approved Indications
DUCORD (HPC, Cord Blood)	Duke University School of Medicine	October 4, 2012	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
ELEVIDYS	Sarepta Therapeutics, Inc.	January 10, 2024	Treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene
GINTUIT	Organogenesis Inc.	March 9, 2012	Mucogingival conditions
HEMACORD (HPC, Cord Blood)	New York Blood Center, Inc.	November 10, 2011	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank	May 24, 2012	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
HPC, Cord Blood	MD Anderson Cord Blood Bank	June 21, 2018	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment

Product Name	**Manufacturer**	**Original Approval Date**	**Approved Indications**
HPC, Cord Blood	LifeSouth Community Blood Centers, Inc.	June 13, 2013	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
HPC, Cord Blood	Bloodworks	January 28, 2016	Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
IMLYGIC	BioVex, Inc.	October 27, 2014	Unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
KYMRIAH	Novartis Pharmaceuticals Corp.	August 30, 2017	Relapsed or refractory B-cell acute lymphoblastic leukemia in pediatric and young adult patients Relapsed or refractory diffuse large B-cell lymphoma in adults after two or more lines of therapy Relapsed or refractory follicular lymphoma in adults after two or more lines of therapy

Product Name	Manufacturer	Original Approval Date	Approved Indications
LANTIDRA	CellTrans Inc.	June 28, 2023	The treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education
LAVIV	Fibrocell Technologies, Inc.	June 21, 2011	Moderate to severe nasolabial fold wrinkles in adults
LENMELDY	Orchard Therapeutics (Europe) Ltd.	March 18, 2024	Indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)
LUXTURNA	Spark Therapeutics, Inc.	December 19, 2017	Confirmed biallelic RPE65 mutation-associated retinal dystrophy
LYFGENIA	bluebird bio, Inc.	December 8, 2023	Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs)
MACI	Vericel Corp.	December 13, 2016	Symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement

Product Name	Manufacturer	Original Approval Date	Approved Indications
OMISERGE	Gamida Cell Ltd.	April 17, 2023	For use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection
PROVENGE	Dendreon Corp.	April 29, 2010	Asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer
RETHYMIC	Enzyvant Therapeutics GmbH	October 8, 2021	Congenital athymia in pediatric patients
ROCTAVIAN	BioMarin Pharmaceutical Inc.	June 23, 2023	Indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test
SKYSONA	bluebird bio, Inc.	September 16, 2022	Early, active cerebral adrenoleukodystrophy in patients less than eighteen years of age

Product Name	Manufacturer	Original Approval Date	Approved Indications
STRATA-GRAFT	Stratatech Corp.	June 14, 2021	Thermal burns containing intact dermal elements for which surgical intervention is clinically indicated in adults
TECARTUS	Kite Pharma, Inc.	July 24, 2020	Relapsed or refractory mantle cell lymphoma in adults* Relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults
VYJUVEK	Krystal Biotech, Inc.	August 7, 2023	For the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene
YESCARTA	Kite Pharma, Inc.	October 18, 2017	Large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within twelve months of first-line chemoimmunotherapy in adults Relapsed or refractory large B-cell lymphoma after two or more lines of therapy in adults Relapsed or refractory follicular lymphoma after two or more lines of therapy in adults*

Product Name	Manufacturer	Original Approval Date	Approved Indications
ZYNTEGLO	bluebird bio, Inc.	August 17, 2022	β-thalassemia requiring regular red blood cell transfusions in adult and pediatric patients
ZOLGENSMA	Novartis Gene Therapies, Inc.	May 24, 2019	Spinal muscular atrophy in pediatric patients less than two years of age with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene

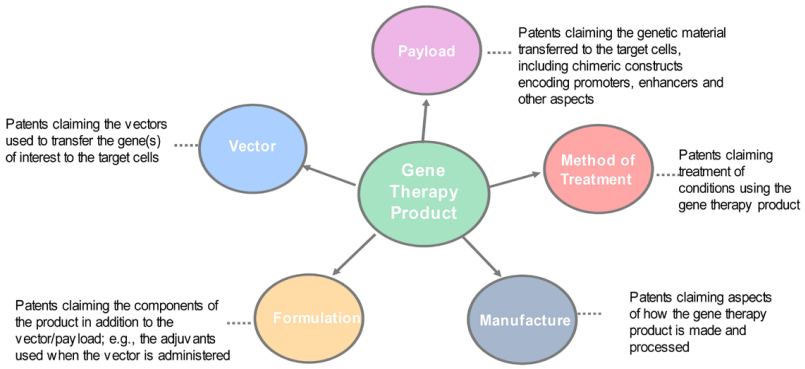
§ 14:2 Patent Landscape for Cell and Gene Therapy Products

At a high level, cell and gene therapies patenting activity has tended to fall into four main areas: patents directed to (1) basic biology of the gene and diseases (e.g., antisense modulation, RNA & DNA editing); (2) diseases being treated (e.g., cancers, diabetes, asthma), (3) methods (e.g., stem cells, vector technologies) for delivering genetic material to the target cells; and (4) potential adverse events (e.g., immune response, immune suppressive treatment).[6] Additional patents surrounding cell and gene therapies include patents directed to formulation of the product (including adjuvants), dosing and administration, and manufacture (including methods of cell growth and culture, processing, and purification). In particular, there has been significant patenting activity directed to viral and non-viral vectors for the delivery of genetic materials to target cells.[7]

6. *See* Zhou & Wang, *supra* note 2, at 5.
7. *See id*. at Fig. 1 (showing patenting activity for vectors).

Figure 14-1

Patent Activity for Vectors



Due to the complexity of the cell and gene therapy patent landscape, and because relevant platform technologies and associated patents may be developed and owned by multiple entities, licensing of patents is expected to be relatively common in the cell and gene therapy field.

§ 14:3 Current Patent Issues and Disputes Relating to Cell and Gene Therapy Products

§ 14:3.1 Section 101 and 112 Issues Impacting Cell and Gene Therapy Products

[A] Patent Eligibility

Under section 101 of the Patent Act, "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" is patent-eligible.[8] However, the Supreme Court has long held that this provision contains an implicit exception for laws of nature, natural phenomena, and abstract ideas, which are not patentable.[9] At the same time, the Court has stressed that an invention is not rendered ineligible for patent protection merely because it involves a law of nature, natural phenomenon, or abstract

8. 35 U.S.C. § 101 (2018).
9. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 70 (2012).

idea because "[a]t some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'"[10]

In 2012, the Supreme Court set forth a two-step framework, commonly known now as the "*Alice/Mayo* test," for distinguishing patents that claim such patent-ineligible exceptions from patents that claim patent-eligible applications of those concepts. In step one of the *Alice/Mayo* test, the court determines whether the claims of the patent are directed to a law of nature, natural phenomenon, or abstract idea, focusing on the claim as a whole. If the claims are directed to such a concept, the inquiry proceeds to step two, where the court examines whether the additional elements, considered individually and as an ordered combination, transform the nature of the claim into a patent-eligible application.

Over the past decade, the Supreme Court has weighed in on the patent eligibility of a range of additional subject matter, including diagnostic claims and gene claims in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* and *Association for Molecular Pathology v. Myriad Genetics, Inc.*, respectively.[11]

At issue in *Mayo* were claims reciting "[a] method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder" comprising a step of administering a thiopurine drug to a patient, a step of determining the resulting metabolite level, and a "wherein" clause providing the metabolite concentrations correlating with the toxicity and efficacy of thiopurine drug dosages.[12] Applying the two-step framework, the Supreme Court found that the claims (1) recited "laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm"; and (2) failed to add steps "sufficient to transform the nature of the claim."[13] In particular, the Court found the "administering" step, "determining" step, and "wherein" clause to "consist of well-understood, routine, conventional activity" previously engaged in by those in the field. Because the combination of the steps "amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients," the Court held that the three steps were insufficient to transform the patent-ineligible natural correlations into patent-eligible applications.[14]

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10. Alice Corp. v. CLS Bank Int'l, 573 U.S. 208, 216–17 (2014).
11. *Mayo*, 566 U.S. at 66; Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).
12. *Mayo*, 566 U.S. at 74–75.
13. *Id.* at 76, 78.
14. *Id.* at 79–80.

At issue in *Myriad* were composition claims for isolated DNA sequences coding for BRCA1 and BRCA2 and related claims to cDNA for the same. The Court distinguished the claims to isolated genomic DNA from the claims to cDNA, holding that "[a] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring."[15] In distinguishing the claims, the Court emphasized that the claims, which were "not expressed in terms of chemical composition" or "[relying] in any way on the chemical changes that result from the isolation of a particular section of DNA," could not be "saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule."[16] The Court further emphasized that its decision did not implicate the patentability of DNA in which the order of the naturally occurring nucleotides has been altered or the patentability of applications of knowledge about genes.[17] The Supreme Court has not opined on such issues to date.[18]

[B] Written Description and Enablement

Section 112 of the Patent Act provides that a patent "specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same."[19] In the decade since the Federal Circuit's en banc decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* reaffirming that the provision contains a written description requirement separate from an enablement requirement,[20] section 112 challenges have garnered additional attention, in particular, in "unpredictable" arts like those surrounding cell and gene therapies. Recent Federal Circuit opinions in *Juno Therapeutics, Inc. v. Kite Pharma, Inc.* and *Amgen Inc. v. Sanofi, Aventisub LLC* provide greater insight into the scope of

15. *Myriad*, 569 U.S. at 576.
16. *Id*. at 593.
17. *Id*. at 595.
18. *See* REGENXBIO Inc. v. Sarepta Therapeutics, Inc., No. 20-1226-RGA (D. Del. Jan. 5, 2024) ("[t]aking 'two sequences from two different organisms and put[ting] them together . . . is no different than taking two strains of bacteria and mixing them together'"—the process does not change "any of the claimed invention's naturally occurring components" and is therefore not patentable under § 101).
19. 35 U.S.C. § 112(a) (2018).
20. Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

disclosure sufficient to meet the written description and enablement requirements of particular import to cell and gene therapies.

[B][1] Juno v. Kite

In *Juno*, the Federal Circuit reversed a $1.2 billion judgment in favor of Juno for infringement of U.S. Patent No. 7,446,190 (the '190 patent) on grounds that the patent lacked adequate written description to support its broad functionally defined genus claims to chimeric antigen receptors (CARs).[21]

At issue were claims directed to a nucleic acid polymer encoding a three-part CAR for a T cell, comprising (1) "the intracellular domain of the human CD3 ζ chain"; (2) "a costimulatory region comprising a specific amino acid sequence" that corresponds to "part of a naturally occurring T cell protein called CD28"; and (3) "a binding element that specifically interacts with a selected target."[22] The broader of the asserted claims, claims 3 and 9, limited the "binding element" to "a single chain antibody" (i.e., a single-chain variable fragment (scFv)), and thus covered "*any* scFv for binding *any* target."[23] The other asserted claims, which depended from claims 3 and 9, further specified that the claimed scFvs bind to CD19, a protein found on blood cancer cells.[24] The specification disclosed two scFv examples, one binding to CD19 and one binding to PSMA, a protein found on prostate cancer cells, but did not disclose the amino acid sequences of these scFvs.

On appeal, Kite argued that the asserted claims failed to disclose representative species or common structural features to identify which scFvs would function as claimed; that the claims covered "millions of billions" of scFv candidates; and that the binding ability of scFvs lacked predictability.[25] Juno raised several counterarguments, including that scFvs in general were well-known in the art and that the specification disclosed two scFv examples representative of all scFvs.[26]

The Federal Circuit rejected Juno's argument that the two scFv examples were representative, explaining that the "mere fact that scFvs in general bind does not demonstrate that the inventors were in possession of the claimed invention."[27] Although it was not necessary

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21. Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1332–33 (Fed. Cir. 2021).
22. *Id*. at 1333–34; '190 patent at claims 3, 5, 9, and 11.
23. *Juno*, 10 F.4th at 1334, 1336.
24. *Id*. at 1334.
25. *Id*. at 1336.
26. *Id*.
27. *Id*. at 1337.

for the patent to disclose the amino acid sequences of the two scFv examples, the court noted that the patent lacked disclosure of any other means of identifying scFvs capable of binding specific targets to demonstrate that the inventors possessed the entire class of possible scFvs that bind to a selected target.[28] The court also found that the '190 patent did not disclose structural features common to the members of the genus of claims 3 and 9, citing expert testimony that (1) "an scFv with the same common structure but with a different amino acid sequence would recognize a different antigen," and (2) "all scFvs have a common structure, regardless of whether they bind."[29] Thus, the fact that scFvs in general were well-known or share the same general structure did not cure the deficiencies with the '190 patent disclosing only two scFv examples and providing no details relating to common characteristics, sequences, or structures for a skilled artisan to identify which scFvs would function as claimed.[30]

With respect to the narrower asserted claims, the Federal Circuit similarly held that the '190 patent lacked written description support for the claimed genus of functional CD19-specific scFvs. The court noted that Juno did not dispute that out of the "millions of billions" of possible scFvs, only four or five CD19-specific scFvs were known in the art as of the priority date of the '190 patent.[31] Relevant considerations included the unpredictability of a scFv's binding ability, the relatively small number of known CD19-specific scFvs compared to the universe of possible scFvs, and the lack of details about the characteristics of any CD19-specific scFv.

Finally, the Federal Circuit rejected Juno's argument that the court's decision in *Ariad* was irrelevant because the real invention of the '190 patent was the claimed two-part "backbone"—comprising the CD3 ζ and costimulatory regions—not the scFv binding element.[32] Citing *Boston Scientific Corp. v. Johnson & Johnson*, the court stated that "[t]he test for written description is the same whether the claim is to a novel compound or a novel combination of known elements. The test is the same whether the claim element is essential or auxiliary to the invention."[33]

On November 7, 2022, the U.S. Supreme Court denied Juno's petition for writ of certiorari.[34]

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28. *Id*.
29. *Id*. at 1339.
30. *Id*. at 1339–40.
31. *Id*. at 1340–41.
32. *Id*. at 1341–42.
33. *Id*. at 1341.
34. Juno Therapeutics, Inc. v. Kite Pharma, Inc., No. 21-1466.

[B][2] Amgen v. Sanofi

In *Amgen*, the Federal Circuit affirmed the district court's judgment as a matter of law of lack of enablement of Amgen's claims to genera of monoclonal antibodies.[35] The decision marked the second time that the Federal Circuit had considered the patents at issue; the court had remanded the case following an earlier jury determination that the patents were not invalid for lack of enablement and written description.[36] On remand, the district court granted Sanofi's motion for judgment as a matter of law for lack of enablement, in part because the claims, which were functionally defined by their ability to bind to one or more of fifteen residues of the PCSK9 protein, encompassed millions of antibody candidates and related to an unpredictable field.

In first discussing precedent on functional claim limitations, the Federal Circuit cautioned that such limitations "pose high hurdles in fulfilling the enablement requirement for claims with broad functional language."[37] The Federal Circuit emphasized that "it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim."[38]

Then, applying the specific *Wands* factors, the Federal Circuit agreed with the district court's findings that (1) the scope of the claims was broad; (2) the invention was in an unpredictable field of science; and (3) a person of ordinary skill in the art could obtain undisclosed claimed embodiments only by a trial and error process that required a substantial amount of time and effort.[39] The Federal Circuit noted that of the disclosed embodiments none bound more than nine residues—despite the claims including antibodies binding up to sixteen—and none bound to three of the claimed residues.[40] With respect to unpredictability of the art, the record also lacked "nonconclusory evidence that the full scope of the broad claims can predictably be generated by the described methods."[41] Taken together, the Federal Circuit determined that undue experimentation would be required to practice the full scope of Amgen's claims.

On November 4, 2022, the U.S. Supreme Court granted Amgen's petition for writ of certiorari with respect to the following Question Presented:

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35. Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080 (Fed. Cir. 2021), *petition for reh'g en banc denied*, 850 F. App'x 794 (Fed. Cir. 2021).
36. *Id*. at 1083–84.
37. *Id*. at 1087.
38. *Id*. at 1086.
39. *Id*. at 1087–88.
40. *Id*. at 1087 n.1.
41. *Id*. at 1087–88.

> Whether enablement is governed by the statutory requirement that the specification teach those skilled in the art to "make and use" the claimed invention, 35 U.S.C. § 112, or whether it must instead enable those skilled in the art "to reach the full scope of claimed embodiments" without undue experimentation—i.e., to cumulatively identify and make all or nearly all embodiments of the invention without substantial "'time and effort,'" Pet. App. 14a.[42]

Oral argument at the U.S. Supreme Court was held on March 27, 2023. The Court unanimously affirmed the Federal Circuit on May 18, 2023, in an opinion authored by Justice Gorsuch.[43] In affirming the invalidity of Amgen's functional genus claims for lack of enablement, the Court reached back to its precedent from the 19th and early 20th centuries holding that claims covering broad classes of subject matter must enable the entire class.

> This Court has addressed the enablement requirement on many prior occasions. *See*, *e.g.*, *Wood v. Underhill*, 5 How. 1 (1846); *O'Reilly v. Morse*, 14 How. 62 (1854); *The Incandescent Lamp Patent*, 149 U. S. 465 (1895); *Minerals Separation, Ltd. v. Hyde*, 242 U. S. 261 (1916); *Holland Furniture Co. v. Perkins Glue Co.*, 277 U. S. 245 (1928). While the technologies in these older cases may seem a world away from the antibody treatments of today, the decisions are no less instructive for it.
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> * * *
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> Our decisions in *Morse*, *Incandescent Lamp*, and *Holland Furniture* reinforce the simple statutory command. If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.[44]

While the Court concluded that its case law established that "a specification may call for a reasonable amount of experimentation to make and use a patented invention," in this case "Amgen has failed to enable all that it has claimed, even allowing for a reasonable degree of experimentation."[45] Referring to its prior precedent, the Court concluded that

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42. Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).
43. *Id*.
44. *Id*. at 1254.
45. *Id*. at 1256.

> [m]uch as Morse sought to claim all telegraphic forms of communication, Sawyer and Man sought to claim all fibrous and textile materials for incandescence, and Perkins sought to claim all starch glues that work as well as animal glue for wood veneering, Amgen seeks to claim 'sovereignty over [an] entire kingdom' of antibodies . . . [I]f our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable. That holds true whether the case involves telegraphs devised in the 19th century, glues invented in the 20th, or antibody treatments developed in the 21st.[46]

The Court also rejected Amgen's argument that the methods that it disclosed in its patent enabled the making of all the antibodies that it functionally claimed:

> We cannot agree. These two approaches amount to little more than two research assignments. The first merely describes step-by-step Amgen's own trial-and-error method for finding functional antibodies. . . . The second isn't much different. It requires scientists to make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too—an uncertain prospect given the state of the art.
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> * * *
>
> Whether [Amgen's] methods . . . might suffice to enable other claims in other patents—perhaps because, as this Court suggested in *Incandescent Lamp*, the inventor identifies a quality common to every functional embodiment, . . . —they do not here. They leave a scientist about where Sawyer and Man left Edison: forced to engage in "painstaking experimentation" to see what works. . . . That is not enablement. More nearly, it is a "hunting license."[47]

Finally, the Court rejected Amgen's arguments that the Federal Circuit had "raise[d] the bar for the enablement of claims that encompass an entire genus by its function." Rather, the Court concluded that the Federal Circuit had "recognized only that the more a party claims for itself the more it must enable. As we have seen, that much is entirely consistent with Congress's directive and this Court's precedents."[48]

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46. *Id*.
47. *Id*. at 1256–57 (citing Brenner v. Manson, 383 U.S. 519, 536 (1966).
48. *Id*. at 1257.

[B][3] Baxalta v. Genentech

In *Baxalta v. Genentech*, Baxalta asserted infringement of patent claims to an isolated antibody that binds to Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa. Genentech's accused product was a bispecific antibody binding to both Factor IXa and Factor X. Judge Dyk, presiding in district court in Delaware, granted summary judgment that Baxalta's claims were invalid due to lack of enablement.[49] The Federal Circuit affirmed this decision based on the precedent set by *Amgen v. Sanofi*, highlighting the insufficiency of disclosed antibodies compared to the expansive claim scope. Despite the millions of potential candidate antibodies, only a few were disclosed, requiring extensive trial and error for others. This inability to predict antibody performance rendered the claims invalid for lack of enablement.[50]

[B][4] Teva v. Eli Lilly

Teva accused Eli Lilly's Emgality® antibody product of infringing patent claims directed to a method of treating migraine headaches by administering humanized antibodies defined by their ability to bind to the protein CGRP. The district court overturned a jury verdict in Teva's favor, granting Eli Lilly judgment as a matter of law after concluding that Teva's patent claims lacked both written description and enablement. The court held that the patent specification did not provide representative species and common structural features sufficient to support written description, citing *Juno* and *Ariad*.[51] Additionally, the court found lack of enablement, citing *Amgen v. Sanofi* and *Baxalta*, due to the functional claim scope compared to the sole disclosed antibody, necessitating extensive trial and error to enable the full scope of the claim.[52]

§ 14:3.2 Potential Implications of Sections 101 and 112 Case Law for Cell and Gene Therapy Patents

- Under current Supreme Court precedent, claims protecting cell and gene therapy products must be carefully drafted to

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49. Baxalta, Inc. v. Genentech, Inc., 579 F. Supp. 3d 595 (D. Del. 2022).
50. Baxalta, Inc. v. Genentech, Inc., 81 F.4th 1362 (Fed. Cir. 2023).
51. Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021); Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010).
52. Teva Pharm. Int'l GmbH v. Eli Lilly & Co., No. 18-cv-12029-ADB, 2023 WL 6282898 (D. Mass. Sept. 26, 2023), *appeal filed*, No. 24-1094 (Fed. Cir. 2023).

avoid claiming a natural gene on its own and natural processes that may lead to challenges based on patent ineligibility under 35 U.S.C. § 101.

- Patents functionally claiming broad aspects of a gene therapy beyond the disclosure may be subject to written description and enablement challenges under 35 U.S.C. § 112.
- Recent Federal Circuit case law highlights the challenge of developing a sufficiently diverse range of examples to support claims of genus scope.
- Innovators should make sure that claim coverage to specific commercial embodiments is solid and well supported.
- A patent strategy must be developed to protect against both innovator and biosimilar competitors.
- Biosimilar challengers will likely have to use same sequences as the innovator and therefore fall within the scope of narrower claims.
- Peer innovators are more likely to use different sequences that may only fall within the scope of broader genus claims that are subject to written description and enablement challenges.
- Per *Juno v. Kite*, the broad features of the claimed construct may not be what the inventors considered the innovative aspect of their invention.

Cell and gene therapy products are likely to implicate patents directed to both broader platform technologies, such as vectors used to carry a genetic payload to a target cell, and technologies specific to a particular product, such as methods of treatment of particular conditions. As such, the patent landscape for cell and gene therapies will continue to be broad and diverse, creating challenges for patent owners seeking to maintain exclusivity and strategic opportunities for patent owners seeking to license or cross-license their innovations.

§ 14:3.3 Pending Cell and Gene Therapy Patent Disputes in District Courts

An indication of the importance of patents to cell and gene therapy products is reflected in currently pending patent litigation at the district court level. These litigations are likely only the beginning as owners of patents in the cell and gene therapy field seek to assert their rights, either to obtain exclusivity in a particular area or to monetize the value of their patent portfolios.

[A] *San Rocco Therapeutics, LLC v. bluebird bio, Inc.*

On October 21, 2021, San Rocco Therapeutics (formerly Errant Gene Therapeutics, LLC) filed a patent infringement suit in the District of Delaware alleging that bluebird's Zynteglo drug product, "which is manufactured using (and containing) the BB305 lentiviral vector," infringes U.S. Patent Nos. 7,541,179 and 8,058,061.[53] On July 26, 2022, the court granted in part bluebird's motion to stay the proceedings and compel arbitration, staying the case pending an arbitrator's determination regarding interpretation of the license and release provisions.[54] As of publication, the case remains stayed pending the results of arbitration.

[B] *Regenxbio Inc. v. Sarepta Therapeutics, Inc.*

On September 14, 2020, REGENXBIO and the Trustees of the University of Pennsylvania filed a patent infringement suit in the District of Delaware alleging that Sarepta's manufacture and use of host cell technology to make recombinant AAV gene therapy products, including SRP-9001, infringe U.S. Patent No. 10,526,617.[55] Defendant moved to dismiss on the basis that its activities in developing its product fell within the "safe harbor" of 35 U.S.C. § 271(e)(*1*), which allows, under certain circumstances, companies to develop products that require FDA premarket approval without risk of patent infringement. The court denied this motion, finding that Sarepta was not developing a product that is "subject to any FDA regulatory approval process."[56] Defendant's answer was filed on January 18, 2022, and the case is proceeding through discovery. The patent-in-suit is expected to expire in November 2022.

[C] *Regenxbio Inc. v. Aldevron LLC*

On September 16, 2020, REGENXBIO and the Trustees of the University of Pennsylvania filed a patent infringement suit in the District of North Dakota alleging that Aldevron's manufacture and use of host cells containing a recombinant nucleic acid sequence

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53. San Rocco Therapeutics, LLC v. bluebird bio, Inc., C.A. No. 21-1478-RGA (D. Del. Oct. 21, 2021).
54. San Rocco Therapeutics, LLC v. bluebird bio, Inc., C.A. No. 21-1478-RGA (D. Del. July 26, 2022).
55. Regenxbio Inc. v. Sarepta Therapeutics, Inc., C.A. No. 20-1226-RGA (D. Del. Sept. 14, 2020).
56. Memorandum Order, Regenxbio Inc. v. Sarepta Therapeutics, Inc., C.A. No. 20-1226-RGA, at 8–9 (D. Del. Jan. 4, 2022).

encoding capsid proteins and a heterologous non-AAV sequence infringes U.S. Patent No. 10,590,435.[57] The parties stipulated to a voluntary dismissal in 2022.

§ 14:4 Conclusion

As more cell and gene therapy products are developed and obtain regulatory approval, it can be expected that patents will play a very important role as the developers of those products seek to protect their substantial investments and may also have to respond to assertions of patent rights by others. Because patents implicating cell and gene therapies may relate to many aspects of the product, its manufacture, and administration, a wide variety of patents can be expected to be raised in the context of adversarial patent proceedings and in licensing and collaboration transactions. Accordingly, those involved in the cell and gene therapy field will want to pay careful attention to these patent developments.

57. Regenxbio Inc. v. Aldevron LLC, No. 3:20-cv-171 (D.N.D. Sept. 16, 2020).

Chapter 15. ITC Litigation: Recent Trends and Practice Tips

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Chapter 15

ITC Litigation: Recent Trends and Practice Tips

Philip W. Marsh

§ 15:1 Introduction

This chapter discusses litigation at the International Trade Commission (ITC), describes some recent trends, and provides some practice tips and strategic considerations for litigating cases in the ITC.

The ITC has broad investigative and research responsibilities concerning trade and has long been a forum for resolving intellectual property (IP) disputes concerning imported goods. In recent years, the popularity of the ITC as a venue for litigating IP disputes has increased dramatically, including in areas that are relatively new for the ITC, such as pharmaceuticals and medical devices. This increase in popularity, along with a series of recent developments, provides an impetus for reviewing the basics of ITC litigation and those recent developments and changes.

§ 15:2 Overview and Background

§ 15:2.1 The ITC

The ITC is an independent, non-partisan, quasi-judicial federal agency that administers U.S. trade laws. It has broad investigative responsibilities and provides the President and the U.S. Trade Representative with independent analysis, information, and support regarding tariffs, international trade, and competitiveness. Among other things, the ITC investigates the effects of dumped and subsidized imports on domestic industries and conducts global safeguard investigations. The ITC lists its mission as follows:

> The mission of the Commission is to (1) investigate and make determinations in proceedings involving imports claimed to injure a domestic industry or violate U.S. intellectual property rights; (2) provide independent analysis and information on tariffs, trade, and competitiveness; and (3) maintain the U.S. tariff schedule.[1]

The ITC accomplishes its mission in three areas of U.S. international trade:

1. **adjudication**, such as import injury investigations (e.g., antidumping and countervailing duty) and intellectual property investigations;
2. **Research and analysis**, such as industry and economic analysis and tariff and trade information services; and
3. **maintaining the Harmonized Tariff Schedule.**[2]

This chapter focuses on the ITC's responsibility for intellectual property investigations, which falls within the adjudication area mentioned above.

§ 15:2.2 Section 337 Investigations

The ITC conducts intellectual property investigations under section 337 of the Tariff Act of 1930, as amended.[3] Section 337 authorizes investigations based on the following:[4]

- unfair methods of competition;
- patent infringement;
- copyright and mask work infringement; and
- trademark infringement.

