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Uncertainty and unsatisfactory incentives

Ha Kung Wong and Melissa Gibson review the US FDA approval pathway for biosimilar applications.

On March 23, 2010, the *Biologics Price Competition and Innovation Act* (BPCIA) was signed into law in the US. The BPCIA amended Section 351 of the Public Health Service Act (PHSA, 42 U.S.C. § 262), which governs the Food and Drug Administration (FDA) approval process for biologic license applications (BLAs). Similar to the *Hatch-Waxman Act*, the BPCIA is intended to create incentives for the manufacture of highly similar biological products (or biosimilars) by creating an abbreviated regulatory approval process and marketing exclusivities for the first interchangeable product. Although biological drug products (or biologics) represented five of the top 10 selling drugs in the United States in 2012, with combined sales over $18.6 billion,[1] there has not been an application for a biosimilar in the three and a half years since the BPCIA has been enacted. This raises the question whether the incentives for filing an application for a biosimilar are outweighed by the uncertainties in the approval process.

Résumés

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What are biologics?

The BPCIA defines three categories of biologics:

- innovative biologics,
- biosimilars, and
- interchangeables.

A biologic is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivate of arsphenamine (or any trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or conditions of human beings."[2] Examples of biologics include human growth hormone, erythropoietins, insulin and monoclonal antibodies.

A biosimilar is highly similar to a reference product, aside from minor differences in inactive ingredients, and has no clinically meaningful differences as compared to the reference product in terms of safety, purity and potency of the product.[3]

An interchangeable is a biologic that may be substituted for a reference product without consent of the prescriber and thus must be more "similar" to a reference product than a biosimilar.[4]

Regulatory approval pathways

Before a drug may enter the marketplace, it must receive regulatory approval from the FDA. There are three approval pathways for biologics:

1) A BLA, which requires full clinical data;
2) An abbreviated application ("351(k) Application") for a biosimilar; and
3) A 351(k) Application for an interchangeable.

The BLA approval process for an innovative biologic in certain aspects resembles the NDA approval process for a small molecule drug. Prior to conducting human studies, a sponsor must file an investigational new drug application (IND) (subject to certain exemptions), which includes preclinical data, a summary of any prior clinical experience with the drug, and a description of the investigational plan for proposed clinical studies