The unfair methods of competition are recited broadly in the statute and have been interpreted broadly as well. Section 337 specifically lists specific categories of injuries from unfair methods of competition to include activities, the threat or effect of which is:

i. to destroy or substantially injure an industry in the United States;[5]

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1. U.S. Int'l Trade Comm'n, About the USITC, https://www.usitc.gov/press_room/about_usitc.htm.
2. *Id*.
3. 19 U.S.C. § 1337.
4. *Id*. § 1337(a)(1).
5. *Id*. § 1337(a)(1)(A)(i).

ii. to prevent the establishment of such an industry;[6] or

iii. to restrain or monopolize trade and commerce in the United States.[7]

Unfair competition has been found to extend to a number of different types of legal claims, including trade secret misappropriation,[8] false advertising and Lanham Act claims,[9] antitrust claims,[10] trade dress claims,[11] and contract claims.[12]

In addition to generalized unfair competition claims, section 337 specifically authorizes the ITC to conduct investigations concerning patent infringement,[13] copyright and mask work infringement,[14] and trademark infringement.[15]

The majority of the ITC's section 337 investigations are patent infringement cases. In 2022, 89.4% of section 337 investigations were for patent infringement alone. That was up somewhat from recent years, with the exception of 2018, which had 85.9% (2021), 85.8% (2020), 86.6% (2019), 91.5% (2018), and 87.2% (2017) of ITC cases concerning only patent infringement.[16] Of the remaining cases, about 3.5% were based on combined grounds that may have also included patent infringement, down from 6.7% the prior year. About 4.2% of the cases in 2022 were trade secret cases, which represents an area where the number of cases has generally been increasing in the past few years: less than 1% (2017), 1.5% (2018), 3.1% (2019), 4.2% (2020), and 6.7% (2021).

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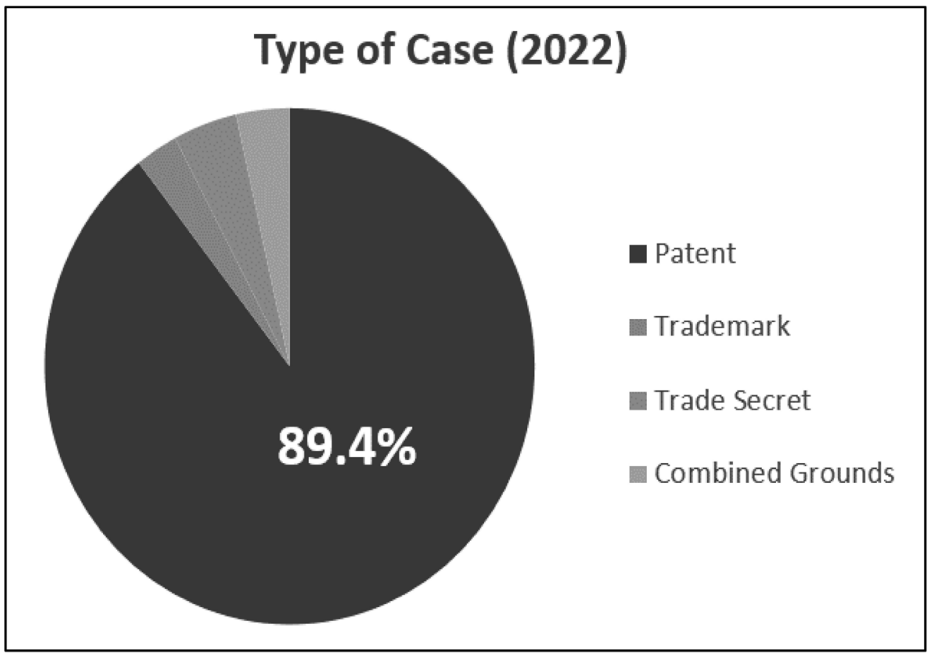
6. *Id*. § 1337(a)(1)(A)(ii).
7. *Id*. § 1337(a)(1)(A)(iii).
8. *See, e.g.*, TianRui Grp. Co. v. Int'l Trade Comm'n, 661 F.3d 1322 (Fed. Cir. 2011).
9. *See, e.g.*, Certain Potassium Chloride Powder Prods., Inv. No. 337-TA-1013; Certain Periodontal Laser Devices, Inv. No. 337-TA-1070; Certain Clidinium Bromide & Prods. Containing Same, Inv. No. 337-TA-1109.
10. *See, e.g.*, Certain Carbon and Alloy Steel Prods., Inv. No. 337-TA-1002; Certain Programmable Logic Controllers, Inv. No. 337-TA-1105.
11. *See, e.g.*, Certain Hand Dryers and Housing for Hand Dryers, Inv. No. 337-TA-1015.
12. *See, e.g.*, Certain Elec. Fireplaces, Inv. No. 337-TA-826.
13. 19 U.S.C. § 1337(a)(1)(B).
14. *Id*. § 1337(a)(1)(B), (D).
15. *Id*. § 1337(a)(1)(C).
16. *See* https://www.usitc.gov/intellectual_property/337_statistics.htm.



§ 15:2.3 Section 337 Investigation Basics

Section 337 investigations are conducted like district court litigations with some differences. The investigations include an additional party and focus on the public interest in addition to resolving the dispute between the private parties.

[A] The Parties

Section 337 investigations are adversarial proceedings like any litigation. The private parties in the ITC are a complainant or complainants (rather than a plaintiff or plaintiffs) and a respondent or respondents (rather than a defendant or defendants). In addition to the private parties, section 337 investigations may involve an additional party from the Office of Unfair Import Investigations (OUII). When applicable, the OUII is represented in the litigation by a "Staff Attorney," who is formally known as the Commission Investigative Attorney.[17] Statutes, rules, and orders relating to "the parties" relate to all parties, including the private parties (complainant(s) and respondent(s)), as well as the OUII or Staff Attorney.

17. U.S. Int'l Trade Comm'n, *Section 337 Investigations at the U.S. International Trade Commission: Answers to Frequently Asked Questions* at 2 (Mar. 2009), https://www.usitc.gov/intellectual_property/documents/337_faqs.pdf.

The Staff Attorney, who is assigned by the Commission and operates as an independent third party in the litigation, represents the public interest and attempts to ensure a complete record. A Staff Attorney is not assigned to each investigation, and the Staff Attorney's level of participation depends on the case. In many cases, the Staff Attorney will fully participate, but in some the Staff Attorney may only partially participate. In such cases, the Staff Attorney's involvement is usually limited to select issues unique to section 337 investigations (e.g., public interest, importation, domestic industry, etc.). In some other cases, a Staff Attorney may not be assigned at all.

When assigned and participating, the Staff attorney may participate fully in discovery, serving discovery requests, for example, and examining witnesses at deposition. In many investigations, the parties conduct regular discovery meetings to discuss potential discovery issues and disputes, and the Staff Attorney participates in those meetings. Additionally, the Staff Attorney may oppose or support motions brought by the private parties. The Staff Attorney also participates at trial and during any other hearings. At trial, this means that the Staff Attorney may examine any witness, may respond to objections, and may advocate positions on behalf of the OUII during any arguments.

Although the Staff Attorney is an ITC employee, the parties may consult with the Staff Attorney on an ex parte basis. It is frequently the case that a complainant will discuss the complaint with the Staff Attorney before filing to ensure that it meets all requirements and to avoid any issues that might cause the complainant to need to re-file. Private parties also frequently consult with the Staff Attorney concerning discovery issues, positions on motions, pre-trial issues, and other issues. In general, the parties try their best to persuade the Staff Attorney of their position to gain support from the OUII for their positions.

[B] The Administrative Law Judges

Each section 337 investigation is assigned to an administrative law judge (ALJ) who presides over the matter. The ALJ is assigned by the Chief ALJ, taking into account the ALJ's schedule, caseloads, and other considerations. The assigned ALJ typically issues a protective order and ground rules for the investigation. The ground rules are analogous to local rules in a district court, except that they are more specific to the presiding ALJ and contain information that might normally be found in a district court judge's standing order. Each ALJ has different ground rules based on his or her preferences. Protective orders in ITC investigations tend to be stricter than protective orders

in district court proceedings and to limit who may obtain confidential business information produced in the investigation.[18]

The ALJ hears and decides discovery disputes, issues subpoenas, issues orders for judicial enforcement of subpoenas, if necessary, and issues "initial determinations" in certain situations.[19] Initial determinations are orders by the ALJ that the Commission has the option to review before the order becomes final. In addition, the ALJ determines how the investigation will be conducted, including the evidentiary hearing or trial.

For example, the ALJ determines how and when to hear and decide claim construction issues. In some cases, an ALJ may elect to have a *Markman* hearing and claim construction briefing, like what would occur in a district court litigation. Frequently, however, ALJs prefer to consider claim construction issues at the end of the case with the other issues. In such situations, there is no separate briefing or hearing for claim construction, but claim construction issues are part of the final Initial Determination that the ALJ issues after trial.

The ALJ also presides over the evidentiary hearing and issues a final initial determination on whether there is a violation of section 337.[20] This includes making a determination on importation, infringement, and domestic industry. The ALJ also makes recommended determinations on whether any permanent relief should be granted, on the amount of bonding, and on public interest, if the Commission has delegated public interest and ordered the ALJ to take evidence on the public interest.[21]

The ITC can have up to six ALJs. The current five sitting ALJs are:[22]

1. Chief Administrative Law Judge Clark S. Cheney;[23]
2. Administrative Law Judge MaryJoan McNamara;[24]
3. Administrative Law Judge Cameron Elliot;[25]
4. Administrative Law Judge Monica Bhattacharyya;[26] and
5. Administrative Law Judge Bryan F. Moore.[27]

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18. *See* 19 C.F.R. § 210.5(b).
19. *See id*. § 210.42.
20. *Id*. § 210.42(a)(1)(i).
21. *Id*. § 210.42(a)(1)(ii).
22. https://www.usitc.gov/alj_bios.
23. https://www.usitc.gov/press_room/bios/cheney.htm_0.
24. https://www.usitc.gov/press_room/bios/mcnamara.htm.
25. https://www.usitc.gov/press_room/bios/elliot.htm.
26. https://www.usitc.gov/press_room/bios/bhattacharyya.htm.
27. https://www.usitc.gov/press_room/bios/moore.htm.

The ITC's ALJs generally have significant IP litigation experience, significant experience as ALJs, and other significant IP and trial experience. Several experienced ALJs have retired in recent years, leaving a younger bench with openings for hiring new ALJs.

[C] The Commission

The Commission consists of up to six commissioners who are nominated by the President and confirmed by the Senate.[28] To maintain the ITC's non-partisan nature, no more than three commissioners may be from any one political party. The commissioners serve overlapping nine-year terms. At the time of writing, there were just four commissioners: three Democrats and one Republican.[29]

The commission has a Chairman and Vice Chairman that are designated by the President from among the sitting commissioners to serve two-year terms.[30] The Chairman and Vice Chairman must be from different political parties, and the Chairman cannot be from the same political party as the immediately preceding Chairman.[31]

The Commission determines whether to institute an investigation based on the filed complaint.[32] The votes of at least three commissioners are needed to institute an investigation. The Commission also has the option to review initial determinations from the ALJ and may issue its own opinions or adopt the ALJ's initial determination either by allowing the time for review to expire or by affirmatively adopting the initial determination.[33] The Commission is advised by its Office of General Counsel.

As of April 2024, the Commissioners are:[34]

- Chairman David S. Johanson,[35]
- Commissioner Rhonda K. Schmidtlein,[36]
- Commissioner Jason E. Kearns,[37]
- Commissioner Amy A. Karpel.[38]

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28. https://www.usitc.gov/commissioner_bios.
29. *Id*.
30. *Id*.
31. *Id*.
32. 19 C.F.R. § 210.10.
33. *See id*. § 210.42(h)(6).
34. https://usitc.gov/commissioner_bios.
35. https://usitc.gov/press_room/bios/johanson.htm.
36. https://usitc.gov/press_room/bios/schmidtlein.htm.
37. https://usitc.gov/press_room/bios/kearns.htm.
38. https://usitc.gov/press_room/bios/karpel.htm.

[D] Review of Decisions on Section 337 Investigations

A section 337 investigation proceeds until the ALJ issues a final initial determination concerning a violation (including determinations of importation, infringement, and domestic industry).[39] The ALJ also makes recommended determinations concerning the remedy (e.g., whether to issue an exclusion order), bonding, and the public interest in cases where it has been delegated by the Commission.[40] The Commission may either review the ALJ's initial determination and recommended determination and either adopt or allow those determinations to become the Commission's determination automatically or further consider them, including ordering briefing and conducting hearings, where necessary.[41]

After the Commission issues its final determination, the President, through the U.S. Trade Representative, has a sixty-day period during which to review the Commission's decision and has an option to reverse the decision for policy reasons.[42] Presidential reversals are rare. In 2013, President Obama waded into a wide-ranging and complex dispute between Apple and Samsung that involved an ITC investigation and reversed the ITC's decision with respect to certain standard-essential patents for the first time since 1987.[43]

In the investigation, Apple raised affirmative defenses that assertion of and licensing of standard-essential patents was contrary to Samsung's FRAND commitments. The Commission disagreed, found a violation by Apple, and issued a limited exclusion order excluding certain Apple iPhones and iPad models. Apple argued to the Commission that the decision was contrary to the public interest. The Commission, after extensive briefing and public comments, determined that a limited exclusion order against older iPhone and iPad models would not adversely affect the public interest. The Obama administration disagreed and overturned the Commission's decision, citing the joint Department of Justice (DOJ) and U.S. Patent and Trademark Office (PTO) *Policy Statement on Remedies for Standard-Essential Patents Subject to Voluntary F/RAND Commitments*, dated January 8, 2013.[44] That statement has since been withdrawn and replaced by the *Policy*

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39. 19 C.F.R. § 210.42(a)(1)(i).
40. *Id*. § 210.42(a)(1)(ii).
41. *See id*. §§ 210.42(h)(6), 210.44, 210.46, 210.50.
42. *Id*. § 1337(j)(2).
43. Certain Electronic Devices Including Wireless Communication Devices, Portable Music and Data Processing Devices, and Tablet Computers, Inv. No. 337-TA-794.
44. https://www.justice.gov/atr/page/file/1118381/download.

Statement on Remedies for Standards-Essential Patents Subject to Voluntary F/RAND Commitments, dated December 19, 2019.[45]

Decisions that become final after the presidential review period are subject to appeal to the Court of Appeals for the Federal Circuit. Enforcement of exclusion orders falls to U.S. Customs and Border Protection. Although ITC cases account for a small percentage of Federal Circuit cases (less than 3%), in recent years the Federal Circuit has considered more cases.[46] For example, in 2019, the Federal Circuit issued eleven decisions in ITC cases and affirmed the ITC in ten of those cases.[47] That affirmance rate of 91% was considerably better than the 60% and 70% affirmance rates of the previous two years.[48]

[E] ITC Investigation vs. District Court Litigation

In many ways, section 337 investigations in the ITC are very similar to IP litigation in district courts. There are, however, some important differences. Many of the differences stem from the fact that a section 337 investigation is a public investigation by an administrative agency charged with certain duties to the public rather than litigation between private parties. That difference drives the use of the OUII and its Staff Attorney to help represent the public interest and ensure a complete record, the inclusion of domestic industry and public interest considerations, and the differences in remedies and enforcement of those remedies.

Below is a comparison table showing some differences between ITC litigation and district court litigation:

ITC	District Court
Public investigation	Private litigation
Fast (avg. 16–18 months total)	Slower (jurisdiction dependent)
In rem jurisdiction; may name multiple respondents at same time	Must show jurisdiction for all parties and meet AIA joinder requirements
Detailed pleading	Notice pleading
ITC serves complaint	Plaintiff serves complaint
No jury; tried to ALJ	Jury trial available

45. https://www.justice.gov/atr/page/file/1228016/download.
46. Dan Bagatell, *Fed. Circ. Patent Decisions in 2019: An Empirical Review*, LAW360.COM (Jan 9. 2020), https://www.law360.com/articles/1232623/fed-circ-patent-decisions-in-2019-an-empirical-review.
47. *Id*.
48. *Id*.

ITC	District Court
Exclusion and cease & desist orders	Money damages; possible injunction
ALJs with IP expertise; handles discovery disputes and hearing	Judge drawn at random; may use magistrate for discovery issues
Target dates are typically 16–18 months	No time limit for completion
No res judicata	Results binding on parties

One big difference between litigation at the ITC and litigation in most district courts is that the ITC investigations proceed much faster. The ITC generally sets a target date for completion of the investigation within sixteen months.[49] That means that trial typically happens about seven to eight months after institution, or about eight to nine months after the complaint is filed.

Because the ITC has in rem jurisdiction over the accused products, jurisdiction can be easier to establish.[50] Likewise, because the joinder rules of the America Invents Act (AIA) do not apply, a complainant may name multiple respondents in the same investigation without concern for those restrictions.[51] Likewise, service of the complaint in the ITC is easier, as the Commission serves the complaint on the respondents, including foreign respondents, avoiding the need for potentially complicated service (e.g., through the Hague Convention).[52]

The ITC has strict requirements for the contents of the complaint, which are generally significantly more detailed than complaints in district court.[53] Complaints in the ITC are filed with specific infringement and domestic industry claim charts and key documents attached, such as patent file histories and prior art references. Thus, ITC complaints can be said to be more like detailed factual pleadings, while district court complaints are more notice pleading documents.

There are no juries in the ITC. Instead, cases are tried before an ALJ, who likely has significant experience with IP litigation. The ALJ also presides over and decides discovery issues and thus may be more familiar with the issues by the time trial arrives than a district

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49. *See* 19 C.F.R. § 210.42(c)(1) (requiring motion to exceed sixteen months).
50. Sealed Air Corp. v. U.S. Int'l Trade Comm'n, 645 F.2d 976, 985–86 (C.C.P.A. 1981).
51. *See* 35 U.S.C. § 299(b).
52. 19 C.F.R. § 210.11.
53. *See id*. § 210.12.

court may be, for example, because of assigning a magistrate judge to preside over discovery matters.[54]

Another important difference between ITC litigation and district court litigation is that the ITC investigations do not always have a preclusive effect on later litigation. In patent cases, in particular, there is no *res judicata* from a final determination in an ITC investigation, even if it involves the same patents, issues, and parties.[55] As discussed below, there may still be judicial estoppel in such patent cases. Other types of ITC investigations have been found to have a preclusive effect over related district court cases.[56]

Procedurally, ITC investigations differ from district court litigation in several other respects. For example, although the presiding ALJ must construe the meaning of any asserted patent claims, many ALJs proceed without separate claim construction briefings or *Markman* hearings. Those ALJs typically wait to construe claims until their final initial determination at the end of the case, which is the same decision in which the ALJ determines whether there is a section 337 violation (e.g., infringement).

Another unique aspect of ITC investigations is the strictness of the protective orders and the protection of confidential business information.[57] ALJs often issue protective orders as the first order of an investigation, and the orders typically require very strict compliance and immediate reporting of any violations.[58]

ALJs typically strictly enforce time limits. Because of this, waiver may result for failure to meet deadlines, and parties will frequently invoke this argument. This is important to be aware of because of the increased speed of the proceeding that can make complying with deadlines difficult if they are not well managed.

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54. *See id*. § 210.15(a).
55. *See* Tex. Instruments Inc. v. Cypress Semiconductor Corp., 90 F.3d 1558, 1569 (Fed. Cir. 1996) (no collateral estoppel, even after Federal Circuit affirmance of ITC infringement decision).
56. **Trade Secret:** *See* Manitowoc Cranes LLC v. Sany Am. Inc., No. 13-C-677, 2018 WL 582334, at *2 (E.D. Wis. Jan. 29, 2018), *aff'g* Sany Heavy Indus. Co. v. Int'l Trade Comm'n, 669 F. App'x 569 (Fed. Cir. 2016). **Trademark & Unfair Trade Practice:** *See* Union Mfg. Co. v. Han Baek Trading Co., 763 F.2d 42, 45–46 (2d Cir. 1985), *abrogated on other grounds*, Two Pesos, Inc. v. Taco Cabana, Inc., 505 U.S. 763 (1992); Balt. Luggage Co. v. Samsonite Corp., 977 F.2d 571 (4th Cir. 1992) (both citing *Han Baek*, 763 F.2d at 45–46). **Antitrust:** Aunyx Corp. v. Canon U.S.A., Inc., 978 F.2d 3, 7 (1st Cir. 1992).
57. *See* 19 C.F.R. §§ 210.5, 210.34.
58. *See id*. § 210.34(c), (d).

The ALJ presides over the evidentiary hearing or the trial in the matter. Trials at the ITC reveal many unique aspects of ITC practice. For example, most ALJs prefer to receive direct testimony in written witness statements. Because documents typically need to be introduced through a sponsoring witness, planning is required to include those documents in the written witness statements. The use of written witness statements changes the dynamic and flow of trial because the first live testimony the ALJ hears from each witness is cross-examination testimony.

Only relevant, material, and reliable information is supposed to be admitted in an ITC trial.[59] The Federal Rules of Evidence are not binding and are not strictly followed but often provide guidance. Because the Federal Rules of Evidence don't apply, hearsay or other evidence not admissible in district court may be permitted in a section 337 investigation. The ALJ will typically weigh the evidence based on how reliable it is, which may mean that hearsay or other less reliable evidence receives less weight.

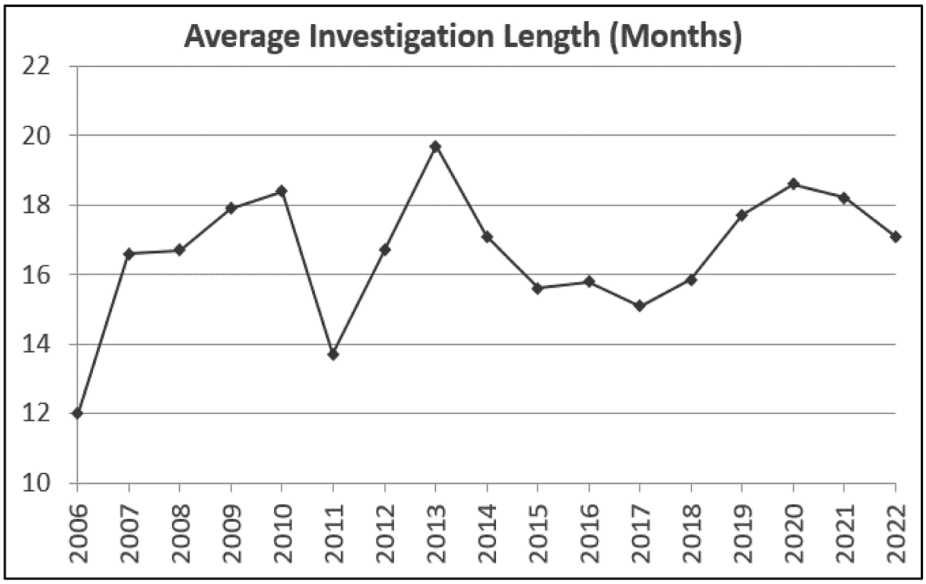
Finally, and importantly, because the ALJ hearings are essentially bench trials before the ALJ who will render a decision later, post-trial briefing and completeness of the record are very important. Only evidence admitted into the record is considered in post-trial briefing.[60] So ensuring that all desired evidence is introduced into the record so that it can be cited later can be critical to success at the ITC.

[F] ITC Investigation Timeline

After a complaint for violation of section 337 is filed, a decision on whether to institute an investigation is supposed to be made within thirty days.[61] The decision to institute an investigation is discretionary. The Federal Circuit recently concluded that the Commission has discretion to deny institution where a complaint fails to state a legally cognizable claim.[62] All dates in an ITC investigation are typically measured from the date of institution. As previously mentioned, the target date for completion of a section 337 investigation is normally sixteen to eighteen months, and the rules presume a default of sixteen months.[63] ITC statistics confirm that, in recent years, average time to the target date has been right around 16.6 months, on average.[64] For example, the average length of investigations in recent years

59. *Id*. § 210.37(b).
60. *Id*. § 210.38.
61. *Id*. § 210.10(a)(1).
62. Amarin Pharma, Inc. v. Int'l Trade Comm'n, 923 F.3d 959 (Fed. Cir. 2019), *cert. denied*, No. 19-152, 2019 WL 6689664 (Dec. 9, 2019).
63. *See* 19 C.F.R. § 210.42(c)(1) (requiring motion to exceed sixteen months).
64. *See* https://www.usitc.gov/intellectual_property/337_statistics.htm.

was: 15.85 (2018), 17.7 (2019), 18.6 (2020), 18.2 (2022), and 17.1 (2021) months.[65] The upturn in average case length during 2020 and 2021 is probably due, at least in part, to the COVID-19 pandemic and related delays because of lockdowns and restrictions.

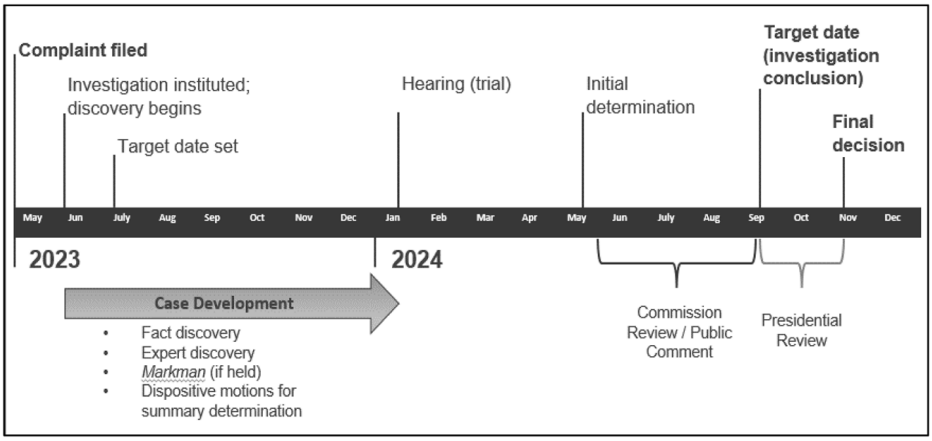


After the investigation is instituted, case development begins almost immediately, as discovery may be served on the date that the investigation is instituted. The case is assigned to an ALJ, and by the second month, the target date is usually set. Fact discovery usually proceeds for the first six months or so after institution, including production of documents and fact depositions. Fact discovery in section 337 investigations can be very intense because of the breadth of permitted discovery, short timeline, short response time, and potential diverse respondents, which may include international respondents. Once fact discovery closes, expert discovery normally begins sometime in the sixth month after institution. This means that experts need to be identified much earlier. Expert reports would generally be exchanged at the end of month six or the beginning of month seven, and expert depositions would be taken during the next month or so.

If the evidentiary hearing is held in the eighth month, then months seven and eight would also typically involve pre-trial motions, motions *in limine*, and pre-trial briefing. Post-hearing briefing immediately follows the evidentiary hearing for the next month and a half or so. The ALJ usually issues the final initial determination

65. *Id.*

on violation and a recommended determination on remedy, bonding, and public interest about four months after the evidentiary hearing and about four months before the target date for completion. During that time, petitions to the Commission seeking review of the initial determination and recommended determination may be made, and the Commission may order briefing and potentially a hearing during that same time either *sua sponte* or in response to petitions filed by the parties.



[G] ITC Investigation Elements

To prevail on claim of violation of section 337, a complainant must establish importation, infringement, and the existence of a domestic industry for the asserted IP.[66] The complainant also should establish which remedy is appropriate should a violation be found and what bond amount is appropriate during the presidential review period.[67] The Commission may also order the ALJ to take evidence on and make a recommended determination concerning the public interest, in which case the private parties will wish to provide evidence that the public interest weighs in favor of their desired result.

Importation is a jurisdictional requirement that must be shown to maintain a section 337 investigation.[68] The ITC has personal jurisdiction over domestic corporations[69] and can obtain personal

66. *See* 19 C.F.R. § 1337.
67. *See id*. § 1337(d)–(f).
68. *See id*. § 1337 (a)(1)(B); Amgen, Inc. v. U.S. Int'l Trade Comm'n, 902 F.2d 1532, 1535–37 (Fed. Cir. 1990).
69. Certain Miniature Hacksaws, Inv. No. 337- TA-237, 1986 WL 379287, at *1 (Oct. 15, 1986).

jurisdiction over foreign entities.[70] The ITC has in rem jurisdiction over imported goods.[71]

The requirements for establishing domestic industry depend on the nature of the investigation. For statutory IP investigations (i.e., investigations involving patents, copyrights, trademarks, mask works, or protected designs), a domestic industry must be established, which includes meeting a technical and economic prong.[72] The economic prong of domestic industry is established by showing:

- significant investment in plant and equipment;
- significant employment of labor or capital; or
- substantial investment in its exploitation, including engineering, research and development, or licensing.[73]

The technical prong is established by showing the domestic industry product is covered by the IP at issue in the investigation. For example, in a section 337 investigation involving patent infringement claims, the technical prong is established by showing that the domestic industry product practices the asserted patent claims.

For investigations based on unfair methods of competition (the so-called non-statutory investigations), the statute explains that a specific injury must be shown that represents a threat or effect:

i. to destroy or substantially injure an industry in the United States;

ii. to prevent the establishment of such an industry; or

iii. to restrain or monopolize trade and commerce in the United States.[74]

These can be thought of essentially like establishing the economic prong of domestic industry for statutory IP cases.

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70. *Id*.
71. Sealed Air Corp. v. U.S. Int'l Trade Comm'n, 645 F.2d 976, 985–86 (C.C.P.A. 1981).
72. *See* Certain Stringed Musical Instruments and Components Thereof, Inv. No. 337-TA-586, Comm'n Op. at 12–14, 2009 WL 5134139 (Dec. 2009); Certain Microsphere Adhesives, Process for Making Same and Prods. Containing Same, Including Self-Stick Repositionable Notes, Inv. No. 337-TA-366, Comm'n Op. at 8, 1996 WL 1056095 (Jan. 16, 1996).
73. 19 U.S.C. § 1337(a)(3).
74. 19 C.F.R. § 1337(a)(1)(A).

[H] ITC Investigation Discovery

Discovery in section 337 investigations is broad.[75] Essentially, discovery is defined by the notice of investigation, which many would consider to be broader than discovery available in district court litigation. Sanctions are available for failure to comply with discovery.[76]

Discovery may be served as soon as the investigation is instituted. The timelines for responding to discovery are short—typically just ten days.[77] Although the ITC has some presumptive discovery limits, those limits are generally set higher than the limits usually encountered in district court. The presumptive limit for interrogatories is 175.[78] The presumptive limits for fact depositions is a maximum of five per respondent and twenty total.[79] There are no presumptive limits for document requests or requests for admissions.[80]

The geographic scope of discovery in section 337 investigations is also broad. Discovery is available against all respondents, including foreign respondents. The ITC also has nationwide subpoena power.[81] Subpoenas are requested ex parte to the ALJ, and judicial enforcement of the subpoenas is available by district courts, if necessary, by requesting that the ALJ certify the request to the Commission, which in turn may seek enforcement of the subpoena through the ITC's Office of General Counsel.[82]

[I] ITC Investigation Remedies

The remedies available for articles that violate section 337 involve excluding those articles from entry into the country.[83] Generally, if a violation is found, the Commission will issue a limited exclusion order (LEO) that is limited to the parties in the investigation found to violate section 337.[84] Another potential remedy option is a general exclusion order (GEO), which prohibits importation of all infringing

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75. *See* 19 C.F.R. § 210.27(a), (b); Certain Set-Top Boxes, & Hardware and Software Components Thereof, Inv. No. 337-TA-761, Order No. 16, 2011 ITC LEXIS 1767, at *5–6 (Aug. 16, 2011) ("Set-Top Boxes"); Certain Cold Cathode Fluorescent Lamp ("CCFL") Inverter Circuits & Products Containing the Same, Inv. No. 337-TA-666, Order No. 16, 2011 ITC LEXIS 1389, at *13 (Aug. 4, 2009).
76. 19 C.F.R. § 210.34.
77. *See* 19 C.F.R. §§ 210.29(b)(2) (interrogatories), 210.30(b)(2) (document requests), 210.31(b) (requests for admission), 210.32(d) (subpoenas).
78. *Id*. § 210.29.
79. *Id*. § 210.28.
80. *See id*. §§ 210.30, 210.31.
81. *Id*. § 210.32.
82. *Id*. § 210.32(d)(1), (g).
83. *See* 19 U.S.C. § 1337(d).
84. *Id*. § 1337(d)(2).

goods by anyone—whether or not they were a party to the investigation.[85] GEOs are rarer, and are only available if "necessary to prevent circumvention of an exclusion order limited to products of named persons" or if "there is a pattern of violation of this section and it is difficult to identify the source of infringing products."[86] Although GEOs are relatively rare, they appear to be slightly more common in recent years.

LEOs and GEOs are enforced by U.S. Customs and Border Control, which prevents importation of goods that infringe the subject IP.[87] Enforcement by Customs is not limited to the specific products and models found to infringe in the investigation but focuses on all products and models that infringe. In the case of attempts by a respondent to design around the IP that they were found to infringe, Customs will hold a hearing and take evidence concerning the potential design-around. Traditionally Customs took evidence ex parte but has recently indicated an intention to introduce new inter partes proceedings.

The Commission also may issue a cease-and-desist order (CDO) to prevent additional sales of domestic inventory of the products found to infringe.[88] A CDO is available for respondents with "commercially significant" domestic inventory.[89] Significant civil penalties are available for violations of CDOs and consent orders of up to $100,000 or twice the value of goods for each days.[90] In some cases civil penalties have totaled in the millions of dollars.[91]

The Commission may also require a respondent found in violation of section 337 to post a bond to avoid injury to the complainant.[92] The bond applies during the period for presidential review and is often based on the price differential between the complainant's products and the accused product, where applicable.

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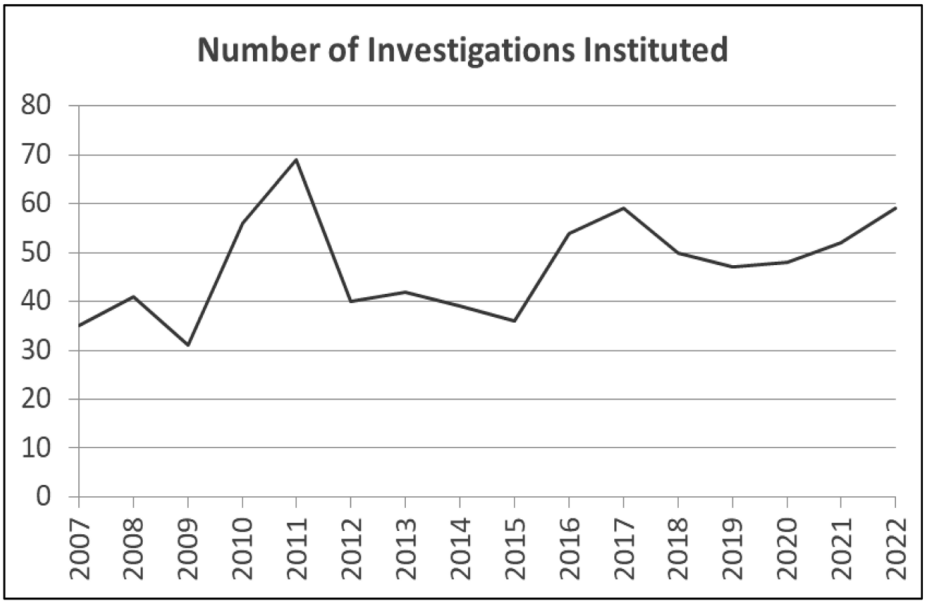
85. *Id*.
86. *Id*.
87. *See* 19 C.F.R. § 210.71(a); *see also* Customs Directive No. 2310-006A (Dec. 16, 1999), https://www.cbp.gov/sites/default/files/documents/2310-006a_3.pdf.
88. 19 U.S.C. § 1337(f)(1).
89. *Id*.
90. *Id*. § 1337(f)(2).
91. *See, e.g.*, Certain Lens-Fitted Film Packages, Inv. No. 337-TA-406 (more than $13 million for violation of CDO); Certain Ink Cartridges and Components Thereof, Inv. No. 337-TA-565 ($11.11 million for violation jointly and severally against respondents); Certain Marine Sonar Imaging Devices, Inv. No. 337-T-921 (ALJ recommending $37 million civil penalty for violation).
92. *Id*.

§ 15:3 Recent Developments and Trends

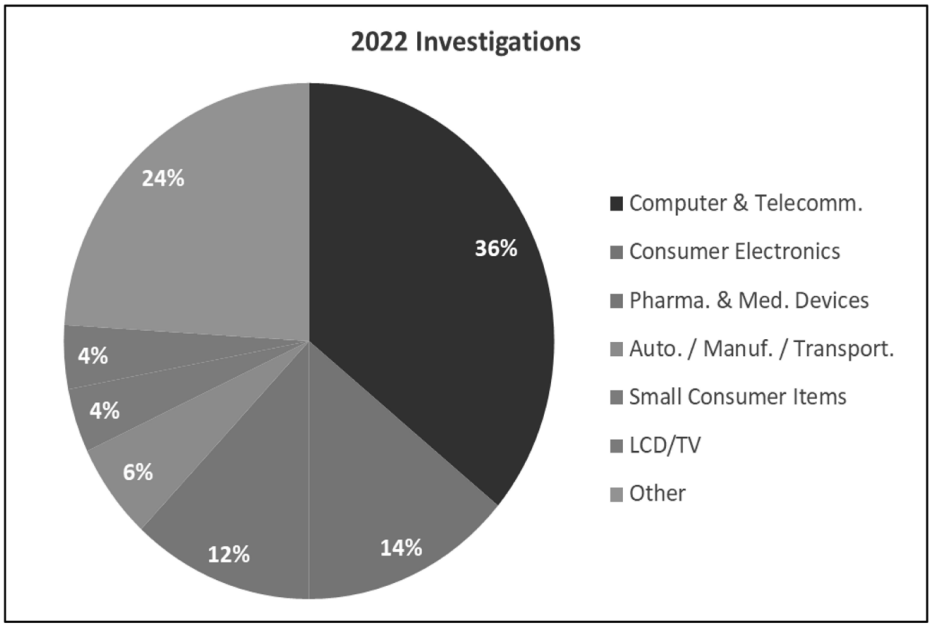
§ 15:3.1 Recent Filing Trends

Over the past decade, section 337 investigations have been on the rise. In 2022, the ITC instituted fifty-nine new investigations. This is up slightly from prior years, dating back to 2016, in which the following number of cases were instituted each year: fifty-four (2016), fifty-nine (2017), fifty (2018), forty-seven (2019), forty-eight (2020), and fifty-two (2021). The number of investigations instituted peaked at sixty-nine in 2011. Over the course of the past decade, the number of investigations instituted is trending upward.[93]

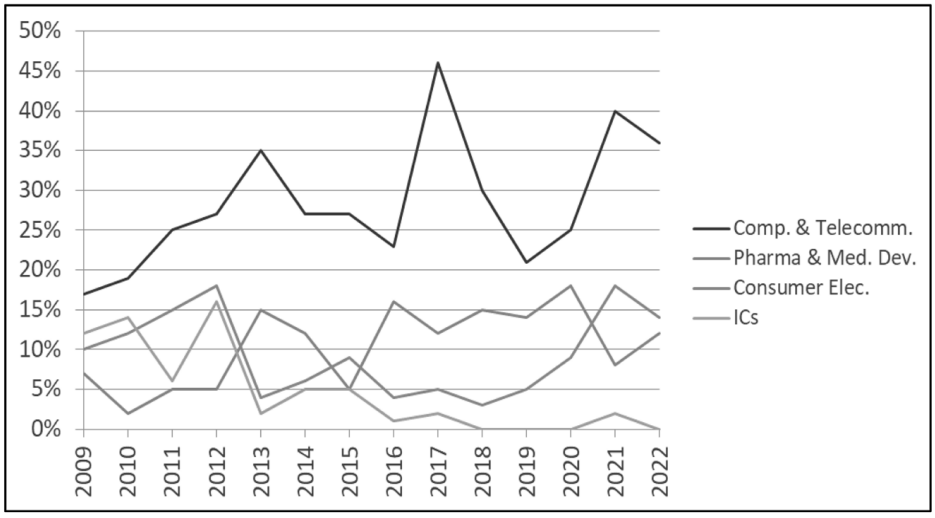


Section 337 investigations cover a broad range of technology. In 2022, the largest percentage of investigations were those involving computer and telecommunications technology (36%). The next three highest percentages of investigations involved consumer electronics (14%), pharmaceuticals and medical devices (12%), and automotive/manufacturing/transportation (6%).[94]

93. *See* https://www.usitc.gov/intellectual_property/337_statistics.htm.
94. *Id.*

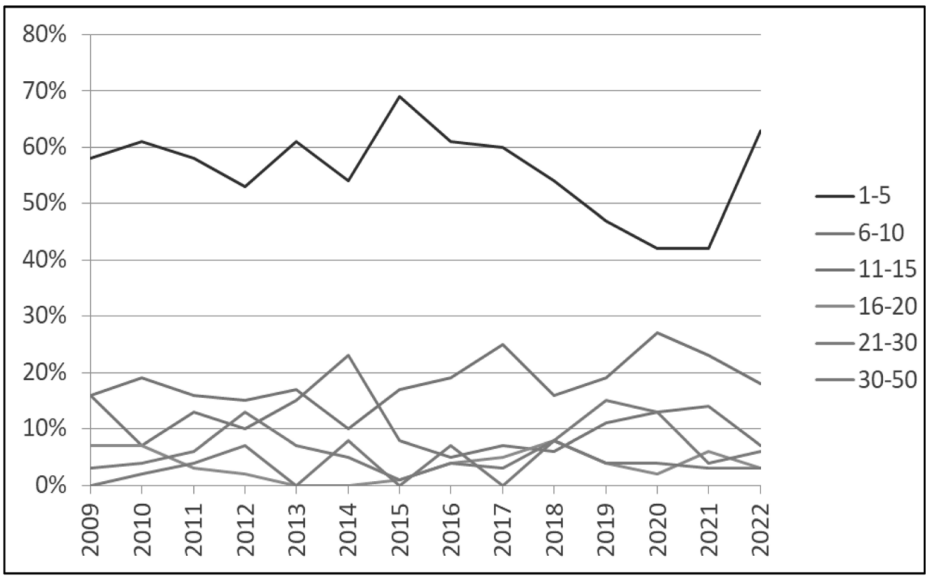


When one analyzes the technologies of investigations looking back a little more than a decade to 2009, investigations involving computers and telecommunications and those involving pharmaceuticals and medical devices appear generally to be on the rise. Over the same period, cases involving integrated circuits appeared to be on the decline. Cases involving consumer electronics have dipped and were on a downward trend from about 2012–2019 but have been on the rise again in recent years.[95]



95. *Id.*

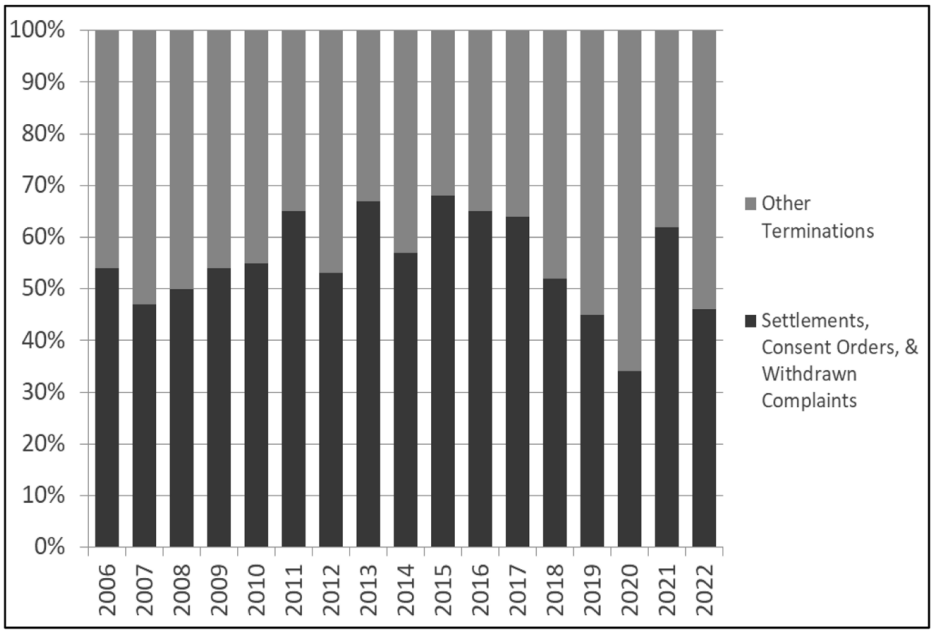
As mentioned previously, numerous respondents may be named in the same investigation. For example, the America Invents Act's (AIA) joinder rules do not apply to section 337 investigations.[96] Since 2009, the ITC has tracked investigations by the number of respondents (from one to fifty in bands). Over that time, most of those investigations have involved one to five respondents at about 56%. Cases involving six to ten respondents average about 18%, while cases involving eleven to fifteen respondents averaged 11% during the same period. All other groups (sixteen to twenty respondents, twenty-one to thirty respondents, and thirty-one to fifty respondents) all averaged less than 10% but were generally not zero in any given year with very few exceptions.[97]



§ 15:3.2 Recent Termination Trends

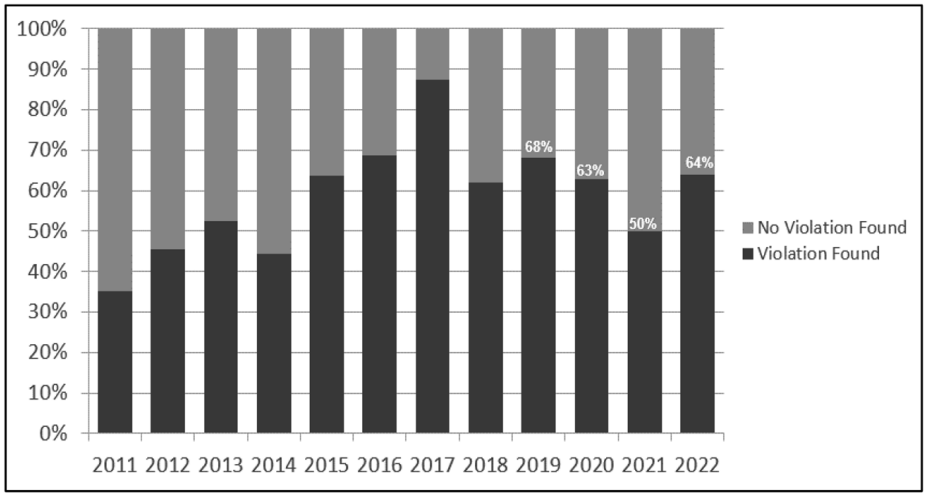
Statistics over the past decade confirm that most investigations are terminated by settlements, consent orders, or withdrawn complaints. The average over the past decade is about 56% of investigations. Since 2006, the average percentage is approximately 55%. The number of investigations that were terminated by settlements, consent orders, or withdrawn complaints dipped slightly in 2022 to 46% from 62% in 2021 but was roughly on par with recent years, which averaged: 34% (2020), 45% (2019), and 52% (2018).[98]

96. *See* 35 U.S.C. § 299(b).
97. *See* https://www.usitc.gov/intellectual_property/337_statistics.htm.
98. *Id.*



The success rate for complainants in the ITC is relatively high. Of those investigations decided on the merits in 2018–2022, a violation of section 337 was found in 62% (2018), 68% (2019), 63% (2020), 50% (2021), and 64% (2022). That represented thirteen of twenty-one cases in 2018, fifteen of twenty-two cases in 2019, twenty-two of thirty-five cases in 2020, nine of eighteen cases in 2021, and twenty-three of thirty-six cases in 2022. The percentage of violations has gone up significantly starting in 2015. For example, in 2011, a violation of section 337 was found in just six of seventeen cases, representing just 35% of investigations. In 2012, a violation was found in ten of twenty-two cases, representing 45%. Except for 2013, the percentage of violations found stayed below 50% until 2015, after which it has not dropped below 50% to date.[99]

99. *Id.*



§ 15:3.3 Interplay with PTO Proceedings

One area of frequent interest is how PTO proceedings, such as proceedings before the Patent Trials and Appeal Board (PTAB), like inter partes reviews (IPRs), might affect related ITC investigations. PTO proceedings rarely affect IPR investigations. The ITC rarely grants stays because of PTO proceedings, in part because it has a statutory mandate to complete section 337 investigations "at the earliest practicable time after the date of publication of the notice of publication" of the investigation.[100]

As a practical matter, IPR proceedings are unlikely to impact ITC investigations. ITC investigations generally conclude within sixteen months.[101] An IPR, on the other hand, is required to be completed within eighteen months but is not final until appeals are exhausted.[102] In *Certain Microelectromechanical Systems and Products*, the ITC denied a motion to stay an investigation based on PTO proceedings (two IPR petitions and three ex parte reexaminations), in part based on the fact that resolution would not be reached on the asserted patents before the investigation's target date.[103] The ITC denied the motion to stay notwithstanding the fact that the parallel district court case had been stayed.[104] More recently in 2019, the ITC refused to stay an investigation, even where the PTAB had already issued a final decision.[105]

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100. 19 U.S.C. § 1337(b)(1).
101. 19 C.F.R. § 210.51(a)(1).
102. 35 U.S.C. § 316(a)(11).
103. *See* Certain Microelectromechanical Sys. & Prods. Containing Same, Inv. No. 337-TA-876, Order No. 6 (May 21, 2013).
104. *Id*.
105. *See* Certain Memory Modules, Inv. No. 337-TA-1089, Order No. 49 (Apr. 11, 2019).

Numerous parties have requested that a section 337 investigation be stayed, but most are denied. For example, in *Certain Laser-Driven Light Sources*, the IPR was scheduled to conclude in November, two months before the deadline for the final initial determination and six months before the target date for the completion of the investigation.[106] Notwithstanding the potentially advantageous timing, the ALJ denied the stay, emphasizing the ITC's statutory mandate to complete section 337 investigations "at the earliest practicable time."[107]

As another example, in *Certain Three-Dimensional Cinema Systems*, the IPR decision cancelling claims came after final initial determination but before the final Commission decision.[108] The Commission still declined to give preclusory weight to the IPR decision, noting that the IPR and the ITC investigation have different standards of proof and different claim construction standards.[109]

In *Certain Network Devices*, the ITC found a section 337 violation for two patents and issued an LEO and CDO on May 4, 2017.[110] Shortly thereafter on May 25, 2017, and June 1, 2017, the PTAB issued decisions finding asserted claims in that investigation unpatentable. The respondent filed an emergency petition to suspend or rescind the LEO and CDO, but the Commission denied that petition on July 20, 2017, despite those decisions from the PTAB.[111] The decision in *Certain Network Devices* appeared to be contrary to an earlier Commission decision in *Certain Three Dimensional Cinema Systems*, in which the Commission suspended enforcement of remedial orders that had given some parties hopes that the ITC might begin to consider staying ITC investigations for IPR proceedings.[112]

That said, in one case in 2018, the ITC did stay an investigation where the complainant did not oppose and the PTAB had issued a final written decision seven months prior to the scheduled hearing date.[113]

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106. *See* Certain Laser-Driven Light Sources, Subsystems Containing Laser-Driven Light Sources, & Prods. Containing Same, Inv. No. 337-TA-983 (Mar. 2016).
107. *Id*.
108. *See* Certain Three-Dimensional Cinema Sys. & Components Thereof, Inv. No. 337-TA-939, 2016 WL 7635412 (Aug. 2016).
109. *Id*.
110. *See* Certain Network Devices, Related Software & Components Thereof (II), Inv. No. 337-TA-945 (July 2017).
111. *Id*.
112. *See* Certain Three Dimensional Cinema Sys. & Components Thereof, Inv. No. 337-TA-939, Comm'n Op. (Aug. 23, 2016) (note that the ITC's suspension had no practical effect because of an exclusion order based on two other asserted patents that was effective immediately).
113. *See* Certain Integrated Circuits, Inv. No. 337-TA-1024, Order 55 (Aug. 31, 2018).

More recently in 2020, in *Certain Unmanned Aerial Vehicles*, the Commission also suspended enforcement of its remedial orders where the PTAB had issued a final decision that all asserted claims were invalid.[114] In that case, the respondents had notified the Commission of the PTAB's decision while petitions to the Commission to review the ALJ's final initial determination were pending. Timing worked out in part because there had already been three extensions in the target date of the investigation.[115] In deciding to suspend its remedial orders, the Commission focused on its power to issue remedial orders where accused articles "infringe a valid and enforceable United States patent."[116] The Commission held that suspending remedial orders was consistent with its approach in previous cases where the final written decision by PTAB issued before a violation was determined.[117] The Commission further emphasized the "PTO's role as the lead agency in assessing the patentability, or validity, of proposed or issued claims" and congressional intent to provide a "quick, inexpensive, and reliable alternative to district court litigation to resolve questions of patent validity."[118] In view of this result, ITC respondents would be well advised to file IPR petitions as soon as possible to maximize the possibility of obtaining any relief in the ITC investigation from the related PTAB proceedings.[119]

The Commission is typically unlikely to stay a decision to institute an investigation. In *Certain Hybrid Vehicles*, the ITC denied a request to suspend or delay institution, even though many of the asserted claims of the five asserted patents were found unpatentable in IPR final determinations, and even though some of those determinations had already been affirmed in Federal Circuit appeals.[120]

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114. *See* Certain Unmanned Aerial Vehicles & Components Thereof, Inv. No. 337-TA-1133, Comm'n Op. (Sept. 8, 2020).
115. *Id.*, at Order No. 9 (Feb. 14, 2019); *id.* at Notice (June 9, 2020).
116. *Id.*, at Comm'n Op. at 35 (quoting 19 U.S.C. § 1337(a)(1)(B)(i), (d)(1)).
117. *Id.* (citing Certain Magnetic Tape Cartridges & Tape Components Thereof, Inv. No. 337-TA-1058, Comm'n Op. at 62–63, 2019 WL 2635509 at *38 (Apr. 9, 2019); Certain Three-Dimensional Cinema Sys. & Components Thereof, Inv. No. 337-TA-939, Comm'n Op. at 60, 2016 WL 7635412 at *37 (July 21, 2016)).
118. *Id.* at 37–38 (quoting S. REP. No. 110-259, at 20 (2008)).
119. *See* Philip Marsh & Michael Nguyen, *IPRs Can Play Important Role in ITC Defense Strategy*, LAW360.COM (Oct. 9, 2020), https://www.law360.com/articles/1317895.
120. *See* Certain Hybrid Vehicles & Components Thereof, Inv. No. 337-TA-1042, Comp. at 61–62 (Feb. 2, 2017).

Estoppel has been held to apply against ITC respondents, regardless of whether the respondent prevailed in the PTAB's final written decision.[121] But at least one ALJ has determined that IPR estoppel does not apply against the OUII staff.[122]

§ 15:3.4 Interplay with District Court Litigation

Frequently when parties file an ITC complaint, they also file a parallel district court action. This is often done to preserve the plaintiff's desired venue. The parallel district court action can be stayed automatically at the request of the respondent in the ITC investigation, as long as the request is made either within thirty days after the party is named as a respondent in the ITC investigation or within thirty days after the district court action is filed, whichever is later.[123] Even if the district court action is not stayed, it is generally so much slower than the ITC investigation that the district court case will not reach any significant milestones before they are reached in the ITC investigation and usually will not impose too heavy of a burden in addition to the work happening in the ITC action.

Some types of section 337 investigations have been found to have a preclusive effect on related district court actions in other types of actions,[124] including trade secret cases,[125] trademark and unfair practice cases,[126] and antitrust cases.[127]

In section 337 investigations over patent infringement allegations, on the other hand, there is no collateral estoppel from an ITC determination of patent infringement.[128] That said, ITC

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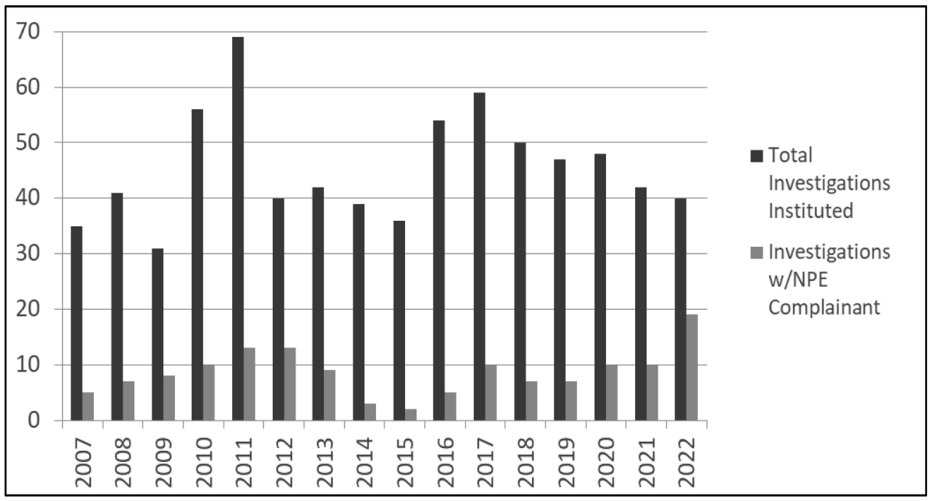
121. *See* Certain Memory Modules & Components Thereof, Inv. No 337-TA-1089, Order No. 51 (June 26, 2019).
122. *See* Certain Magnetic Tape Cartridges & Components Thereof, Inv. No. 337-TA-1058, Initial Determination (Aug. 18, 2018).
123. *See* 28 U.S.C. § 1659(a).
124. *See, e.g.*, B&B Hardware, Inc. v. Hargis Indus., Inc., 575 U.S. 138, 148 (2015) ("courts may take it as given that Congress has legislated with the expectation that the principle of issue preclusion will apply, except when a statutory purpose to the contrary is evident") (quoting Astoria Fed. Sav. & Loan Ass'n v. Solimino, 501 U.S. 104 (1991)).
125. *See* Manitowoc Cranes LLC v. Sany Am. Inc., No. 13-C-677, 2018 WL 582334, at *2 (E.D. Wis. Jan. 29, 2018), *aff'g* Sany Heavy Indus. Co. v. Int'l Trade Comm'n, 669 F. App'x 569 (Fed. Cir. 2016).
126. *See* Union Mfg. Co. v. Han Baek Trading Co., 763 F.2d 42, 45–46 (2d Cir. 1985), *abrogated on other grounds*, Two Pesos, Inc. v. Taco Cabana, Inc., 505 U.S. 763 (1992); Balt. Luggage Co. v. Samsonite Corp., 977 F.2d 571 (4th Cir. 1992).
127. Aunyx Corp. v. Canon U.S.A., Inc., 978 F.2d 3, 7 (1st Cir. 1992).
128. Tex. Instruments Inc. v. Cypress Semiconductor Corp., 90 F.3d 1558, 1569 (Fed. Cir. 1996) (no collateral estoppel, even after Federal Circuit affirmance of ITC infringement decision).

determinations may be considered persuasive by a district court judge on one or more issues (but they would likely be precluded from reaching a jury). Moreover, although res judicata may not apply to ITC decisions in a district court proceeding, in at least some cases, judicial estoppel might still apply.[129]

§ 15:3.5 NPE Litigation

The proliferation of non-practicing entity (NPE) litigation has been a topic of concern for some parties. In the ITC over the past decade, the number of ITC investigations filed by NPEs has been relatively small compared to the overall number of investigations.



On average, over the past decade, the number of ITC investigations filed by NPEs constitutes approximately 15% of the total number of investigations filed but has ticked up in recent years. Until 2021 and 2022, the percentage of NPE-initiated investigations had held more or less steady from 2017 to 2019: 14.5% (2017), 12.3% (2018), and 12.9% (2019). The percentages of NPE-initiated investigations has been increasing since 2020: 17.2% (2020), 19.2% (2021), and 32.2% (2022).

§ 15:3.6 Recent Programs and Rule Changes

[A] 100-Day Program

In the face of an increase in the number of complaints filed, the ITC introduced a 100-day "pilot program" in 2013, which provides an

129. *See* Solomon Techs., Inc. v. Toyota Motor Corp., No. 8:05-CV-1702-T-MAP, 2010 WL 715243, at *3 (M.D. Fla. Jan. 26, 2010).

opportunity to attempt to resolve an investigation early. It was rarely used.[130]

The ITC adopted rules making the 100-day pilot program a permanent program.[131] The goal of the program is to address certain issues early that could resolve or significantly narrow the case. Under the program, within 100 days of institution, the Commission may order the ALJ to issue an initial determination on potentially dispositive issues.[132] Under the program, the ALJ may (1) temporarily stay unrelated discovery and (2) hold expedited hearings on dispositive issues.[133] The 100-day program has been used only sparingly but has been used for domestic industry[134] and invalidity for patent ineligibility under section 101.[135]

[B] Interim Initial Determination Pilot Program

The ITC introduced a new "pilot program" in 2021 that would allow ALJs to issue interim initial determinations.[136] The pilot program is available for all investigations instituted on or after May 12, 2021. Unlike the 100-day program, where the Commission decides whether to place the investigation into the program, the presiding ALJ decides whether to invoke this interim initial determination pilot program. The goal of the program is to decide issues on an interim basis that either will be case-dispositive or will resolve significant issues in the case. The program allows that ALJ to hold an evidentiary hearing and receive evidence and/or briefing as the ALJ sees fit. The decisions under the program are intended to be fast; typically, interim initial determinations will take forty-five days to issue and forty-five additional days to the ITC's final determination.

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130. **Review denied re: Importation:** Certain Shaving Cartridges (Inv. No. 337-TA-1079); Certain Insulated Beverage Containers (Inv. No. 337-TA-1084); **Review denied re: public interest:** Certain Industrial Control Sys. Software (Inv. No. 337-TA-1084) (review by standard-setting organization of whether patents were "essential" was outside scope of program).
131. *See* 19 C.F.R. §§ 210.10(b)(3), 210.42(a)(3).
132. *Id*. §§ 210.10(b)(3), 210.42(a)(3).
133. *Id*. § 210.10(b)(3).
134. Certain Products Having Laminated Packaging, Laminated Packaging, & Components Thereof (Inv. No. 337-TA-874); Certain Silicon-On-Insulator Wafers (Inv. No. 337-TA-1025); Certain IoT Devices (Inv. No. 337-TA-1094).
135. Certain Portable Electronic Devices (Inv. No. 337-TA-994).
136. https://www.usitc.gov/press_room/featured_news/337pilotprogram.htm.

This program represents an opportunity to raise and have a significant or case-dispositive issue decided quickly and presents a number of potential strategic applications.[137] So far, however, the program has not been used in very many cases. This may be because there is a risk that the ALJ could go to the work of having an evidentiary hearing on a rush basis but still need to go through the rest of the case, including a final evidentiary hearing.

[C] NEXT Advocates Program

In 2022, the ITC introduced a new program called the NEXT Advocates program, which stands for "Nurturing Excellence in Trial Advocates," to help more junior attorneys have more opportunities for oral advocacy and trial opportunities.[138] The program focuses on providing oral advocacy opportunities for less-experienced attorneys who have three or fewer substantive oral arguments or witness examinations in any federal tribunal.

This program was implemented by the ITC's ALJs (rather than by the Commission), and so it has the buy-in of all of the ALJs, most of whom have amended their ground rules to integrate the program. Because of this, it is clear that the ALJs want parties to use the program, and parties that use it can experience a number of benefits.[139] Some ALJs have incentivized parties to use the program. For example, ALJs Elliot, Bhattacharyya, and Moore have permitted arguments in situations where they would normally not hear arguments, such as motions for summary determination.[140] Judge Elliot has permitted a party using the program an additional fifteen minutes to present arguments during a *Markman* hearing and allowed argument on additional claim terms, while Judges Bhattacharyya and Moore

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137. *See, e.g.*, Philip Marsh, Michael Gershoni & Bridgette Boyd, *Strategic Applications of ITC Admin Law Judge Pilot Program*, LAW360.COM (May 25, 2021), https://www.law360.com/articles/1387772.

138. https://www.usitc.gov/next_advocates_nurturing_excellence_in_trial_advocates.htm.

139. *See* Victoria Reines & Philip Marsh, *How ITC's Junior Atty Program Can Benefit Firms, Clients*, LAW360.COM (Oct. 4, 2022), https://www.law360.com/ip/articles/1536780/how-itc-s-junior-atty-program-can-benefit-firms-clients.

140. *See* Certain Video Processing Devices & Prods. Containing the Same, Inv. No. 337-TA-1323, Order No. 2, at 31 (Aug. 8, 2022); Certain Pneumatic Compression Devices & Components Thereof, Inv. No. 337-TA-1316, Order No. 5, at 29 (June 28, 2022); Certain Barcode Scanners, Scan Engines, Mobile Computers with Barcode Scanning Functionalities, Prods. Containing the Same, & Components Thereof II, Inv. No. 337-TA-1321, Order No. 2, at 30 (June 27, 2022).

will allow a junior attorney an additional fifteen minutes for trial examination.[141]

The ITC's NEXT Advocates program is also a sister program to the PTO's LEAP Program (short for "Legal Experience and Advancement Program"), which is aimed at giving junior patent practitioners more oral advocacy opportunities.[142] The ITC ALJs will serve as judges in the LEAP mock argument sessions—offering an opportunity for junior attorneys to get in front of these judges early—and the ALJs are encouraging junior attorneys to participate in the LEAP program.

[D] Subpoena Rules

The ITC has adopted rules related to subpoenas relatively recently. Under the previous practice, subpoena recipients had ten days to move to quash or obtain an extension from the ALJ, and there was the threat of potential waiver of all objections to the subpoena if the recipient failed to meet the ten-day deadline. This would sometimes cause subpoena recipients difficulty because subpoenas were routinely sent to corporate headquarters addressed to the general counsel or chief legal officer, which could mean that a significant portion of the ten-day response period was taken up just locating the subpoena and identifying the need to respond.

The ITC's new practice is intended to bring the ITC practice more in line with the Federal Rules of Civil Procedure.[143] Under the new rules, a subpoena recipient may serve objections within ten days (or other allowed response period). After serving objections, the burden then shifts to the requesting party to move to compel or to seek judicial enforcement. Thus, under the new rules the burden is on the requesting party; under the prior practice, the burden remained with the responding party.

[E] Mediation Program

The ITC recently established a formal mediation program.[144] The program is based on the Federal Circuit's mediation program and uses experienced professionals as mediators. It is designed to provide heightened confidentiality and cannot be used to delay the schedule of the investigation. The mediation program is intended to narrow

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141. *See, e.g.*, Certain Digital Set-Top Boxes & Sys. & Services Including the Same, Inv. No. 337-TA-1315, Order No. 16 (Aug. 10, 2022 and Aug. 16, 2022), Tr. (EDIS Doc ID: 778265) at 74:23–75:25; Certain Graphics Systems, Components Thereof, & Digital Televisions Containing the Same, Inv. No. 337-TA-1318, Order No. 16 (Aug. 29, 2022).
142. *See* https://www.uspto.gov/patents/ptab/leap.
143. *See* 19 C.F.R. § 210.32.
144. *See* 5 U.S.C. §§ 556(c)(6)–(8), 572–74, 583.

issues and claims in dispute, potentially shorten time for case resolution, provide businesses more certainty about settlement outcomes, and reduce costs for businesses while allowing them to maintain IP control.

[F] Customs Inter Partes Proceedings

U.S. Customs and Border Control enforces remedial orders from the ITC, including LEOs and GEOs. Customs also hears disputes regarding enforcement of exclusion orders, including any disputes over efforts to redesign products so that they are no longer subject to existing exclusion orders. Previously, contacts with Customs regarding redesigned products were made ex parte on a somewhat ad hoc basis.

Customs has introduced new inter partes proceedings to replace the old ex parte proceedings, which are intended to increase transparency, streamline issues for adjudication, augment the record, maximize accuracy of determinations, and support timely issuance of determinations.[145] Customs issued rules to govern the inter partes proceedings.[146] Early proceedings to this point have been expeditious—taking approximately sixty to sixty-five days to decision—and reportedly included the use of expert reports, depositions, pre-hearing briefs, hearings, and post-hearing briefs.[147]

[G] Changes in Domestic Industry Requirements

The ITC also recently changed its practice regarding domestic industry. Traditionally, establishing domestic industry based on licensing only (under section 337(a)(3)(C)) did not require establishing a technical prong, and evidence of licensing alone was sufficient.[148]

In 2013, the ITC changed the practice for establishing this licensing-based domestic industry.[149] In *Certain Computers and Computer Peripheral Devices*, the ITC definitively held that there is a technical prong requirement with respect to the "articles protected by the patent" for a licensing-based domestic industry assertion under

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145. *See, e.g.*, https://www.ipo.org//wp-content/uploads/2015/01/TerrillDax_Slides.pdf.
146. *See* 19 C.F.R. § 177 *et seq.*
147. *See* Robert Mattson, *After the ITC: Inter Partes Proceedings at Customs and Border Patrol*, BLOOMBERGLAW.COM (Feb. 8. 2018), https://news.bloomberglaw.com/ip-law/after-the-itc-inter-partes-proceedings-at-customs-and-border-patrol.
148. *See* 19 U.S.C. § 1337(a)(3)(C); InterDigital Commc'ns, LLC v. Int'l Trade Comm'n, 690 F.3d 1318, 1330 (Fed. Cir. 2012).
149. *See* Certain Computers & Computer Peripheral Devices & Components Thereof, Inv. No. 337-TA-841, Comm'n Notice of Determination at 3 (Dec. 19, 2013).

section 337(a)(3)(C).[150] Thus, the ITC now requires establishing a technical prong for establishing all domestic industry allegations for statutory IP cases.

[H] Changes in Jurisdiction Related to Importation

There have been a couple of important, recent cases concerning ITC jurisdiction related to importation. In particular, section 337 prohibits "importation . . . of articles that infringe" a patent.[151] Two recent cases discuss whether certain activities fall within the statutory jurisdiction of section 337. The first is the *Suprema* case,[152] which addresses the question of whether articles that infringe a method after importation are within the ITC's section 337 jurisdiction. The other is the *ClearCorrect* case,[153] which answers the question of whether importation of electronic data is within the ITC's section 337 jurisdiction.

[H][1] Suprema—*Articles That Infringe Method After Importation*

In *Suprema*, the ITC determined that *Suprema* had violated section 337 by inducing infringement of a method claim by importing a fingerprint scanner product that infringed only when combined with domestic scanning software after importation.[154] The Federal Circuit panel that heard the appeal held that there was no section 337 violation "where direct infringement does not occur until after importation of the articles the exclusion order would bar."[155]

The Federal Circuit, sitting en banc, reversed the panel decision and upheld the ITC's infringement determination, thereby affirming the Commission's interpretation of section 337's scope.[156] In particular, the en banc court held that "the Commission's interpretation that the phrase 'articles that infringe' covers goods that were used by an importer to directly infringe post-importation as a result of the seller's

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150. *Id.*; 19 U.S.C. § 1337(a)(3)(C).
151. 19 C.F.R. § 1337(a)(1)(C).
152. Suprema, Inc. v. Int'l Trade Comm'n, 796 F.3d 1338 (Fed. Cir. 2015) (en banc).
153. ClearCorrect Operating, LLC v. Int'l Trade Comm'n, 810 F.3d 1283 (Fed. Cir. 2015), *reh'g en banc denied*, 819 F.3d 1334 (Fed. Cir. 2016).
154. *See* Certain Biometric Scanning Devices, Components Thereof, Associated Software, & Prod. Containing the Same, Commission Notice, Inv. No. 337-TA-720 (Oct. 24, 2011).
155. Suprema, Inc. v. Int'l Trade Comm'n, 742 F.3d 1350, 1352 (Fed. Cir. 2013).
156. Suprema, Inc. v. Int'l Trade Comm'n, 796 F.3d 1338 (Fed. Cir. 2015) (en banc).

inducement is reasonable."[157] Important to the Federal Circuit's decision was the fact that induced infringement under section 271(b) is also prohibited under section 337.[158]

[H][2] ClearCorrect—*Importation of Electronic Data*

ClearCorrect involved the Invisalign teeth repositioning trays. ClearCorrect U.S. used ceramic models to create digital data sets that were electronically transmitted to Pakistan. The data sets were manipulated in Pakistan, and the changed data sets were electronically transmitted back to the United States. ClearCorrect U.S. then used 3D printers to create three-dimensional models of the patient's teeth, which were used to make the dental aligners for the patient.

At the ITC, ClearCorrect argued that the data sets are not "articles" within the meaning of section 337 and that the uploading of data received from abroad to a U.S.-based server does not constitute "importation" under section 337. Despite this argument, on May 6, 2013, the ALJ determined that there had been a violation based on "importation of the accused digital data sets."[159] On April 10, 2014, the Commission agreed with the ALJ, holding that importation of data sets was within the statutory language of "importation . . . of articles that infringe." Commissioner Johanson dissented, arguing that an exclusion order against electronic transmissions "makes no sense and would not be enforce[able]."[160]

The Federal Circuit reversed the Commission, holding that the ITC's section 337 jurisdiction does not extend to "electronically transmitted digital data."[161]

[I] Some Additional Recent Rule Changes

The ITC has implemented additional rule changes recently. For example, the ITC has expanded its options for electronically filing and serving documents.[162] Practically speaking, this will be helpful for litigants in the ITC timely receiving notices, orders, and other documents from the Commission, which traditionally had been sent

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157. *Id*. at 1352–53.
158. *Id*. at 1350 (citing 35 U.S.C. § 271(b)).
159. Certain Digital Models, Digital Data, & Treatment Plans for Use, in Making Incremental Dental Positioning Adjustment Appliances Made Therefrom, & Methods of Making the Same, Notice of Initial Determination, Inv. No. 337-TA-833 (May 6, 2013).
160. ClearCorrect Operating, LLC v. Int'l Trade Comm'n, 810 F.3d 1283, 1295 (Fed. Cir. 2015) (citing Final Comm'n Op., Johanson dissenting at 6).
161. *Id*. at 1293–94 (Fed. Cir. 2015) ("we conclude that 'articles' does not cover electronically transmitted digital data"), *reh'g en banc denied*, 819 F.3d 1334 (Fed. Cir. 2016).
162. *See* 19 C.F.R. § 201.16(a)(1) and (4).

only to lead counsel for each party and often by means that did not allow for immediate access to the documents. Because of the fast-paced and high-stakes nature of many of these investigations, many will undoubtedly be grateful for this increased ability to receive documents electronically.

The ITC has also provided the ALJ additional flexibility to instruct parties regarding requirements for secure electronic communications in investigations.[163] This will allow each ALJ to spell out what measures should be taken when transmitting confidential business information to ensure protection of the information and compliance with the ALJ's protective order in each case.

The ITC has also committed to define the scope of each investigation in plain language and with additional precision.[164] Hopefully, this will help provide additional clarity to the parties and others interested in the investigation. This rule change could prove helpful in the context of discovery disputes in particular, as discovery is defined by the scope of the notice of investigation.

The ITC has adopted new rules that allow institution of multiple investigations from a single complaint[165] and that allow the ALJ to sever a single investigation into multiple investigations.[166] These rules will allow the Commission and ALJs to better manage cases and to ensure that parties and claims are grouped into separate investigations where that makes sense. On severing a single investigation into multiple investigations, the new rule permits severance within thirty days of institution based on a motion by any party or based on the ALJ's judgment.[167] The ALJ will keep the newly severed cases, unless the Chief ALJ reassigns them.[168]

The ITC also adopted rules that clarify that expert reports and communications between experts and counsel are protected from discovery.[169] These rules more closely align with the protections regarding expert discovery now available under the Federal Rules of Civil Procedure.[170]

Finally, the ITC adopted a rule permitting ALJs to use deposition testimony in lieu of live witness testimony.[171] While application of this rule will undoubtedly vary among the ALJs, it seems likely that

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163. *Id*. § 201.16(f).
164. *Id*. § 210.10(b)(1).
165. *Id*. § 210.10(a)(6).
166. *Id*. § 210.14(h).
167. *Id*.
168. *Id*.
169. *Id*. § 210.27(e)(5), (g)(3).
170. *See* FED. R. CIV. P. 26(b)(4)(B), (C); 26(b)(3)(A), (B).
171. 19 C.F.R. § 210.27(e)(5), (g)(3).

the rule may help parties use deposition testimony of third parties in lieu of trial subpoenas and live testimony.

§ 15:4 Strategy and Practice Tips

§ 15:4.1 Complainant's View

[A] Potential Advantages for Complainants

Litigation at the ITC has many potential advantages from the complainant's perspective. One of the main advantages for a complainant is the speed of the proceeding. This is evident in both the speed of the overall investigation, which generally has a target date for completion of sixteen months from institution,[172] and in the speed of each of the events during the course of litigation. For example, responses to most discovery requests and subpoenas are due within ten days.[173] Similarly, responses to motions are also due within ten days.[174] Thus, speed can be a significant factor in ITC investigations and can keep respondents on their heels through much of the investigation.

Another potential advantage that complainants may see in ITC proceedings is the availability of injunction-like remedies. Since the 2006 *eBay* decision, getting an injunction in district court against an infringer has become more difficult.[175] In particular, after *eBay*, obtaining an injunction against a party found to infringe a patent is no longer "automatic" but requires consideration of the traditional four-factor equitable test for issuance of an injunction.[176] In the ITC, however, the remedial orders are general or limited exclusion orders that have an injunctive effect of preventing importation of infringing articles or cease-and-desist orders that also have an injunctive effect.[177] Exclusion orders may also be viewed as advantageous to complainants because they are enforced by U.S. Customs and Border control.

Many complainants may also see the lack of joinder restrictions and the ability to name as many respondents as they wish in a single investigation to be an advantage. That may, for example, allow parties to address infringement by numerous different parties economically in a single proceeding. It may also allow a complainant to name all

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172. *See id*. § 210.42(c)(1) (requiring motion to exceed sixteen months); https://www.usitc.gov/intellectual_property/337_statistics.htm.
173. *See id*. §§ 210.29(b)(2) (interrogatories), 210.30(b)(2) (document requests), 210.31(b) (requests for admission), 210.32(d) (subpoenas).
174. *Id*. § 210.15(c).
175. *See* eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006).
176. *Id*.
177. 19 U.S.C. § 1337(d)(2), (f)(1).

parties along a supply chain in a single proceeding. Along with this, the fact that the ITC has relaxed service requirements may also be viewed as a plus. The Commission serves the complaints in investigations, including on foreign respondents, obviating the need for the complainant to effect service and avoiding complex rules like service under the Hague Convention.[178]

The fact that the ITC's ALJs have significant patent and IP experience may also be viewed as an advantage to complainants. When choosing a forum in which to assert a patent, for example, a complainant may prefer to choose the ITC and its ALJs with significant patent experience over a district court judge who may or may not have any patent experience and may even dislike patent cases.

Complainants may also prefer the ease of establishing jurisdiction at the ITC, which has in rem jurisdiction over imported goods.[179] The Commission also may find parties that are served the complaint but fail to respond to be in default, which can result in an exclusion order and/or a cease-and-desist order, even if the respondent does not show up.[180]

[A][1] Suggested Strategies for Complainants

There are several strategies that may help complainants take advantage of the potential advantages they enjoy in ITC investigations. For example, complainants may wish to take advantage of the speed of the proceeding by preparing its case well before the complaint is filed and the investigation is instituted. For example, before the complaint is filed, the complainant will want to meet with the Staff Attorney before filing the complaint to make sure that everything is in order and to ensure that institution within the shortest time is likely. A complainant may also want to retain and have the benefit of consulting an expert to prepare and develop its case before the case is ever filed, which is a luxury that respondents do not have.

Likewise, a complainant may wish to have an initial round of discovery prepared and ready to serve upon institution of the investigation. Doing this will help keep respondents on their heels and can be helpful and even critical to developing the complainant's liability case (e.g., on importation and infringement) within the few months available in the investigation for case development. Along the same lines, to minimize the possibility of respondents' filing motions to compel and potentially seizing the initiative, complainants should

178. 19 C.F.R. § 210.11.
179. Sealed Air Corp. v. U.S. Int'l Trade Comm'n, 645 F.2d 976, 985–86 (C.C.P.A. 1981).
180. 19 U.S.C. § 1337(g).

have documents that they know that they will need to produce ready to produce, such as domestic industry and other documents.

Complainants also should act quickly on all outstanding items. For example, complainants should act quickly to seek defaults where necessary, to amend the complaint, to move to compel, and to issue subpoenas. Resolution of these issues can take time, and there is precious little time during an ITC investigation. Failure to timely serve subpoenas, for example, may result in a complainant not receiving needed discovery and facing the potential for a failure of proof on one or more issues.

Complainants may want to name differently situated respondents to create and exploit differences in the respondents' positions on different issues (e.g., infringement, claim construction). Respondents will likely form a joint defense group, and exploiting differences between the respondents' positions can help negate some of the advantages they may enjoy because of such joint defense groups.

In investigations involving multiple respondents, complainants also may want to try to force respondents to coordinate discovery and filings as much as possible. For example, rather than responding to multiple sets of discovery from each respondent that are substantially similar to each other, ITC complainants should try to have respondents serve a single set of requests wherever possible. Likewise, where respondents have similar interests on a motion, complainants should try to have respondents file a single responsive brief rather than multiple, substantially similar briefs.

Complainants should also meet and talk with the Staff Attorney often. It is critical for a complainant to explain its positions as clearly as possible and to allow the Staff Attorney time to consider and ask relevant questions and then to hopefully agree with the complainant's position. Winning a battle in the ITC can be easier with the Staff Attorney on your side, so if the complainant can successfully win over the Staff Attorney, that will be helpful to the complainant.

Complainants should also consider managing the number of patents and claims in the case strategically. For example, at the beginning of the case where a complainant can leverage pre-investigation research and work, the complainant may wish to advance a larger number of patents and claims. As the case progresses and the strengths and weaknesses of certain asserted patents and claims become apparent, complainant should consider reducing the number of claims and patents in the case. These reductions should be made with an eye toward trial efficiency and good presentation at trial.

Finally, although respondents are entitled to an automatic stay of any parallel district court proceeding should they wish it,[181] complainants should nonetheless consider filing a concurrent district court case in their preferred venue to preserve their choice of venue. Absent a complainant's filing a companion district court case, a respondent sued in the ITC will likely be able to establish declaratory judgment jurisdiction and file in the venue of its choosing, which may not be the best venue for the complainant.[182]

§ 15:4.2 Respondent's View

[A] Potential Advantages for Respondents

Litigation at the ITC also has potential advantages from the respondent's perspective. One such potential advantage is the additional defenses and avenues of attack available at the ITC that are not available in district court. In addition to traditional defenses that one might raise in a district court litigation, respondents in the ITC also can raise arguments regarding the public interest, for example.[183] Respondents can also challenge the complainant's proof on things like importation[184] and domestic industry.[185]

Another potential advantage for respondents in ITC investigations is the potentially persuasive effect of an ITC decision in district court. As mentioned above, decisions in section 337 investigations do not always have preclusive effects in district court litigation and, in particular, are not preclusive in patent cases.[186] But such ITC decisions may have a persuasive effect, even where there is no actual preclusion. While this is true for both sides of the ITC investigation, the argument for a district court to view an ITC decision as persuasive may be stronger against a complainant who chose to file an ITC complaint and to purposely avail itself of the ITC's jurisdiction.

In ITC investigations involving multiple respondents, the ability of respondents to leverage joint defense groups may be advantageous. In joint defense groups involving multiple respondents, the ability to

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181. *See* 28 U.S.C. § 1659(a).
182. *See* MedImmune Inc. v. Genentech Inc., 549 U.S. 118, 121 (2007).
183. *See, e.g.*, 19 U.S.C. § 1337(e)(1) (requiring consideration of the effect of exclusion order on "public health and welfare, competitive conditions in the United States economy, the production of like or directly competitive articles in the United States, and United States consumers").
184. *See id*. § 1337(a)(1).
185. *See id*. § 1337(a)(3).
186. Tex. Instruments Inc. v. Cypress Semiconductor Corp., 90 F.3d 1558, 1569 (Fed. Cir. 1996) (no collateral estoppel, even after Federal Circuit affirmance of ITC infringement decision).

pool resources, to share burdens, and to divide work can be a real advantage against a single complainant or a group of related complainants. Where multiple respondents are in the same investigation, they may be able to pool significantly more resources than the complainant can access. Taking advantage of this imbalance requires additional planning and coordination but can help respondents negate some of the advantages the complainant may otherwise enjoy in ITC investigations.

Respondents can also take advantage of the ITC's new 100-day program to try to obtain an early dispositive ruling.[187] While this will not apply in every case, in some cases it can provide a real asymmetry that favors the respondent and can permit the ALJ to stay unrelated discovery,[188] which buys the respondent time and potentially negates some of the complainant's timing advantage.

If respondents can seize the initiative in the litigation, then the respondent may be able to take advantage of some of the aspects of the investigation that usually favor the complainant, such as the speed of the proceeding, the limited time to develop the case, the broad discovery and short deadlines, and the potential for waiver. The idea is to change the dynamic so that the complainant, rather than respondent, is on its heels. The respondent that can successfully change that dynamic will then potentially enjoy many benefits and advantages inherent in the ITC investigation process.

[A][1] Suggested Strategies for Respondents

There are several strategies that may help respondents take advantage of the potential advantages that they enjoy in ITC investigations. One of the main things that respondents should consider doing to gain an advantage in ITC investigations is to invest heavily up front to try to seize the initiative. Respondents can do this in several ways, such as through early challenges. For example, the respondent may wish to challenge institution of the investigation or the sufficiency of the complaint, if there is a good basis to do so. Respondents also may wish to consider seeking relief under the 100-day program, if there is a good and viable basis for doing so. Similarly, respondents should conduct interviews and documents searches as soon as possible to prepare document productions and initial discovery ahead of when they need to be served so that respondents can produce them without difficulty and without disrupting their case preparations when the time comes.

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187. *See* 19 C.F.R. §§ 210.10(b)(3), 210.42(a)(3).
188. *See id*. § 210.10(b)(3).

Respondents may also wish to seek early discovery on certain key issues. For example, respondents may wish to explore through early discovery the basis for the complainant's allegations, especially if those allegations appear to have weak points. Similarly, respondents may wish to seek early discovery with an eye toward potential summary determination motions. If a viable ground for seeking summary determination is uncovered, respondents should consider an early summary determination motion, which may dispose of or narrow the case and make it more difficult for a complainant to develop its affirmative case.

To take advantage of a joint defense group, respondents should coordinate early and closely with counsel for other respondents in the case. It is critical to coordinate and to plan an overall case strategy. Without prior planning, respondents may not have enough time during the heat of an active investigation to develop their positions and receive approval from each respondent on every issue, potentially causing the respondents to take inconsistent positions and potentially yielding the initiative and the advantage of the speed of the investigation to the complainant.

Respondents should also meet and talk with the Staff Attorney early and often in an attempt to win the Staff Attorney's support. As with the complainant, respondents want to get feedback and buy-in from the Staff Attorney wherever possible. For respondents, like for the complainant, winning a battle in the ITC can be easier with the Staff Attorney on their side. Generally, it's better to have two sides (respondents and the Staff) against one (complainant) wherever respondents can achieve it.

Respondents in ITC investigations should try to force the complainant to narrow its claims and finalize its positions as soon as possible. This can be done through discovery requests, summary determination or other motions, stipulations, or other mechanisms. All parties usually know that the complainant will be narrowing its claims at trial, so respondents should push for this as early as possible. Reducing the number of issues the complainant is advancing can dramatically reduce the work, effort, and cost of an investigation and can help respondents focus on the issues that are truly important to the case to help it achieve the best possible outcome.

Finally, as mentioned above, to the extent that respondents intend to file IPR petitions and hope that the PTAB decision will impact the investigation, they should file as early as possible. Generally, respondents will need a final decision from the PTAB to have a chance for either the ALJ or the Commission to consider and possibly follow the PTAB's decision.

§ 15:5 Conclusion

While some aspects of ITC litigation are different from district court litigation, there are many similarities that allow attorneys that primarily practice in district court to practice in the ITC. But there are some potential stumbling blocks for the unwary. Early planning and knowledge of the potential pitfalls are essential for success. With proper planning, it is possible to create advantages to help give your side of the investigation the maximum chance of success.

Appendix A. Glossary of Biotechnology Terminology from Case Law

Pharmaceutical and Biotech Patent Law (2024)
Format: Treatise Chapter
Date: Jul 2024
Author(s): Arnold & Porter Kaye Scholer LLP (Arnold & Porter Kaye Scholer LLP)
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Appendix A

Glossary of Biotechnology Terminology from Case Law

Antibody: "Vertebrates defend themselves against invasion by microorganisms by producing antibodies, proteins which can complex with the invading microorganisms and target them for destruction or removal. In fact, any foreign molecule of sufficient size can act as a stimulus for antibody production."[1]

Amino Acids: "There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine."[2]

Chimeric Antibody: "A chimeric antibody combines DNA encoding regions from more than one type of species. For example, a chimeric antibody may derive the variable region from a mouse and the constant region from a human."[3]

Cloning: "The process of making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into procaryotic cells and then growing those cells is called *cloning* the gene."[4]

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* The definitions supplied here are simplified and have been extracted from judicial opinions. For more complete (and sometimes more scientifically accurate) definitions, see BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL (4th ed. 2002) (prior edition cited by *In re* O'Farrell, 853 F.2d 894, 895 n.1 (Fed. Cir. 1988)).

1. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1368 (Fed. Cir. 1986).
2. *O'Farrell*, 853 F.2d at 896 n.2.
3. Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1250 (Fed. Cir. 2004).
4. *O'Farrell*, 853 F.2d at 898.

Codon: "The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 (4×4×4) possible codons."[5]

Complementary DNA (cDNA): A cDNA library "is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known."[6]

Degeneracy: "Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a 'redundancy' or 'degeneracy' in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA."[7]

Deoxyribonucleic Acid (DNA): "DNA consists of two complementary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from one strand weakly bond to the bases of the opposite strand."[8] "The sequence of these bases along the DNA molecule specifies which amino acids will be inserted in sequence into the polypeptide chain of a protein. . . . DNA molecules do not participate directly in the synthesis of proteins. DNA acts as a permanent 'blueprint' of all of the genetic information in the cell, and exists mainly in extremely long strands (called *chromosomes*) containing information coding for the sequences of many proteins, most of which are not being synthesized at any particular moment."[9]

Eucaryotic Organisms: "Man, other animals, plants, protozoa, and yeast are *eucaryotic* (or eukaryotic) organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus."[10]

Fully-Degenerate Set of Probes: "Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she

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5. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1208 n.4 (Fed. Cir. 1991).
6. *Id.* at 1208 n.4.
7. *Id.*
8. *Id.* at 1207 n.4.
9. *O'Farrell*, 853 F.2d at 896–97.
10. *Id.* at 898.

may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a 'fully-degenerate' set of probes."[11]

Gene: "The region of DNA on the chromosome that codes for the sequence of a single polypeptide is called a *gene*."[12]

Genetic Code: "The code whereby a sequence of nucleotides along an RNA molecule is translated into a sequence of amino acids in a protein (*i.e.*, the 'genetic code') is based on serially reading groups of three adjacent nucleotides. Each combination of three adjacent nucleotides, called a *codon*, specifies a particular amino acid."[13]

Genomic Library (gDNA): A gDNA library "contains a set of all the DNA sequences found in an organism's cells" and can be used for screening. The gDNA "is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization."[14]

Heterologous Genes: These are genes "from a foreign source" that have been "integrated into [an organism's own] genetic makeup." Such organisms "are said to be *transformed*."[15]

Hybridization: "*A* bonds with *T*, and *G* bonds with *C* to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule."[16]

Messenger RNA: "The transcribed RNA" copied from the DNA is "called *messenger RNA*." It "moves to a location in the cell where proteins are synthesized."[17]

Monoclonal Antibody: "A monoclonal antibody is a protein produced by an organism such as a mouse in response to a challenge to the organism's immune system with a foreign material (often a protein), or 'antigen'. . . . The monoclonal antibody so produced is able to form a complex with the challenging antigen that can be readily observed through standard procedures in the art, thus making

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11. *Amgen*, 927 F.2d at 1208 n.4.
12. *O'Farrell*, 853 F.2d at 897; *see also* Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 304 F.3d 1221, 1224 n.2 (Fed. Cir. 2002), *vacated*, 314 F.3d 1299 (Fed. Cir. 2002).
13. *O'Farrell*, 853 F.2d at 897.
14. *Amgen*, 927 F.2d at 1208 n.4.
15. *O'Farrell*, 853 F.2d at 898.
16. *Amgen*, 927 F.2d at 1208 n.4 (emphasis added).
17. *O'Farrell*, 853 F.2d at 897.

monoclonal antibody technology a convenient method to identify and isolate antigens."[18]

Mutation: "A mutation is a change in a gene and the resulting change in a protein produced by the gene."[19]

Nucleic Acids: "A single strand of DNA is made up of subunits, termed 'nucleic acids' or 'bases', which link together to form a long chain. These subunits are Adenine, Thymine, Guanine and Cytosine. Depending on the sequence in which they occur, they define every protein in an organism."[20]

Nucleotides: "A nucleotide consists of a nitrogen-containing ring compound (called a *base*) linked to a 5-carbon sugar that has a phosphate group attached."[21]

Peptide: "Specific amino acid sequences, also referred to as peptides."[22]

Plasmid: "A *plasmid* is a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates like a chromosome. It is like a tiny auxiliary chromosome containing only a few genes. Because of their small size, plasmids are convenient for the molecular biologist to isolate and work with."[23]

Polyclonal Antibody: "In order to create antibodies for use in their research, scientists inject immunized animals with an antigen, triggering the animal to produce antibodies against the antigen. Scientists then draw the animal's antibody-rich blood, which is referred to as antiserum. The antibodies harvested in this manner are referred to as polyclonal antibodies."[24]

Procaryotic Organism: "Bacteria (*procaryotic* or prokaryotic organisms)" have DNA that "is not contained in any specialized compartment" and usually exists in a circular loop.[25]

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18. Evans Med. Ltd. v. Am. Cyanamid Co., 52 U.S.P.Q.2d (BNA) 1455, 1456 n.1 (Fed. Cir. 1999).
19. *Elan*, 304 F.3d at 1224 n.2.
20. Enzo Biochem, Inc. v. Calgene, Inc., 14 F. Supp. 2d 536, 543 (D. Del. 1998), *aff'd in part, vacated in part*, 188 F.3d 1362 (Fed. Cir. 1999).
21. *O'Farrell*, 853 F.2d at 895–96.
22. Nichols Institute Diagnostics, Inc. v. Scantibodies Clinical Lab., Inc., 195 F. App'x 947 (Fed. Cir. 2007).
23. *Id.* at 898.
24. Yeda Research & Dev. Co. v. ImClone Sys. Inc., 443 F. Supp. 2d 570, 579 (S.D.N.Y. 2006).
25. *O'Farrell*, 853 F.2d at 898.

Protein: "Proteins are biological molecules of enormous importance. Proteins include enzymes that catalyze biochemical reactions, major structural materials of the animal body, and many hormones. . . . The basic organization of all protein is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called *amino acids*, that are linked together covalently. The chemical bonds linking amino acids together are called *peptide* bonds, so proteins are also called *polypeptides*. It is the exact sequence in which the amino acids are strung together in a poly peptide chain that determines the identity of a protein and its chemical characteristics."[26]

Recombinant DNA (rDNA): "Recombinant DNA technology involves insertion of a specific double-stranded DNA, via a cloning vector, into a target organism. Generally, one strand of the inserted DNA encodes a desired protein. This strand is termed the 'coding' strand and is transcribed to yield RNA which, in turn, is translated to yield the protein."[27]

Ribonucleic Acid (RNA): "RNA is a molecule that closely resembles DNA. It differs, however, in that it contains a different sugar (ribose instead of deoxyribose) and the base thymine (T) of DNA is replaced in RNA by the structurally similar base, uracil (U)."[28]

Ribosomes: "The cellular machinery involved in synthesizing proteins is quite complicated, and centers around large structures called *ribosomes* that bind to the messenger RNA. The ribosomes and associated molecules 'read' the information in the messenger RNA molecule, literally shifting along the strand of RNA three nucleotides at a time, adding the amino acid specified by that codon to a growing polypeptide chain that is also attached to the ribosome."[29]

Stop Codon: "When a stop codon is reached, the polypeptide chain is complete and detaches from the ribosome."[30]

Transcription: "Making an RNA copy of DNA is called *transcription*. The transcribed RNA copy contains sequences of A, U, C, and G that carry the same information as the sequence of A, T, C, and G in the DNA."[31]

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26. *Id.* at 895–96.
27. Kridl v. McCormick, 105 F.3d 1446, 1448 (Fed. Cir. 1997).
28. *O'Farrell*, 853 F.2d at 897.
29. *Id.*
30. *Id.*
31. *Id.*

Transformation: "The process whereby a DNA construct (also called a 'vector' or 'vector construct' or 'plasmid') carrying foreign (called 'heterologous') genes is introduced into and accepted by a host cell is called 'transformation' or 'transfection.'"[32]

Translation: "The conversion of the information from a sequence of codons in an RNA molecule into the sequence of amino acids in a newly synthesized polypeptide is called *translation*."[33]

Vector or Cloning Vector: "A *cloning vector* is a piece of DNA that can be introduced into bacteria and will then replicate itself as the bacterial cells grow and divide."[34]

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32. Biogen, Inc. v. Berlex Labs., Inc., 318 F.3d 1132, 1134 (Fed. Cir. 2003).
33. *O'Farrell*, 853 F.2d at 897.
34. *Id.* at 898.

Appendix B. Primer on Basic Biotechnology Concepts

Pharmaceutical and Biotech Patent Law (2024)
Format: Treatise Chapter
Date: Jul 2024
Author(s): Laurence Borden
PLI Item #: 397729
Practice Areas: Health care, Intellectual property, Life sciences

Appendix B

Primer on Basic Biotechnology Concepts

Laurence A. Borden, Ph.D.

§ B:1 The Cell

All living organisms, be they plant, animal or bacteria, are made of cells—which form the basic unit of life. (Fig. B-1) Some organisms, like bacteria and amoebae, consist of a single cell, while more complex organisms contain trillions. And yet, the essential structure and function of the cell is relatively constant for all organisms. All cells synthesize macromolecules, metabolize sugars and other substances that fuel the cell, and reproduce by a process of cell division known as mitosis.

§ B:1.1 Macromolecules

Macromolecules are relatively large molecules often consisting of long chain polymers formed by linking together a variety of subunits. Proteins made from a sequence of amino acids, DNA and RNA made from a sequence of nucleic acids, and complex carbohydrates made from simple sugars are all long chain polymers described further below. Although lipids are not long chain polymers, because of their size and their importance as structural elements, they can be regarded as macromolecules.

[A] Proteins

Each protein is composed of hundreds to thousands of individual amino acids linked together into a chain. The amino acids are joined to one another via peptide bonds as shown in Fig. B-2, which shows a chain of two amino acids.

Fig. B-1
The Cell

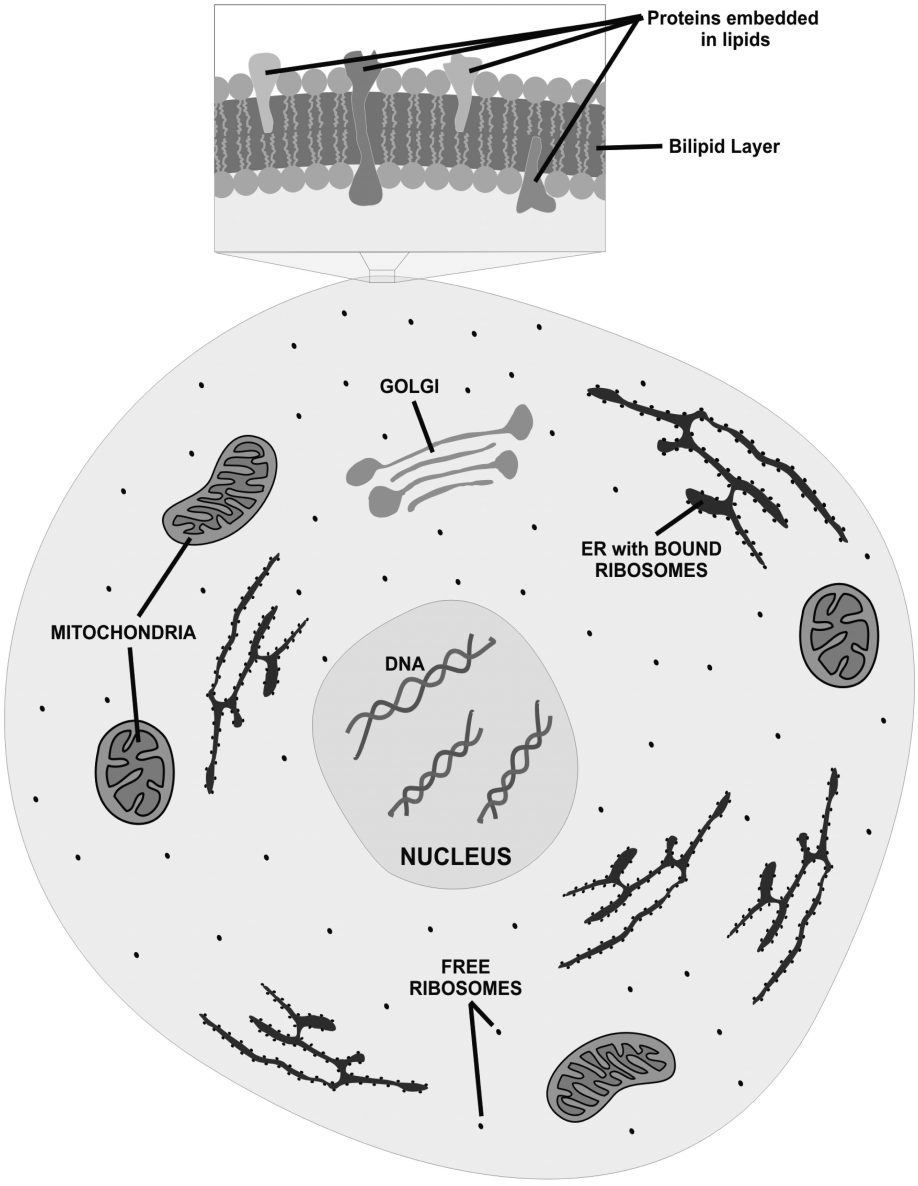

Fig. B-2
Peptide Bonds Between Amino Acids

Glycine Alanine Gly-Ala

Irrespective of its length or sequence, each protein has a free amino group (N-terminus) on one end and a free carboxy group (C-terminus) on the other. By convention, proteins are depicted with the N-terminus to the left and the C-terminus to the right.

One protein differs from another in the sequence of its constituent amino acids, which confers a unique three-dimensional structure, or conformation, to the protein. Proteins perform a variety of tasks in the cell. Some proteins, like collagen and actin provide physical structure and support to cells and tissues.[1] Others have enzymatic activity that catalyzes (facilitates) various chemical reactions in the cell. A protein's function is a direct consequence of its amino acid sequence and its environment in the cell.

[B] Lipids

Lipids, or fats as they are commonly called, are less structurally complex than proteins but still perform many functions in the cell. Some lipids form the cell membranes that surround the exterior of the cell and form interior compartments within the cell. Other lipids are hormones that serve as a signal to other cells throughout the body, and still others form the myelin sheath surrounding the nerves.

[C] Carbohydrates

The primary role of carbohydrates, sugars, is to serve as an energy source. The sugar most commonly used by mammalian cells is the simple hexose, glucose. Carbohydrates are stored in the form of long chain polymers, such as glycogen in mammals and starch[2] in plants. Another long chain polymer carbohydrate, cellulose, forms the cell wall of plant cells. Carbohydrates can also be attached to proteins, where they serve as cellular recognition markers or alter a protein's stability. Fig. B-3 shows the structure of glucose, and the way glucose molecules bond to one another to form the polymer amylose (a form of starch).

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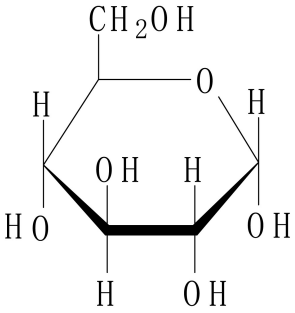
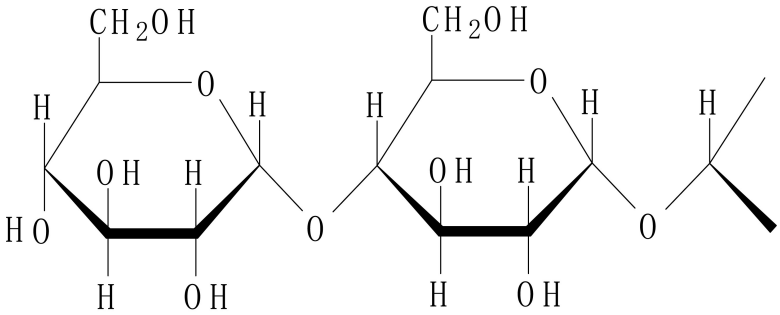
1. Some structural proteins, such as actin, are found within the cell, whereas others, such as collagen, are secreted into the extracellular space that surrounds the cells.
2. The two forms of starch are amylose and amylopectin.

Fig. B-3
Monosaccharides Such As Glucose
Can Form Long Chain Polymers



GLUCOSE



AMYLOSE

[D] Nucleic Acids

The nucleic acids deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) encode the amino acid sequences of an organism's proteins, and serve as the physical template used to synthesize proteins.

[D][1] Structure

DNA and RNA are long chain polymers of nucleotides. Nucleotides consist of a nitrogen-containing base, a 5-carbon sugar (pentose), and one or more phosphate groups (Figs. B-4 though B-7). A base and a sugar, without the phosphate group, are called a nucleoside. DNA contains four different nucleosides (and nucleotides), each with its own base, as shown in the following table:

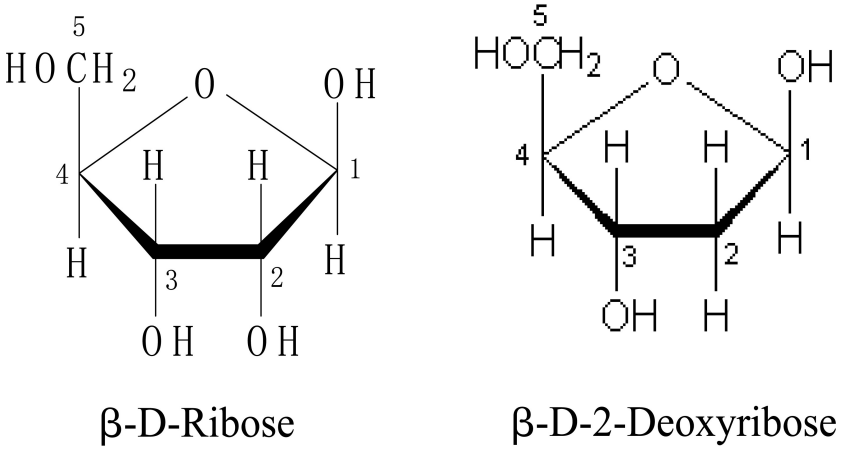
Table B-1
Nucleosides and Nucleotides Contained in DNA

BASE	NUCLEOSIDE	NUCLEOTIDE
adenine (A)	adenosine	adenosine monophosphate
guanine (G)	guanosine	guanosine monophosphate
cytosine (C)	cytidine	cytidine monophosphate
thymine (T)	thymidine	thymidine monophosphate

The bases adenine and guanine belong to the chemical class purines, while cytosine and thymine are pyridines.

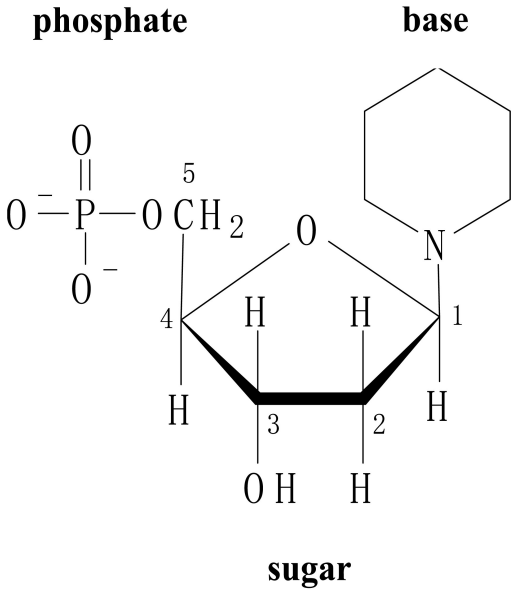
The sugars found in nucleic acids are the pentoses ribose (found in RNA) and deoxyribose (found in DNA). The numbering system of the six carbon molecules (five of which are within the ring) is shown in Fig. B-4.

Fig. B-4
Sugars Found in Nucleic Acids



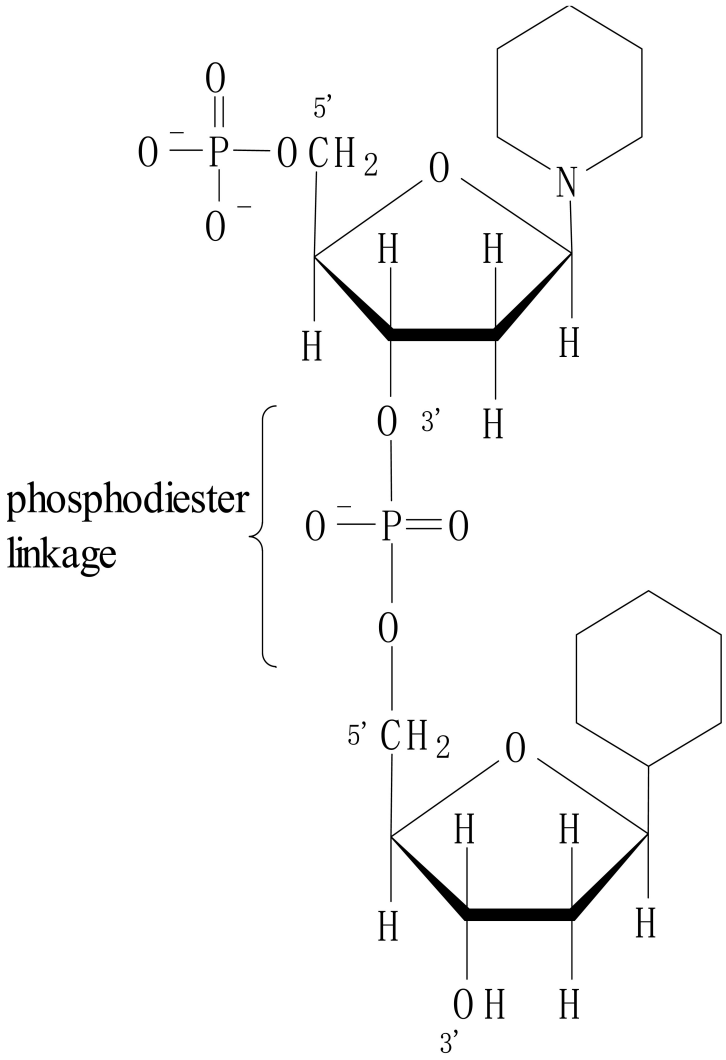
As shown in Fig. B-5, the phosphate group in a nucleotide is attached to the 5′ carbon of the sugar, and the nucleotide base to the 1′ carbon.

Fig. B-5
Nucleotide = Base + Sugar + Phosphate



Nucleotides are linked to one another via phosphodiester bonds between 5′ and 3′ carbons on the pentose molecules, as shown in Fig. B-6. By convention, the 5′ end of the polymer is shown to the left. Thus, a sequence might be depicted as 5′CCATTGTACCTGGT3′.

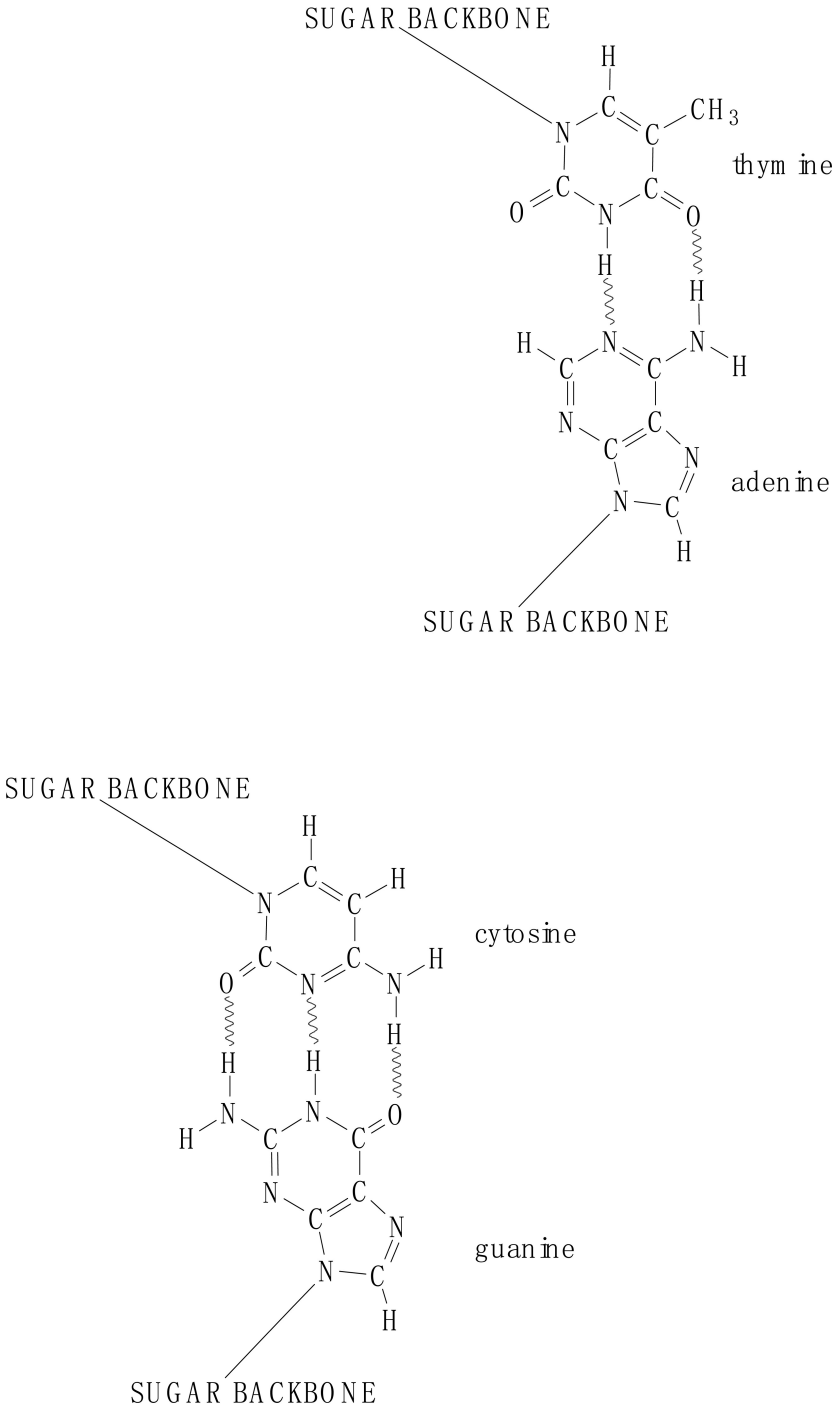
Fig. B-6
Nucleic Acid Chain



DNA exists as a double-stranded anti-parallel helix. Anti-parallel refers to the fact that one strand runs in the 5′ to 3′ direction, while the other strand runs in the 3′ to 5′ direction. As shown in Fig. 7, the two strands attach to one another via weak chemical bonds between the nitrogen-containing base: Thymine (T) binds to adenine (A), and cytosine (C) to guanine (G). Accordingly, the two anti-parallel strands are referred to as being complementary to one another. If, for example, one strand has the sequence 5′ AATCGGTAT 3′, the complementary

strand will have the sequence 3′ TTAGCCATA 5′. As discussed below, this property of nucleic acid sequences forms the basis of many of the techniques in molecular biology. A cell's entire DNA does not exist in a single linear array but in individual segments called chromosomes, the number of which is species-dependent.

Fig. B-7
Nucleotide Base Pairing



RNA is structurally similar to DNA, but differs in several ways. First, RNA uses the base uracil (nucleoside = uridine) instead of thymine (nucleoside = thymidine) used by DNA. Second, the pentose in RNA is β-D-ribose, whereas in DNA the pentose is β-D-2-deoxyribose. Third, RNA is usually single stranded whereas DNA is double stranded.

RNA comes in three types: messenger RNA (mRNA), transfer RNA (tRNA) and ribosomal RNA (rRNA). Each of these types performs a different role in protein synthesis. Like DNA, mRNA serves as a template for protein synthesis. rRNA is a component (along with various proteins) of ribosomes, which form the machinery that assembles proteins from the soup of available amino acids. Soluble proteins destined to float free in the cytoplasm are synthesized on ribosomes that themselves float free in the cytoplasm that fills the interior of the cell. Proteins slated to be embedded within the cell's plasma membrane or secreted from the cell are synthesized on ribosomes that are attached on the membrane-bound intracellular compartment known as endoplasmic reticulum. tRNA shuttles individual amino acids onto a growing protein chain being synthesized against an mRNA template. There are twenty distinct tRNA subtypes, each corresponding to one of the twenty amino acids. Each tRNA molecule has one portion that binds a particular amino acid and a second portion complementary to the codon[3] in the mRNA that encodes that particular amino acid.

[D][2] The Genetic Code

Each amino acid is encoded by a sequence of three nucleotides, termed a codon. Because each nucleotide in a codon can be A, T, C, or G, there exist 4^3 or sixty-four distinct codons. Since there exist only twenty different amino acids, each amino acid is encoded by more than one codon sequence; this is referred to as "degeneracy" of the genetic code. The variation between different codons encoding the same amino acid usually occurs at the third nucleotide and is thus referred to as third base wobble. For example, the amino acid glutamate is encoded by GAA and by GAG. Mutations in the third nucleotide position are often "silent" because they do not cause a change in the encoded amino acid. Because of the degeneracy of the code, one cannot use the amino acid sequence of a protein to unambiguously predict the nucleotide sequence of the gene encoding that protein. Similarly, one cannot use the nucleotide sequence of a gene from one animal to predict with certainty the nucleotide sequence of that same gene from another animal (even if they encode the

3. *See infra* section B:1.1[D][2].

same amino acid sequence, which also is not always the case). In contrast, knowledge of the nucleotide sequence does allow unambiguous prediction of an amino acid sequence.

Certain nucleotide sequences have special functions. For example, the sequence ATG, which encodes the amino acid methionine, is a "start" codon, so named because it designates the beginning of a gene (and thus the starting point of transcription). UAA and UGA are "stop" codons and signal the end of a gene. Additionally, many genes have at their 3′ end the sequence AAUAAA, which signals the addition of typically 80–250 adenosine residues at the 3′ end of the mRNA. This "poly A tail" increases stability of the mRNA, thereby increasing the synthesis of the protein it encodes.

In many eukaryotes (cells with a nucleus), the coding sequence of genes (exons) are interrupted by sequences that do not encode amino acids. Such intervening sequences are termed "introns" and vary in size typically from approximately 100 to 10,000 nucleotides. A given gene may contain numerous introns that alternate with the exons. During transcription,[4] both introns and exons serve as templates for synthesis of RNA. While still in the nucleus, this initial RNA, termed heterogeneous RNA (hnRNA), undergoes cleavage whereby the sequences corresponding to introns are excised and the sequences corresponding to exons are spliced together. However, the introns are not always reassembled in the order in which they existed in the hnRNA. Moreover, the order in which they are re-assembled varies between cells and possibly even within a given cell at different times. A single intron-containing gene can thus yield multiple mRNAs that encode different proteins termed splice variants.

§ B:1.2 Organelles

Various intracellular structures known as organelles exist within the cell.

[A] Plasma Membrane

The interior of a cell is separated from the extracellular space by the plasma membrane (also called the "plasmalemma" or "cell membrane"). The plasma membrane is a bilipid membrane. Embedded within it are numerous proteins, some of which span the entire thickness of the membrane. Because of its high lipid content, hydrophilic (water loving) molecules are unable to passively traverse the membrane. Various active transport mechanisms (transporters, channels, pumps, etc.) have evolved to facilitate the movement of specific substances in and out of the cell.

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4. *See infra* section B:2.1.

[B] Cell Wall

Plant cells have a cellulose-containing cell wall located external to the cell membrane. The cell wall provides the plant cell with physical support, rigidity, and protection.

[C] Nucleus

The cell's nucleus is a double membrane-bound organelle found (by definition) in eukaryotic cells, but absent from procaryotes (such as bacteria). In procaryotes the DNA (in the form of chromosomes) is found free in the cytosol, whereas in eukaryotes the genetic material is contained within the nucleus. The nuclear membrane selectively regulates passage of substances between the nucleus and the cytosol.

[D] Ribosomes

Ribosomes are composed of both rRNA and protein. A ribosome consists of a small subunit that binds mRNA and tRNAs, and a large subunit that catalyzes peptide bond formation. The small subunit contain three binding sites: One site binds mRNA, and two sites bind tRNA. The two tRNA bindings sites on the ribosome are termed P-site and A-site, which stand for peptidyl-tRNA-binding site and aminoacyl-tRNA-binding site, respectively, The P-site binds the tRNA that is linked to the end of the polypeptide chain at which elongation occurs, while the A-site binds the incoming tRNA (with bound amino acid). The two tRNA-binding sites thus act like two hands; one holds the end amino acid chain that needs to be completed to form the protein, and the other grabs the next amino acids that need to be added to the growing chain.

[E] Mitochondria

Mitochondria are often described as the power plants of the cell, because these membrane-bound organelles contain many of the enzymes necessary to convert nutrients into energy. Mitochondria contain their own DNA, distinct from that found in the chromosomes. Whereas an organism's non-mitochondrial DNA is inherited from both parents, mitochondrial DNA is inherited solely from the mother.

[F] Endoplasmic Reticulum

The endoplasmic reticulum (ER) is a network of membrane-enclosed compartments. As mentioned above, proteins destined for secretion or insertion in the plasma membrane are synthesized on ribosomes attached to the ER.

[G] Golgi Apparatus

The Golgi apparatus is a set of sacular membrane-enclosed compartments, in communication (directly, or via vesicles) with the ER. Within the Golgi, secreted and membrane-bound proteins destined for the cell surface are glycosylated.

§ B:2 Protein Synthesis

Like all cellular constituents, proteins are in a continual state of turnover. Old proteins are degraded and new proteins are synthesized to take their place. Cells also need to vary the level of certain proteins due to alterations in things like metabolic demands. For these reasons, cells must synthesize new proteins. Protein synthesis is a two-step process in which DNA is first transcribed into mRNA, then the mRNA serves a template for the actual production of the poplypeptide chain.

§ B:2.1 Transcription

A gene comprises a sequence of nucleotides that encodes a single protein.[5] The first step in transcription is the binding of an RNA polymerase enzyme complex to a specialized region of the gene termed the promoter, which contains the start site. This causes the strands of the DNA double helix to separate and unwind, thereby exposing the nucleotides on a short stretch of each DNA strand. One of the two DNA strands acts as a template whereby complementary ribonucleoside triphosphate monomers base pair to the DNA nucleotides. The polymerase forms a bond between two ribonucleoside triphosphate monomers, then the polymerase moves down the DNA chain and unwinds a new region, allowing additional complementary base pairs to be added. The process continues in the 5′ to 3′ direction along the gene until the polymerase encounters a stop signal (for example, UAA), at which point it stops addition of bases and releases both the DNA template and the nascent RNA chain.

§ B:2.2 Translation

The process of translation begins when the newly synthesized mRNA strand exits the nucleus[6] and binds to a ribosome. Proteins are synthesized by the sequential addition of amino acids that become

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5. *See supra* section B:1.1[D][2].
6. As noted in *supra* section B:1.2[C], prokaryotes lack a nucleus.

linked via peptide bonds: the free amino group on an amino acid binds to the carboxyl group of the growing peptide chain. In this manner, a protein is synthesized from its N-terminal end to its C-terminal end. The elongation process occurs as follows:

1. An amino acid-tRNA complex binds to an unoccupied ribosomal A-site by base-pairing with the codon on the mRNA.
2. The tRNA molecule present in the P-site of ribosome dissociates from the carboxyl end of the peptide chain; the carboxyl end then becomes linked via a peptide bond to the amino acid linked to a tRNA in the A-site.
3. The new peptide-tRNA in the A-site is translocated to the P-site as the ribosome moves along the mRNA a distance of three nucleotides (that is, one codon). The free tRNA in the A-site is released into the cytoplasm, and the A-site then becomes occupied by a new tRNA-amino acid complex, as dictated by the available codon.

§ B:2.3 Post-Translational Modifications

Many proteins are modified within the ER and Golgi apparatus, concurrent with or following translation. One of the most important modifications is glycosylation, whereby carbohydrate residues are added to certain specific amino acids. The sugars are added sequentially and can form elaborate arrays of linear and branched chains.

Amino acids can also be chemically modified by a number of processes, including alkylation (addition of carbon chains), acetylation (addition of an acetic acid ion group), phosphorylation (addition of a phosphate group), and isoprenylation (addition of isoprene, a type of fat), amongst others.

§ B:3 Gene Regulation

With the exception of reproductive cells, sperm and ova, all cells in an organism contain the same genetic material. The reason a liver cell is different from a skin cell is not because of different DNA, but rather because of qualitative and quantitative differences in gene expression between the two cell types. Even within a given cell, gene expression changes in response to a variety of stimuli; a readily observable example is the increased expression of muscle contractile proteins that occurs in response to exercise. The regulation of gene expression is thus critically important to cellular function, and numerous mechanisms exist for

controlling gene expression at various places in the pathway from DNA to protein.

One of the most important regulatory mechanisms occurs at transcription. At any one instant in time, the vast majority of genes in a given cell are not being transcribed; non-transcription may be thought of as the default option.[7] For transcription to occur, it is generally necessary for a transcription factor to bind to a promoter region of a gene. Transcription factors are proteins that have a DNA-binding domain, and often other domains through which the transcription factors themselves are activated. Factors that influence the activity of a transcription factor can originate within the cell (for example, a metabolite) or externally to the cell (for example, a hormone).

§ B:4 Antibodies and Antigens

The immune system protects the host from infection. Immune responses may be divided into two broad classes, termed cellular and humoral. The cellular system uses macrophages and cytotoxic T-lymphocytes (amongst others) to kill invading organisms such as bacteria, while the humoral system utilizes antibodies (also called immunoglobulins). Antibodies are Y-shaped multi-chain proteins whose production is elicited by exposure to an antigen. (Fig. B-8).

7. There are, however, also factors that inhibit transcription.

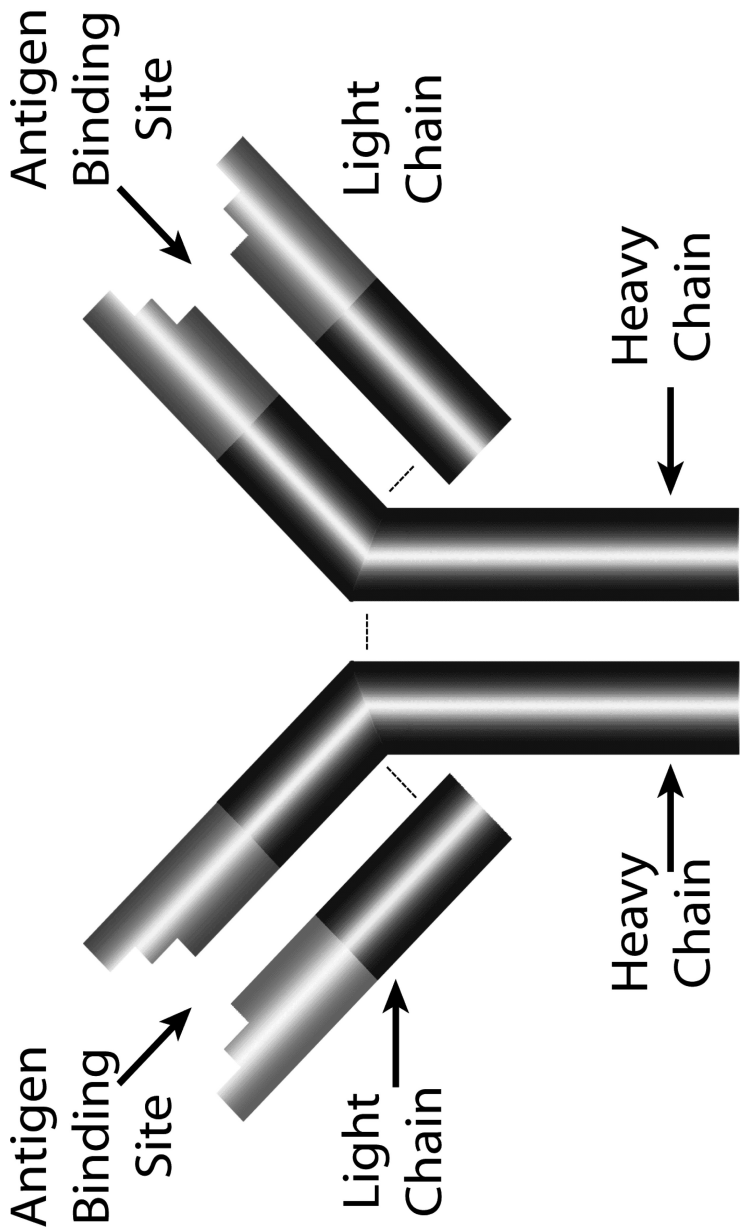

Fig. B-8
An Anitobody Molecule

The portion of a macromolecule, the antigen, to which an antibody binds is called an epitope. Antibodies are comprised of light chains and heavy chains that mediate binding to antigen as well as other effector mechanisms such as binding of the antibody to macrophages. Antibodies bind to their respective antigens with remarkable affinity and specificity. Because antibodies can be developed against virtually any target (that is, antigen) of interest, they have proven to be extremely useful as research tools and more recently, as therapeutics.

§ B:4.1 Clonal Generation of Antibodies

Antibodies are produced by B-lymphocytes (also called B-cells), which are a type of white blood cell. During fetal development, B-cell precursor cells undergo random rearrangement of the genes encoding immunoglobulins. As such, the antibody encoded by each cell (and its progeny) differs from the antibody encoded by other cells.

[A] Polyclonal Antibodies

When an organism is exposed to an infectious agent, such as a bacterium, virus, or parasite, the B-cells that express antibody to the molecules expressed by these organisms begin to divide and mature into cells (termed plasma cells) which secrete large amounts of antibody. The progeny of a particular B-cell are identical to one another, and are thus termed a clone. Because these infectious agents express numerous antigens, and because each macromolecule contains numerous potential epitopes, the infectious agents trigger an immune response from many clonal B cell populations, each of which expresses a distinct antibody. For this reason, the immune response is termed "polyclonal."

[B] Monoclonal Antibodies

Despite their widespread use in research, polyclonal antibodies have a number of limitations. First, because they are prepared in animals, their supply is finite. Moreover, each time a new animal is immunized—even with the same antigen—the antibodies elicited will differ slightly from those elicited in another animal. Second, because the polyclonal antibody is, by definition, a mixture of numerous distinct antibodies, it specificity is somewhat limited.

These limitations were overcome with the introduction in 1975 by Kohler and Milstein of a methodology to produce monoclonal antibodies.[8] The basic steps involved in the generation of a monoclonal antibody are as follows:

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8. The term monoclonal reflects the fact that the antibodies are derived from a single clonal population of antibody-producing cells.

1. An animal, usually a mouse, is immunized with an antigen of choice.
2. After a suitable interval, the serum is checked for the presence of antibodies reactive with the antigen of interest.
3. The spleen, which contains lymphocytes, is removed from the mouse, and dispersed into individual cells.
4. The spleen cells are fused with immortalized myeloma cells (a type of leukemia).
5. The cells are grown in special medium in which those myeloma cells that have not fused with spleen cells cannot survive. Because the spleen cells have limited ability to be maintained in cell culture, the surviving cells are only those that represent a fusion between a spleen cells and a myeloma cell.
6. The cells are diluted and grown in multi-well plates, such that each well receives only a single cell.
7. Each cell (in its own well) is allowed to multiply into a colony. The progeny cells in a given well are identical to one another, having been derived from a single clone. The antibody they secret is thus "monoclonal" in nature.
8. The medium from each of the wells (containing secreted antibody) is tested for activity. Those cells containing the best activity are expanded into larger plates, and some are frozen for later use. In this way, an infinite supply of a given monoclonal antibody is provided. Because the monoclonal antibody-producing cells result from the fusion of two different cell types, they are often referred to as "hybridomas." When a particular hybridoma, and/or the monoclonal antibody it secretes, is claimed in a patent, a sample of the hybridoma cell line is often submitted to the American Type Culture Collection (ATCC), a repository for biological materials.

§ B:4.2 Chimeric and Humanized Antibodies

Shortly after the initial description of monoclonal antibodies, it was postulated that they might represent a therapeutic "magic bullet" for a wide variety of diseases. The initial enthusiasm was tempered when early clinical trials revealed that the human immune system recognized the mouse antibodies as foreign and mounted a host versus graft response termed HAMA (Human Anti-Mouse Antibody) response, which neutralized the monoclonal antibodies. Efforts were then directed to producing monoclonal antibodies in which portions of the

molecules were replaced with sequences from human antibodies, thereby rendering them less immunogenic. A number of approaches have been utilized to decrease immunogenicity:

- Chimeric antibodies are genetically engineered fusion proteins containing both mouse and human segments. In general, approximately one third of the sequences (including those portions mediating binding to antigen) are mouse and the reminder are human. While the immune response to such antibodies is typically less than with entirely murine antibodies, HACA (Human Anti Chimeric Antibody) responses are still problematic.
- Humanized antibodies are genetically engineered antibodies in which small portions of a mouse antibody are attached onto a human antibody. Generally, 90–95% of the sequence is human in origin, with the remainder murine. Anti-murine antibody responses are generally slight.
- Fully humanized antibodies, also referred to as humanized, are antibodies derived from human cells or from transgenic animals (typically mice) with express human antibody genes. Such antibodies elicit little if any immunogenic response.

§ B:5 Molecular Biology

Molecular biology may be arbitrarily defined as the branch of biology that concerns itself with the structure, function, and regulation of DNA and RNA, and with the processes these molecules facilitate. Not surprisingly, molecular biology overlaps with other disciplines including biochemistry and cell biology. Some of the methodologies that have "revolutionized" molecular biology are the ability to clone genes, to quantify DNA and RNA levels, to amplify DNA, to manipulate DNA sequences, and to heterologously express genes. The following sections will describe some of these methodologies.

§ B:5.1 Hybridization

As mentioned above, naturally occurring DNA is double stranded. The complementary strands are held together by weak bonds between adenosine and thymidine (2 hydrogen bonds) and between cytosine and guanosine (3 hydrogen bonds). Hybridization, which makes use of this property, is the binding together (hybridizing) of two DNA (RNA) strands and forms the basis of many molecular biological techniques. Hybridization can occur in solution, to cells in which the membrane has been rendered permeable to large molecules, or to polynucleotides

immobilized on a solid support such as a nylon membrane or a column.

A number of factors influence the ability of one strand to hybridize with another. First is the length of the strands; assuming perfect complementarity, the longer the strands the "tighter" the binding. Second, binding is tighter between GC pairs (3 hydrogen bonds) than between AT pairs (2 hydrogen pairs). Thus, the greater the proportion of CG pairs, the tighter the binding. Third, for a given stretch of DNA, the greater the degree of complementarity, the tighter the binding. The possibility of hybridization occurring despite less than perfect complementarity, is critical to many molecular biological techniques. Last, binding is tighter as temperatures are lowered and salt concentrations raised. This last point forms the basis for the concept of high- versus low-stringency hybridization. High-stringency conditions, that is, lower salt concentrations and a temperature of approximately 65°C, allow hybridization to occur only when there is a high degree of complementarity between the strands. Relaxing conditions to those of lower stringency (higher salt concentration and temperature of approximately 55°C) permits binding between strands with less than perfect complementarity, but increases non-specific binding.

§ B:5.2 *Detecting DNA*

[A] Southern and Northern Blots

Southern and Northern blots are commonly used to detect DNA and RNA sequences, respectively, in a given sample. In both cases, polynucleotides are isolated from an appropriate sample, then separated by size using gel electrophoresis.[9] The polynucleotides are transferred to a nylon sheet that is then incubated with a radioactive nucleotide probe, the sequence of which is based on the gene of interest. A sufficient amount of time is allowed for hybridization to occur, the nylon is washed to remove non-specifically bound probe, and the labeled probe is visualized by exposing the nylon sheet (with bound probe) to X-ray film. Such experiments can reveal not just the presence of the polynucleotide but also its relative abundance, as well as its size.

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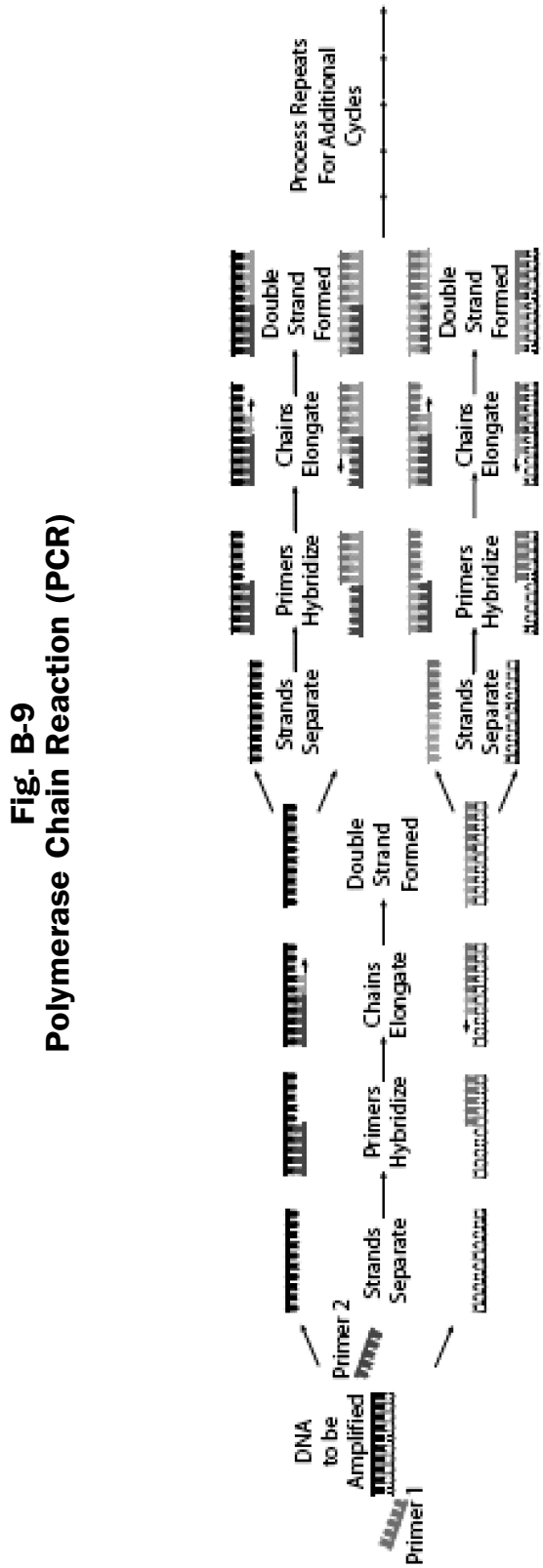
9. Electrophoresis is a method in which an electrical charge is used to separate molecules from one another. The separation can be due to differences in the relative charge on the molecules to be separated, or to differences in their molecular weight.

[B] Polymerase Chain Reaction (PCR)

Polymerase Chain Reaction, for which its inventor Kary Mullis shared the Nobel Prize in 1993, has had a profound impact on molecular biology. In general terms, PCR allows one to amplify, infinitely, if desired, virtually any desired DNA sequence.

To amplify DNA with PCR, one must use a pair of primers (typically, each approximately twenty-five nucleotides in length) that are complementary to sequences that bracket the sequence to be amplified; one primer is complimentary to one strand, and the other primer complementary to the other strand (Fig. B-9). In the first step of the process, the double stranded DNA is heated, causing the two strands to dissociate. Primers and a DNA polymerase enzyme are added and the sample is cooled, thus allowing the primers to hybridize to their respective complementary sequences. The polymerase forms and extends new DNA strands based on the sequence of the original strands to which the primers hybridized. For each original double stranded DNA there are now two double strands. The sample is then heated again to dissociate the strands, cooled and hybridization/extension allowed to proceed as before. The result is now four double strands. This process is repeated, typically for approximately twenty to twenty-five cycles. Because each cycle doubles the number of strands—that is, an exponential process—twenty cycles yields greater than a one million-fold (that is, 2^{20}) increase in the amplified sequence.

Fig. B-9
Polymerase Chain Reaction (PCR)



[C] Cloning

Cloning is the process by which a gene of interest is isolated from other genetic material. Many methods exist by which genes can be cloned; these may arbitrarily be divided into those based on the gene sequence, and those based on functional properties of the encoded protein.

[C][1] Sequence-Based Cloning

Homology cloning is a commonly used cloning method based on gene sequence, which relies heavily on hybridization.

[C][1][a] DNA Libraries

The first step in homology cloning is usually preparing a DNA library. A DNA library is a pool or collection of DNA sequences. Broadly speaking, there are two classes of DNA libraries: genomic and cDNA. Genomic DNA libraries are prepared from DNA and thus include not only coding DNA (that is, exons) but also regulatory sequences, introns, promoters, etc. Because the DNA is prepared with enzymes (referred to as nucleases) that cut randomly, some fragments will contain entire genes, others will contain gene fragments, and still others will contain non-coding DNA sequences. In contrast, complementary DNA (cDNA) libraries are derived from mRNA, which is converted (using the enzyme "reverse transcriptase") to complementary DNA. cDNA libraries have the obvious advantage that all the clones are coding sequences. A further advantage of cDNA libraries is that if one is interested in a relatively rare gene, the library can be prepared from a tissue or cell in which the gene is expressed more abundantly than in the body as a whole. On the other hand, if one is interested in intron/exon structure and splicing, or in regulatory regions, then a genomic library is necessary.

Irrespective of the source of the genetic material, it is usually necessary to insert the DNA or cDNA into vectors, which are more readily manipulated. Commonly used vectors are plasmids, which are circular strands of DNA from bacteria. Numerous different plasmids are commercially available. Such plasmids have been genetically engineered to contain a variety of useful properties such as:

(1) restriction sites that allow the plasmid to be enzymatically cleaved at specific sites, thus making it relatively easy to insert a gene of interest;

(2) specific promoter sequences, which increase expression of the gene of interest; and

(3) antibiotic resistance genes, which serve as selection markers.

Once the library fragments have been inserted into plasmids (one gene per plasmid), the plasmids are introduced into bacteria (a process termed "transformation") under conditions such that each bacterial cell gets one or no plasmids. By using a plasmid that contains a gene conferring resistance to a specific antibiotic, those bacterial cells that were not transformed can be eliminated by growing the cells in the presence of that antibiotic. Only those bacterial cells that contain the plasmid survive.

[C][1][b] Library Screening

Once the bacteria have been transformed with plasmids containing the genetic material, the next task is finding those bacteria that contain the clone of interest. The collection of such bacteria is called a library. Finding the bacteria containing the clone of interest is like finding a needle in the haystack because there will be so many bacteria and so few that have the desired clone. Fortunately, a number of methods exist for screening libraries. The method used is dictated in large measure by the properties of the protein encoded by the DNA of interest and by the availability of various reagents.

Homology cloning is a common and straightforward method that is based on the ability of related nucleotide strands to hybridize with one another. One generally uses a labeled probe that has sufficient sequence identity to the gene of interest to hybridize under appropriate conditions. The sequence of the probe may be based on partial (or complete) sequencing of the encoded protein. Alternatively, a probe based on a previously sequenced DNA may be used to identify closely related genes. Importantly, the probe need not be the entire length of the gene of interest; a length of ten to sixteen nucleotides is usually adequate.

Commonly, a bacterial library is added to plates at low densities; in this way each bacterial cell (containing a single plasmid) can form a colony yet the colonies remain sufficiently separate from one another so as to allow unambiguous identification. One then makes a "replica" by gently apposing a sterile sheet of filter paper to the colonies, whereby some cells from each colony adhere to the filter paper. The membranes of the cells on the filter paper are then chemically opened to expose the interior of the cell, and incubated with a labeled probe. After allowing a sufficient amount of time for hybridization to occur, free (that is, unbound) probe is washed away. The probe, which is typically labeled with a radioactive or colored substance, is detected visually, and the corresponding colony on the original plate is harvested. It is then a relatively simply matter to excise the inserted DNA from the plasmid, and sequence it. If the DNA is not full-length, additional probes may be prepared based on the new sequence, and the process repeated in an iterative manner until the entire sequence of the

gene has been determined. The various overlapping fragments may then be assembled into a single full length strand.

As mentioned above, many variations on this theme are known.

[C][2] Function-Based Cloning

Cloning methodologies based on the function of a gene are often referred to as expression cloning. While there are many variations of this technique, the common element is that pools of polynucleotides (DNA, cDNA, or RNA) are introduced into cells (bacteria, insect cells, mammalian cells, etc.), which are then tested for a functional property of the gene of interest. When the cell bearing the desired property is identified, the foreign DNA is extracted, typically placed into a cloning vector, and sequenced.

[D] Mutated Sequences

Once a gene has been cloned it is possible to alter its sequence. There are numerous reasons why this is done, including:

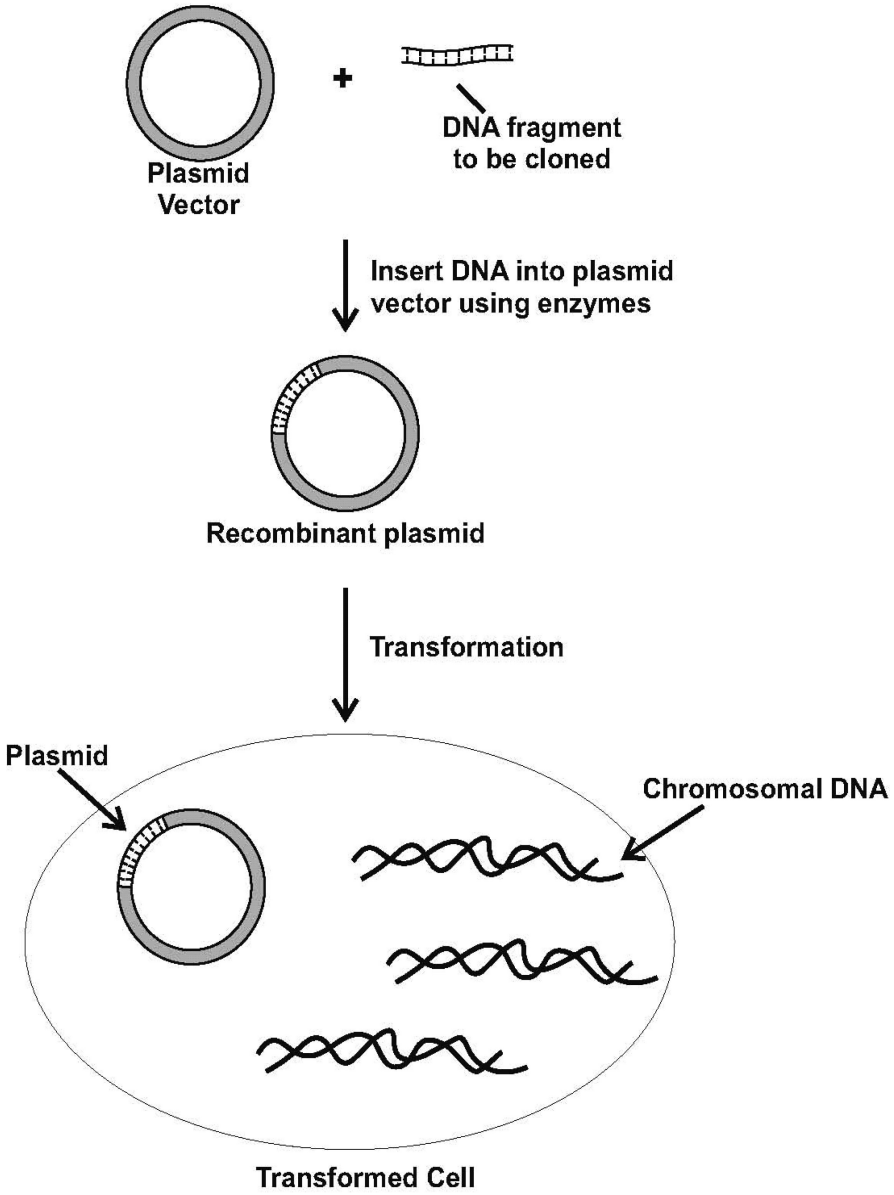
- to determine the functions of various amino acids or domains of the protein
- to alter the protein's function
- to alter the protein's expression
- to ease purification of the protein.

A cloned gene may be altered by changing the codons for one or more amino acids via site-directed mutagenesis. Alternatively, portions of a gene may be swapped with portions from a related gene. In other cases, a portion of the gene encoding one protein may be attached to the gene encoding another protein to generate a fusion protein. Such non-naturally occurring genes, and the proteins they encode, may be patentable.

[E] Heterologous Expression

Heterologous expression refers to the process by which a "foreign" gene is expressed in a cell (Fig. B-10). The gene can be from another species, or from a different cell from the same species. The process by which the gene is introduced into the cells is termed "transformation" or "transfection." The process allows one to study regulation and/or function of the gene, and to produce large amounts of the encoded protein.

Fig. B-10
Transforming a Cell



A variety of methods for transforming bacteria and animal cells are well known. Such methods include the following:

- *Electroporation*, whereby an electrical current induces small pores to form in the cell membrane, thus allowing DNA to enter the cell.
- *Calcium phosphate-mediated transfection*, whereby a co-precipitate of calcium phosphate and DNA attaches to the cell surface and is internalized by endocytosis.

- *Lipid-mediated transfection*, in which complexes are formed between the negatively charged DNA backbone and positively charged cationic liposomes. The complex then interacts with negatively charged membrane residues, aiding delivery into the cell.
- *Baculovirus-mediated transfection*, whereby insect cells are infected with baculovirus into which a gene of interest has been inserted.

Due to the presence of a cell wall, plant cells are more difficult to transfect. Three methods that have proven effective are:

1 a "gene gun," in which DNA coated particles are accelerated and essentially shot through the cell wall;

2 "whiskers," which are small hollow tubes that are mixed together with DNA and the cells to be transfected; and

3 agrobacterium-mediated transformation, whereby the plant cells are infected with a virus that has been modified to contain the gene of interest.

Irrespective of the method of transformation, it is common for a sample of such cells to be submitted to a depository for biological material such as the ATCC.

Methods now exist for inserting foreign genes into animals; such animals are termed "transgenic." There are a number of methods by which this is accomplished, two of which are described below.

[F] Microinjection of DNA

In this method linear DNA is injected into fertilized eggs (oocytes). This method relies on the DNA becoming incorporated into the egg's DNA prior to the DNA replication that precedes the first cleavage; only in this way will all cells of the organism contain the foreign gene. The injected oocyte is then transferred to the uterus of a pseudo-pregnant animal.

[G] Injection of Embryonic Stem Cells

Embryonic stem cells are pleuripotent cells that can, by definition, develop into any (or almost any) cell or tissue in the body. In this technique embryonic stem cells are removed from a blastocyst (an early embryonic stage) and transfected with a gene of interest. The transfected stem cell is then injected into a blastocyst in which the transfected stem cells multiply. The resulting chimeric animals will pass the gene to their offspring only if the transfected embryonic stem cells contributed to the germ cell.

Appendix C. The Science of Biosimilars

Pharmaceutical and Biotech Patent Law (2024)
Format: Treatise Chapter
Date: Jul 2024
Author(s): Laurence Borden
PLI Item #: 397729
Practice Areas: Health care, Intellectual property, Life sciences

Appendix C

The Science of Biosimilars

Laurence A. Borden, Ph.D.

§ C:1 Introduction

The Food and Drug Administration (FDA) distinguishes between two classes of pharmaceutical drugs. The more common class, so-called "small molecules," requires approval of a New Drug Application (NDA). The second and less common class, known as "biologics," requires approval of a Biologics License Application (BLA). Whereas the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act) established the legal framework for approval of generic versions of small molecule drugs, until recently there was no equivalent mechanism for follow-on biologic drugs. The Biologics Price Competition and Innovation Act of 2009 (BPCIA), passed in 2010 as a part of the Patient Protection and Affordable Care Act, remedies this gap by providing a legal framework for the approval of "biosimilars" that are similar to, or interchangeable with, corresponding BLA-approved biologics. Below we provide an overview of (1) the structural differences between small molecules and biologics, (2) the proposed criteria for establishing biosimilarity, and (3) the special problems associated with proteins.

§ C:2 What Is a Biologic?

Because biosimilars are intended as "substitutes" for biologic drugs, to understand biosimilars one must first understand biologics. Section 262 of Title 42 of the United States Code defines a biological product as follows:

> The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.[1]

"Biologics" are thus products produced in or by biological systems. As discussed below, the FDA's focus for biosimilars is predominantly on proteins. In most cases, protein biologics will be produced using the techniques of molecular biology: A DNA encoding the protein of interest will be inserted into host cells, which then serve as "factories" that synthesize the protein. The host cells can be derived from bacteria, fungi, vertebrates (including mammals), insects, or plants. In contrast, small molecules are produced by traditional chemical synthetic means, though this distinction is not absolute. For example, certain forms of penicillin, though classified as small molecules, are synthesized by microorganisms.

§ C:3 Criteria for Biosimilars and Bioequivalents

§ C:3.1 42 U.S.C. § 262

Section 262 of Title 42 of the United States Code states that "biosimilar" or "biosimilarity" means:

> that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
>
> that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Section 262 states that the term "interchangeable" or "interchangeability," in reference to a biological product, means

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1. Prior to enactment of the BPCIA, the definition of "biologic" in 42 U.S.C. § 262 did not include the term "protein." Despite this, BLAs had been filed for numerous protein pharmaceuticals.

> that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

Section 262 further states that

> An application submitted under this subsection shall include information demonstrating that—
>
> (I) the biological product is biosimilar to a reference product based upon data derived from—
>
> (aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
>
> (bb) animal studies (including the assessment of toxicity); and
>
> (cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product;
>
> (II) the biological product and reference product utilize the same mechanism of mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanisms of action are known for the reference product;
>
> (IV) the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and
>
> (V) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

§ C:3.2 Food and Drug Administration

While Congress enacted the laws establishing legal requirements for gaining approval of a biosimilar drug, the FDA must establish the regulatory criteria for defining biosimilarity and interchangeability. In addition, the FDA must decide, on a case-by-case basis, whether a given drug meets the requirements to be approved as biosimilar to

(or interchangeable with) the reference drug.[2] As of September 2013, the FDA has not yet provided definitive requirements for establishing biosimilarity and/or interchangeability. However, the FDA has provided four "Draft Guidance" documents, which provide a framework for the criteria for establishing biosimilarity and/or interchangeability; these documents are as follows:

- Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. February 2012.
- Guidance for Industry. Quality Considerations in Demonstrating Biosimilarity to a Reference Product. February 2012.
- Guidance for Industry. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. February 2012.
- Guidance for Industry. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants. March 2013.

§ C:4 Most Biologics and Biosimilars Are Proteins

As noted above, though there are various forms of biologics (and thus potentially, biosimilars), the FDA's focus is primarily on proteins. The FDA states:

> This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product (hereinafter "proposed product") is biosimilar to a reference product for purposes of the submission of a marketing application under section 351(k) of the Public Health Service Act (PHS Act). The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001-through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111-148) (Affordable Care Act)). *Although the 351(k) pathway*

---

2. In June 2003, the FDA transferred to the Center for Drug Evaluation and Research (CDER) some of the biological products that previously been regulated by the Center for Biologics Evaluation and Research (CBER). The therapeutic biological products now under CDER's review include (1) monoclonal antibodies for *in vivo* use; (2) cytokines, growth factors, enzymes, immunomodulators, and thrombolytics; (3) proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); and (4) other non-vaccine therapeutic immunotherapies.

> *applies generally to biological products, this guidance focuses on therapeutic protein products* and gives an overview of important scientific considerations for demonstrating biosimilarity.[3]

With regard to analytical studies, the Guidelines address certain properties unique to proteins, which are discussed in greater detail below. Specifically, the Guidelines state that:

> Sponsors should use an appropriate analytical methodology with adequate sensitivity and specificity for structural characterization of the proteins. Generally, such tests include the following comparisons of the drug substances of the proposed product and reference product:
>
> - Primary structures, such as amino acid sequence
> - Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation)
> - Enzymatic post-translational modifications, such as glycosylation and phosphorylation
> - Other potential variants, such as protein deamidation and oxidation
> - Intentional chemical modifications, such as PEGylation sites and characteristics[4]

§ C:5 Differences Between Small Molecules and Proteins

As the criteria for bioequivalence of small molecules, per Hatch-Waxman, have been well-established for decades, why did new rules have to be established for biosimilars? The answer lies in the fact that proteins are structurally far more complex than small molecules. This complexity creates two interrelated problems. First, a compete structural analysis of a protein is a far more daunting task than a structural determination of small molecules, which is, for the most part, routine. Second, the structural complexity of proteins allows for considerable variation in proteins with identical amino acid sequences. The basis of these structural complexities of proteins is discussed below.

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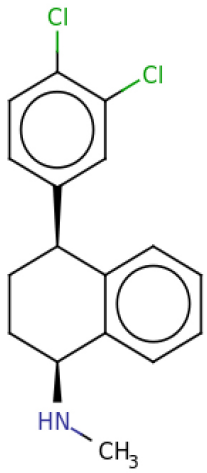
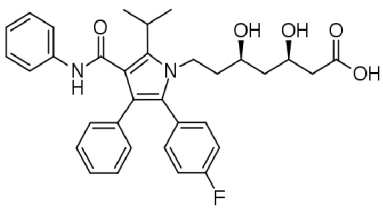
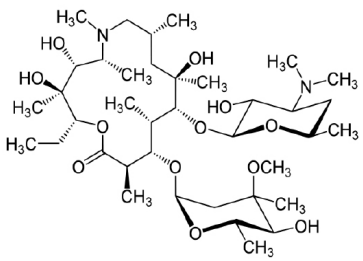
3. Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 1 (Feb. 2012) (emphasis added; internal citations omitted). Prior to enactment of the BPCIA, BLAs had been filed for numerous protein pharmaceuticals. As such, the significance of the addition of the term "protein" is not clear.
4. Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 9 (Feb. 2012).

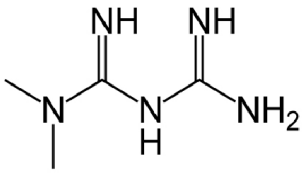
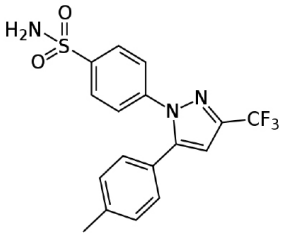
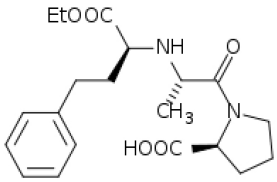
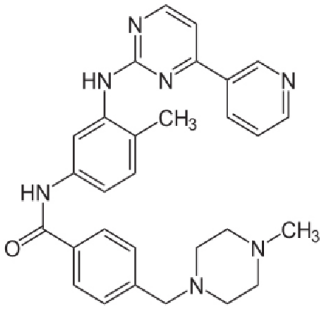
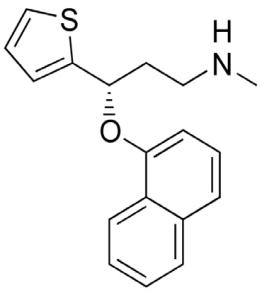
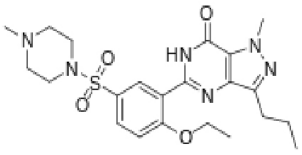
§ C:5.1 Small Molecules

As noted above, the Hatch-Waxman Act pertains to small molecules. Though there is no precise definition or cutoff for a "small" molecule, the term generally applies to non-proteinaceous molecules with molecular weights typically in the range of 300-500. Table C-1 shows examples of some commonly prescribed small molecule pharmaceuticals.

Table C-1

Some Common "Small Molecule" Drugs

TRADE NAME	COMMON NAME	STRUCTURE	MOLECULAR WEIGHT (g/mol)
Zoloft®	sertraline HCl		306.229
Lipitor®	atorvastatin		558.64
Zithromax®	azithromycin		748.984

TRADE NAME	COMMON NAME	STRUCTURE	MOLECULAR WEIGHT (g/mol)
Glucophage®	metformin		129.16
Celebrex®	celecoxib		381.373
Vasotec®	enalapril		376.447
Gleevex®	imatinib		493.603
Cymbalta®	duloxetine		297.41456
Viagra®	sildenafil citrate		666.7.g/mol

With few exceptions, small molecules are synthesized using the techniques of traditional synthetic chemistry. Such methods allow for an extremely high degree of purity, typically 99% or higher. As discussed below, this is an important difference from biologics.

§ C:5.2 Biologics

The three-dimensional structure of a protein, commonly referred to as its "conformation," is critically important to its biological function. The conformation of a protein is considerably more complex than that of a small molecule, a reflection of the protein's greater size.[5] A protein's amino acid sequence is the main determinant of its conformation, but conformation is also influenced by various chemical alterations to which proteins are susceptible.[6] Inter-molecular

---

5. The molecular weight of small molecules is typically in the range of 300-500, whereas proteins are considerably larger. The FDA defines a protein as an amino acid polymer greater than 40 amino acids in length. Because the molecular weight of amino acids is, on average, about 100, a protein (per the FDA criteria) will have a molecular weight greater than 4000. Many proteins have molecular weights around 40,000. Thus, on average, biologics (and their biosimilars) are 10- to 100-fold larger than typical small molecules.

6. The FDA recognizes the importance of such modifications:

> Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Because even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences.

Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 4 (Feb. 2012).

> [M]ost protein products undergo some post-translational modification that can alter the functions of the protein: by attaching it to other biochemical groups such as phosphate, various lipids and carbohydrates; by proteolytic cleavage following translation; by changing the chemical nature of an amino acid (e.g., formylation); or by many other mechanisms. Such modifications can result from intracellular activities during cell culture or by deliberate modification of the protein, for example, by PEGylation. Other post-translational modifications can be a consequence of manufacturing process operations—for example, glycation may occur with exposure to reducing sugars. In other cases, storage conditions may be permissive for certain degradation pathways such as oxidation, deamidation, or aggregation. As all of these product-related variants may alter the biological properties of the expressed recombinant protein,

heterogeneity often exists within proteins (unlike the situation with small molecules), and it stands to reason that the makeup of a biosimilar might differ from that of the branded biologic. It is for this reason that the Hatch-Waxman Act is inadequate for biosimilars, thus prompting the need for the BPCIA and FDA guidelines. In the following sections we provide an overview of proteins' three-dimensional conformation, and some of the more common chemical alterations.

[A] The Primary Structure of Proteins

As described in Appendix B, proteins are chains of amino acids, held together by peptide bonds. The linear amino acid sequence of a protein is considered its *primary structure*.

Amino acid chains exhibit considerable diversity in length. For example, the naturally occurring mammalian molecules met-enkephalin and leu-enkephalin are each only five amino acids long, whereas titin, the largest known protein, contains 34,350 amino acids.

The FDA states:

> *Protein* means any alpha amino acid polymer with a specified defined sequence that is greater than 40 amino acids in size.
>
> *Chemically synthesized polypeptide* means any alpha amino acid polymer that is (a) made entirely by chemical synthesis, and (b) is less than 100 amino acids in size.[7]

As the average molecular weight of an amino acid is approximately 100, one can approximate the molecular weight of a protein by multiplying the number of amino acids in that protein by 100. Thus, the smallest protein per the FDA criteria would have a molecular weight of approximately 4,000. However, an "average" protein contains about 500 amino acids, and thus has a molecular weight of around 50,000. The molecular weight of an "average" protein is thus about 100 times that of a typical small molecule.

> identification and determination levels of these protein variants should be included in the comparative analytical characterization studies.
>
> Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Product, at 7 (Feb. 2012).

7. Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Product, at 5 (Feb. 2012).

[B] Higher-Order Structure of Proteins

As noted above, the linear amino acid sequence of a protein is considered its primary structure. Like all molecules, proteins exist in three dimensions. However, because of their considerable size, the three-dimensional structures of proteins are far more complex than those of small molecules. All higher-order protein structures are ultimately dependent on the primary amino acid sequence though, as described below, other factors can and do influence the three-dimensional structures and thus, protein function.

[B][1] Secondary Structure

The secondary structure of a protein refers to the organization of the sub-structures within the primary structure. Two types of secondary structure are known to exist, the α-helix and β-sheet (also called β-pleated sheet). Both α-helices and β-sheets are defined by the patterns of hydrogen bonding between the peptide groups. An α-helix is a right-handed coiled or spiral conformation (i.e., helix) in which each backbone N-H group donates a hydrogen bond to the backbone C=O group of the amino acid four residues before it. In contrast, a β-sheet consists of β-strands[8] connected laterally by at least two or three backbone hydrogen bonds, thereby forming a twisted, pleated sheet. It should be noted that a given protein can contain one or more α-helices and one of more β-sheets, wherein one portion of the protein is an α-helix, and another portion of the protein is a β-sheet. Representations of α-helix and β-sheet, and of a protein with both, are shown in Figs. C-1–C-3, respectively.

8. The β-strand, which comprises the β-sheet, is a stretch of typically three to ten amino acids, in which the backbone is in a nearly fully extended conformation.

Fig. C-1

α-Helix

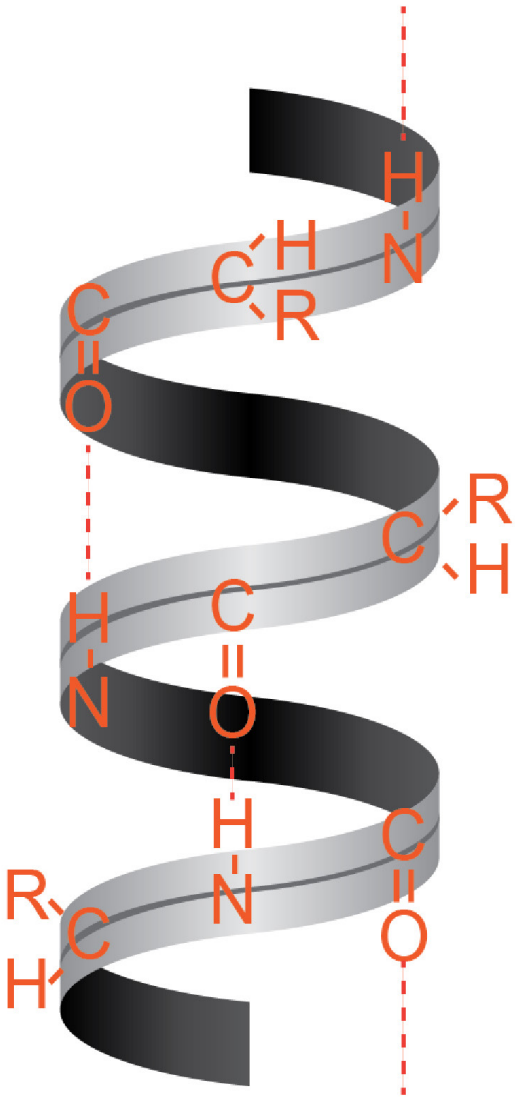


Fig. C-2

β-Sheet

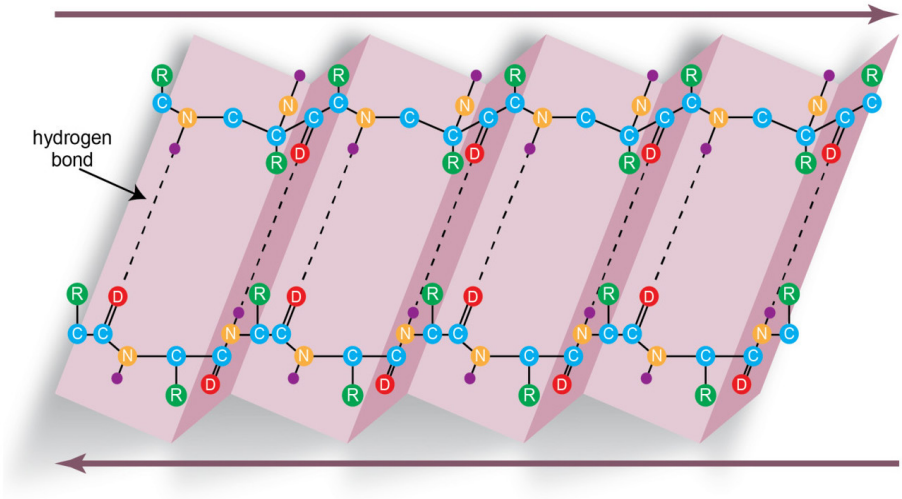
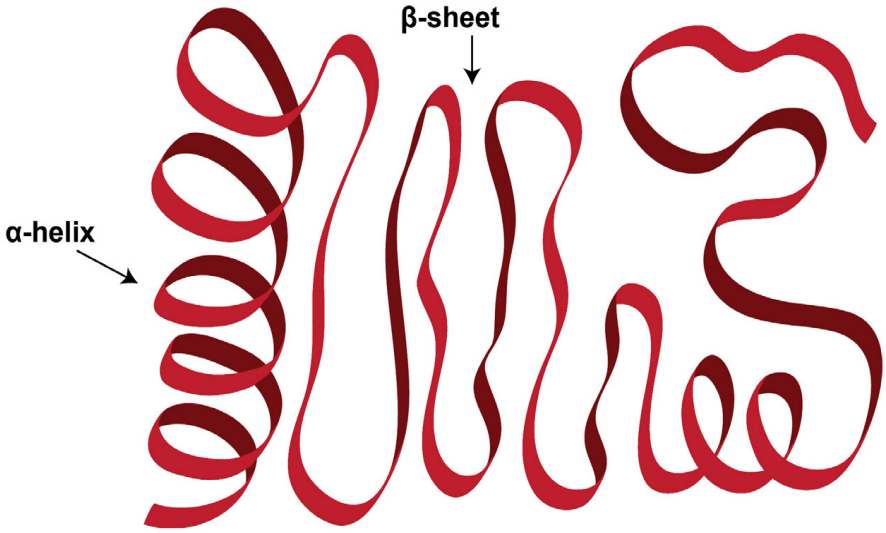


Fig. C-3

Protein With α-Helix and β-Sheet



[B][2] Tertiary Structure

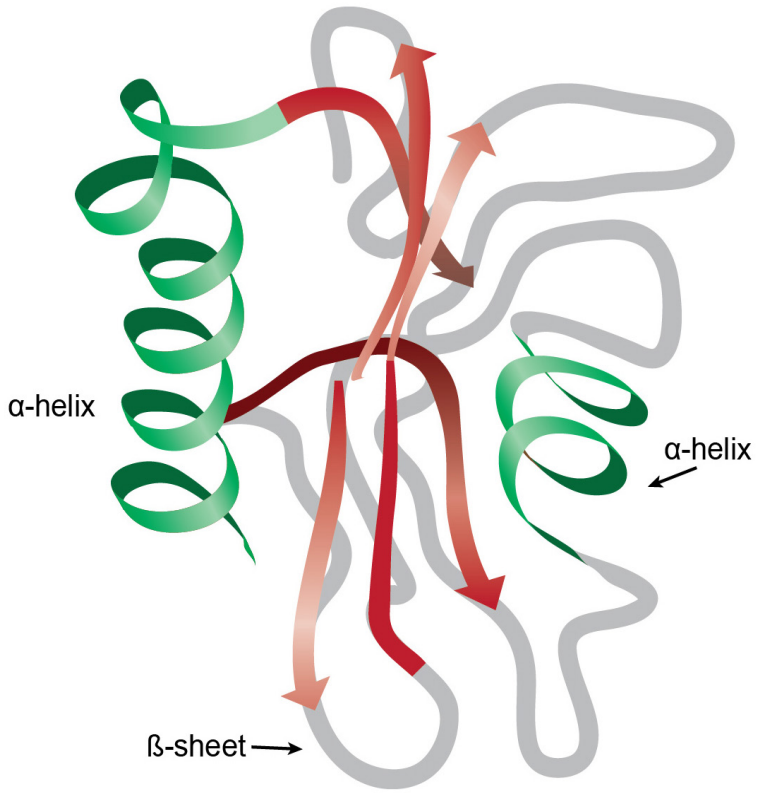
The tertiary structure of a protein refers to the folding of an α-helix (or helices) and/or a β-sheet(s) into a compact globule or globules. The tertiary structure results from four types of bonding interactions between the amino acid side chains:

1. hydrogen bonding
2. salt bridges
3. disulfide bonds
4. non-polar hydrophobic interactions.

Fig. C-4 shows the tertiary structure of a protein comprising a α-helices and β-sheets:

Fig. C-4

Tertiary Structure

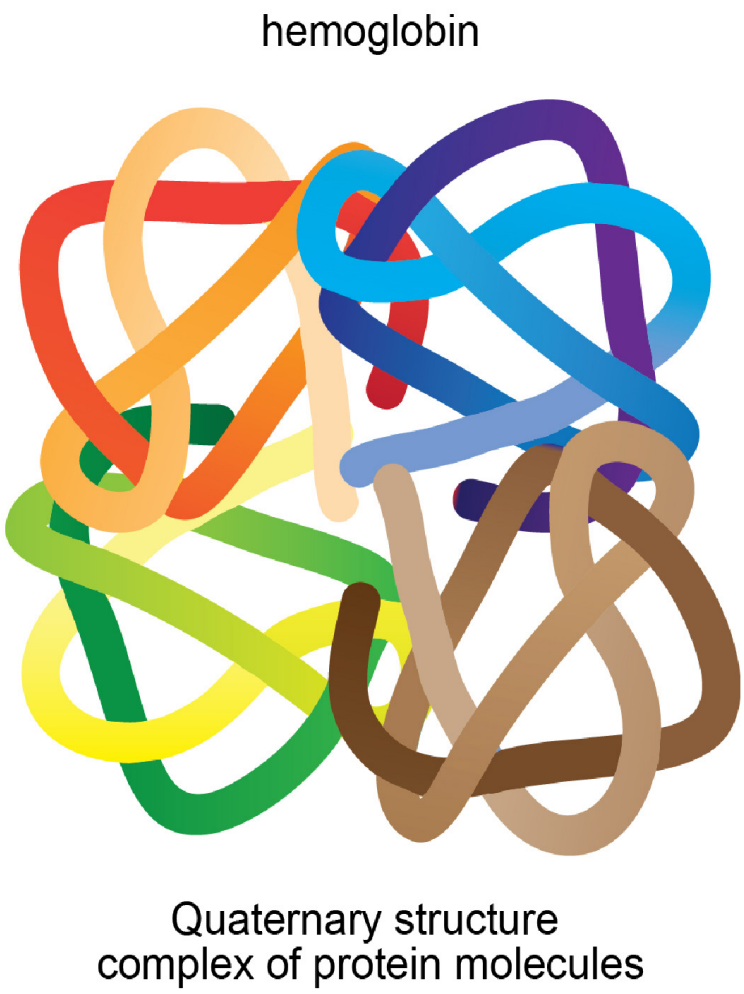


[B][3] Quaternary Structure

Many proteins consist of more than one amino acid chain; each amino acid chain is then commonly referred to as a subunit. Quaternary structure refers to the three-dimensional structure formed by the interaction of the various subunits, wherein each subunit has its own primary, secondary, and tertiary structure. In some cases the subunits are identical (for example, a homodimer, homotrimer, etc.), whereas in other cases they are different (for example, a heterodimer, heterotrimer, etc.). Fig. C-5 illustrates quaternary structure.

Fig. C-5

Quaternary Structure



§ C:6 Variation and Alterations in Protein Structure

The complex structure of proteins, and their synthesis *in vivo*, create the potential for considerable structural variation of biosimilars—variations that have no counterpart in small molecules.

§ C:6.1 Amino Acid Sequence

Unlike the situation with small molecules, in which the generic drug is assumed and required to have a chemical structure identical to that of the reference product, the FDA will in some cases allow the amino acid sequence of the proposed biosimilar to differ from that of the reference biological drug. The FDA states:

> It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N or C terminal truncations that will not have an effect on safety, purity, or potency, may be justified by the applicant.[9]

As noted above, whereas small molecules are synthesized by traditional chemical methods, protein biologics are synthesized *in vivo*, inside cells. However, the cellular processes involved in protein synthesis from a given DNA sequence are not foolproof, thus creating the potential for further deviations in the primary amino acid sequence. Thus, whereas in a small molecule drug, or its generic, every molecule is assumed to be identical to every other,[10] in the case of biologics (and their biosimilars) heterogeneity is not uncommon. Such differences may be clinically important, as the FDA states:

> Primary structure of some protein products can be highly heterogeneous and could affect the expected clinical performance of a protein product.[11]

§ C:6.2 Post- and Co-Translational Modifications

As described in Appendix B, protein synthesis consists of two major steps. In the first step, transcription, the DNA comprising the gene serves as a template for synthesis of a complementary strand of messenger RNA (mRNA). In the second step, translation, the mRNA attaches to a ribosome, where it serves as a template for the sequential addition of amino acids which become linked to one another by peptide bonds. As also described in Appendix B, in many cases, the nascent polypeptide is chemically modified either while it is being formed, or subsequently; these processes are referred to as co-translational modifications and post-translational modifications, respectively. Many of these modifications occur only in eukaroytic cells; as such, prokarytic and eukaryotic host cells can yield quite different proteins, despite the amino acid sequence (i.e., primary structure) being identical. As might be supposed, co- and post-translational modifications affect the higher order structure of proteins, and thereby their function.

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9. Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Product, at 9 (Feb. 2012).
10. An exception is a racemic drug, in which half the molecules are isomers with one configuration, and the other half are mirror image isomers.
11. Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Product, at 7 (Feb. 2012).

The FDA states:

> Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. many potential differences in protein structure can arise. Because even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences."[12]

And further:

> [M]ost protein products undergo some post-translational modification that can alter the functions of the protein: by attaching it to other biochemical groups such as a phosphate, various lipids and carbohydrates; by proteolytic cleavage following translation; by changing the chemical nature of an amino acid (e.g., formylation); or by many other mechanisms. Such modifications can result from intracellular activities during cell culture or by deliberate modification of the protein, for example, by PEGylation. Other post-translational modifications can be a consequence of manufacturing process operations—for example, glycation may occur with exposure to reducing sugars. In other cases, storage conditions may be permissive for certain degradation pathways such as oxidation, deamidation, or aggregation. As all of these product-related variants may alter the biological properties of the expressed recombinant protein, identification and determination of the relative levels of these protein variants should be included in the comparative analytical characterization studies.[13]

The following sections provide an overview of some of the more common modifications that proteins undergo.

[A] Glycosylation

Sugar residues are added to many cellular proteins, in particular those that are destined either to be secreted, or to be inserted in the cell membrane. The process of glycosylation occurs within intracellular compartments, while the protein is in transit to the cell surface. Broadly speaking, there are two classes of glycosylation, "O-linked" and "N-linked." In the former, the sugar residues are covalently bonded to the oxygen (O) in the R group of the amino acids serine

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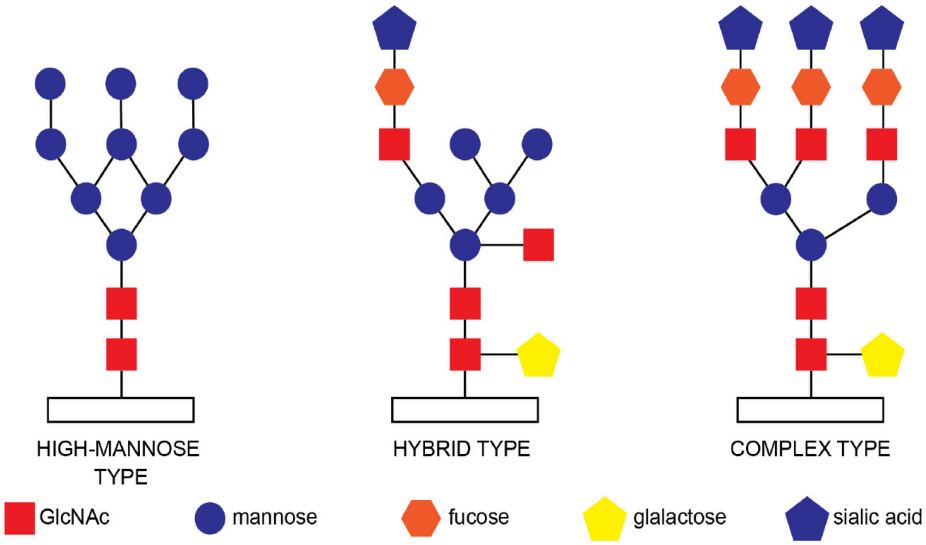
12. Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 4 (Feb. 2012).
13. Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Product, at 7 (Feb. 2012).

and/or threonine, whereas in the latter the sugar residues are covalently bonded to the nitrogen (N) in the R group of the amino acid asparagine. Glycosylation is a feature of eukaryotic cells but does not occur in prokaryotes (that is, bacteria); thus the choice of host cell can significantly influence glycosylation of the expressed biosimilar protein.

N-linked oligosaccharides are of three main types: high-mannose, complex, and hybrid, as shown in Fig. C-6.

Fig. C-6

N-linked Glycosylation



Importantly, glycosylation differs between various cell types, and moreover, even within a given cell type, glycosylation is to some degree a stochastic process. That is, the glycosylation pattern will differ between individual protein molecules, even if those molecules were synthesized in the same cell. This heterogeneity of glycosylation is true of the reference biologic product, as well as the proposed biosimilar. Determining variations in glycosylation patterns is not a trivial analytical procedure, and the FDA will have to clarify the level of analysis it requires, as well as the acceptable deviation (if any) between the proposed biosimilar and the reference biologic drug.

[B] Phosphorylation

One common mechanism by which cells regulate the activity of proteins, in particular (though not exclusively) those that serve signaling functions (such as enzymes), is via phosphorylation/dephosphorylation, wherein phosphate groups are attached to or detached from the

protein, respectively. Enzymes that add phosphate groups to proteins are referred to as kinases; those that remove phosphate groups are referred to as phosphatases. There are two broad classes of kinases: (1) tyrosine kinases, which, as their name implies, attach phosphate to tyrosine amino acids of a substrate protein; and (2) serine/threonine kinases, which attach phosphates to serine and/or threonine residues of a substrate protein.[14] A given kinase will generally have selectivity for particular substrates, though the selectivity is usually not absolute. In contrast, phosphatases tend to be more promiscuous, though this too is not absolute.

The extent of phosphorylation of a biologic or biosimilar drug, and the particular amino acids which are phosphorylated, are dependent on a number of factors, including but not limited to (1) the protein itself; (2) the cell in which the protein was synthesized; and (3) the physiological state of the synthesizing cell (because kinases and phosphatases are themselves regulated). As is the case with glycosylation, heterogeneity of phosphorylation will exist between individual protein molecules, even those synthesized by the same host cell, or the same culture of host cells. Thus, the FDA will again have to determine not only the degree of analysis required to determine the phosphorylation status of the biosimilar, but also how much variation is acceptable between the biosimilar and the reference biologic drug.

[C] Acetylation

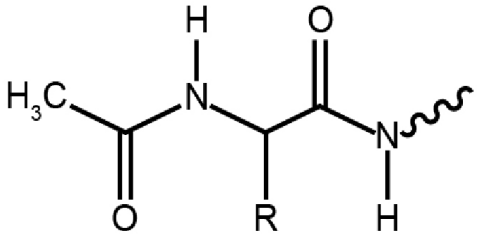
Yet another mechanism by which the activity of certain proteins is regulated is acetylation, wherein an acetyl group is added to a protein. See Fig. C-7. This reaction occurs most often on the amino terminus of a protein, in which cases it is mediated by an N-terminal acetyltransferase enzyme. N-terminal acetylation is often irreversible, and functions to mark the protein for degradation. As is true for glycosylation and phosphorylation, the extent of acetylation will depend on the host cell, and will vary between molecules.

---

14. Not all tyrosines and/or serines/threonines in a given substrate protein are susceptible to phosphorylation. Rather, specificity is determined by the amino acids surrounding the target tyrosines and serines/threonines.

Fig. C-7

Acetylation

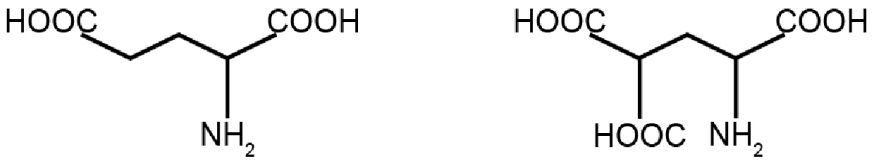


[D] Carboxylation

Carboxylation is a posttranslational modification in which glutamate residues are converted to γ-carboxyglutamate. This reaction occurs primarily with various proteins of the blood clotting cascade, in particular Factors II, VII, IX, X, and protein C, which represent potentially important biological therapeutics. The structure of glutamic acid (left) and carboxyglutamic acid (right) are shown in Fig. C-8.

Fig. C-8

Carboxylation of Glutamic Acid



[E] Membrane Anchoring: Lipidation

Many membrane-bound proteins contain a signal sequence that causes the ribosome to which the mRNA is bound to attach to the endoplasmic reticulum (ER). As translation takes place, the protein is inserted into the membrane of the ER. Membranous vesicles containing the newly synthesized protein bud off the ER, fuse with other membranous organelles, and eventually with the outer cell membrane, such that the protein comes to reside in the cell membrane.

However, other membrane-bound proteins lack a signal sequence; these proteins are synthesized on "free" ribosomes (that is, those not bound to the ER). Either co- or post-translationally, a lipid-containing moiety is attached to the nascent protein. The lipid moiety attaches to the cell membrane, thereby anchoring the protein to the cell membrane. "Lipidation" influences a protein's activity predominantly

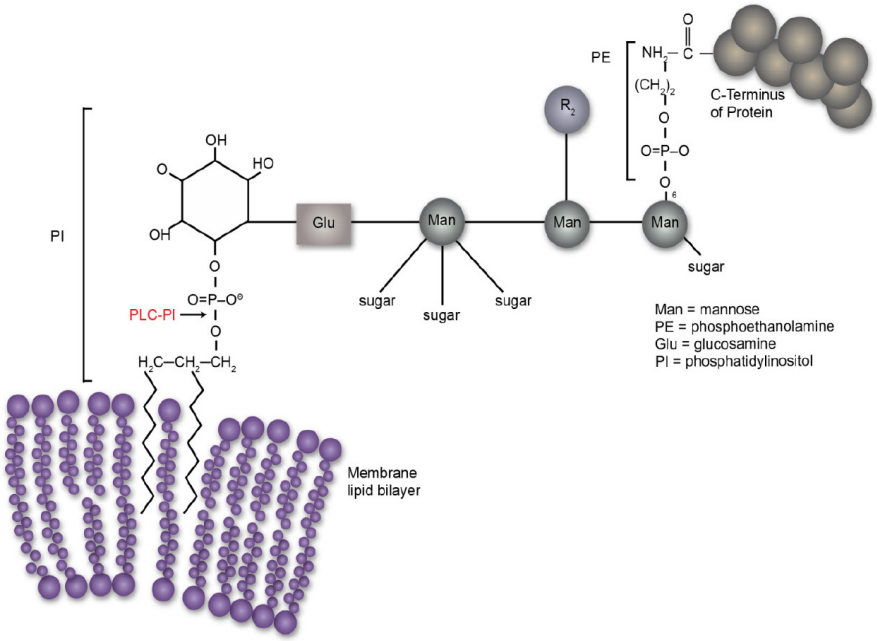
indirectly, by altering its subcellular location, though it may also have direct affects. As described in the subsequent sections, there are a number of different lipid moieties that serve this function.

[E][1] Addition of GPI Anchor

Another form of modification is the addition of a glycosylphosphatidylinositol (GPI) residue. GPI is attached post-translationally to the C-terminus of a protein. GPI consists of a number of components: a phosphotidylinositol group attached to a carbohydrate linker (typically, glucosamine or mannose bound to the inositol residue), which is then attached via an ethanolamine phosphate to C-terminal amino acid of the protein. The phosphatidylinositol group contains two fatty acids, which anchor the protein to the cell membrane. This linkage is shown in Fig. C-9.

Fig. C-9

GPI Anchor



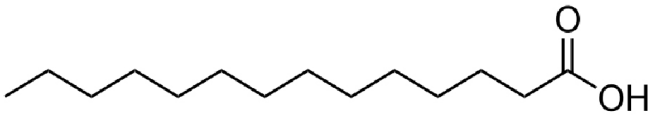
[E][2] Myristoylation

A myristoyl group is covalently attached via an amide bond typically to a glycine residue following removal of the N-terminal methionine. The reaction is catalyzed by the enzyme N-myristoyltransferase.

The myristoyl group is derived from myristic acid, the structure of which is shown in Fig. C-10.

Fig. C-10

Myristic Acid

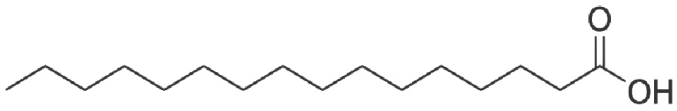


[E][3] Palmitoylation

Palmitoylation is the covalent attachment of a palmitoyl group to a protein. The fatty acid usually attaches to a cysteine residue, and less commonly to a serine or threonine. Palmitoylation increases the protein's hydrophobicity, and thus its association with the cell membrane. The palmitoyl group is derived from the fatty acid palmitic acid, the structure of which is shown in Fig. C-11.

Fig. C-11

Palmitic Acid

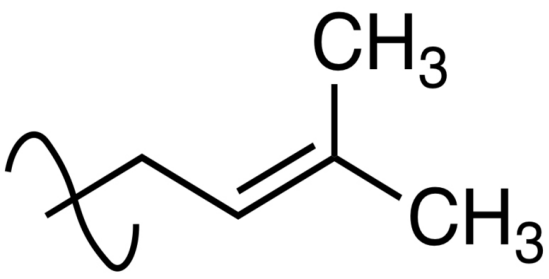


[E][4] Prenylation

Prenylation, also called isoprenylation, is the addition, to the C-terminus of a protein, of a farnesyl molecule or a geranyl-geranyl moiety. These prenyl groups are hydrophobic, and are thought to facilitate attachment of the prenylated protein to the cell membrane. Prenylation is typically catalyzed by the enzymes farnesyl transferase and geranyl-geranyl transferase I. The generic structure of the prenyl group is shown in Fig. C-12.

Fig. C-12

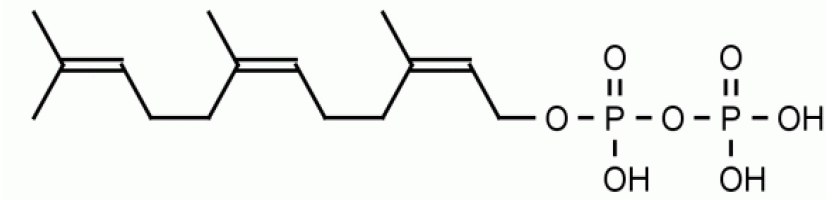
Prenyl Group



The farnesyl moiety is derived from farnesyl diphosphate, the structure of which is shown in Fig. C-13.

Fig. C-13

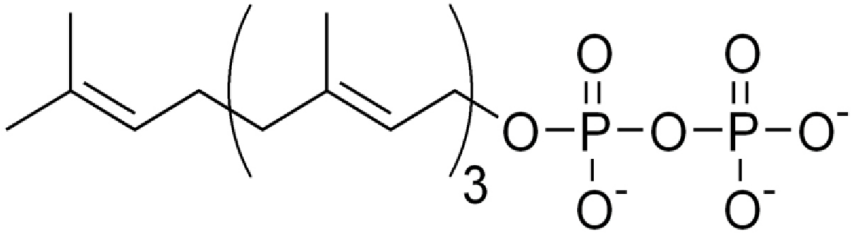
Farnesyl diphosphate



The geranyl-geranyl moiety is derived from geranyl-geranyl diphosphate, the structure of which is shown in Fig. C-14.

Fig. C-14

Geranyl-geranyl diphosphate



[F] Sulfation

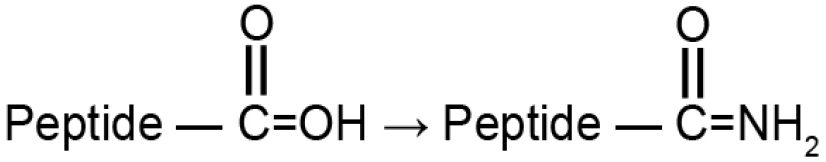
Sulfation is yet another modification, in which a sulfate group is added to tyrosine residues of a protein, via the action of enzymes referred to as tyrosylprotein sulfotransferases. It is thought that tyrosine sulfation strengthens protein-protein interactions. As is the case for glycosylation, sulfation may predominate with proteins destined to be secreted, or inserted in the cell membrane. Sulfation does not occur in prokaryotes.

[G] Amidation

Another modification is amidation, which occurs at the C-terminus of the protein. See Fig. C-15. The penultimate amino acid of the protein to be amidated is glycine, which provides the amide group. The reaction occurs in two steps. In the first step, glycine is oxidized to form α-hydroxy-glycine. In the second step, α-hydroxy-glycine is cleaved into the C-terminally amidated peptide. C-terminal amidation is important for certain neuropeptides and hormones.

Fig. C-15

Amidation

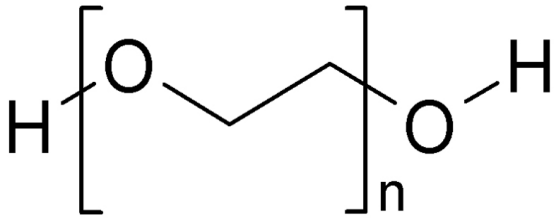


§ C:6.3 Intentional Alterations

In certain cases, biologic drugs might be intentionally modified, so as to improve activity or pharmacokinetics. One common alteration is the covalent attachment of polyethylene glycol to a protein, a process commonly referred to as "PEGylation." The structure of PEG is shown in Fig. C-16.

Fig. C-16

PEG



PEGylation can, in certain circumstances, "mask" the PEGylated protein from the patient's immune system, thereby decreasing the likelihood of immune system-mediated inactivation and clearance of the therapeutic biologic. In addition, PEGylation increases the size of the biologic, which tends to reduce clearance by the kidney, thereby increasing the amount of time it remains in the body (and thus, increasing the amount of time in which it can exert its therapeutic effect).

Because PEG is a polymer, its exact length varies from molecule to molecule. In addition, during the PEGylation procedure, there is variability in the extent of PEGylation, and even in which amino acids become PEGylated. As with other modifications, intended or not, the FDA will have to determine the degree of analytical determination required for a prospective biosimilar, as well as the degree to which it may differ from the reference biologic drug.

§ C:6.4 "Environmentally" Induced Modifications

In addition to the physiological co- and post-translational modifications, and intentional modifications described above, proteins are also susceptible to various alterations that are "environmentally" induced.

[A] Denaturation

Denaturation refers to the process in which proteins lose their secondary and/or tertiary structure. Denaturation can be reversible, or permanent. A common example of permanent protein denaturation is that which occurs when an egg is hard-boiled. Heat causes the egg protein albumin to irreversibly unfold, thereby causing a dramatic change in the protein's physical characteristics. It should be apparent that denaturation of a biologic medicine (or its biosimilar) would profoundly influence its intended biological activity.

[B] Oxidation

Proteins are susceptible to oxidation which, like denaturation, alters their biologic activity. The oxidation can occur intracellularly, for example, if the host cells undergo oxidative stress; or extracellularly, for example, during purification or storage.

[C] Aggregation/Dissociation

Proteins are also susceptible to aggregation. This occurs most commonly with mis-folded proteins, which usually result from mutations. Conversely, proteins can lose their quaternary structure, wherein the subunits dissociate from one another.

§ C:7 Summary and Conclusions

As a result of great advances in molecular biology, genes for an increasing number of proteins have been cloned, then expressed in host cells. Therapeutic use of such proteins has the potential to dramatically alter the treatment of disease, and in many cases this potential has already borne fruit. Because proteins differ so dramatically from the more common small-molecule therapeutics, Hatch-Waxman rules covering generics were deemed inadequate, and separate laws covering biosimilars have now been enacted.

Proteins are much larger than small molecules, and their three-dimensional structures are far more complex. In addition, proteins are subjected to a wide variety of modifications, some intended, others not. Moreover, because proteins are synthesized in cells, it is more difficult to control the modifications, many of which are, to varying degrees, stochastic. Even those modifications intentionally

introduced are difficult to precisely control. For these and other reasons, inter-molecular variability exists for biologic drugs, as well as for their biosimilars. Moreover, because (as noted above) many of the modifications are cell-type specific, even greater differences may exist between the biosimilar and its reference biologic.

Further complicating the situation is that analytical techniques for proteins are far more complicated and difficult than those for small molecules. The FDA will ultimately have to decide the level and type of structural analyses required, as well as the degree of difference that is acceptable between the biosimilar and its reference biologic. Considerable challenges and hurdles await both the FDA and those seeking approval for biosimilars.

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Pharmaceutical and Biotech Patent Law (2024)
Format: Treatise Chapter
Date: Jul 2024
Author(s): Arnold & Porter Kaye Scholer LLP (Arnold & Porter Kaye Scholer LLP)
PLI Item #: 397729
Practice Areas: Health care, Intellectual property, Life sciences

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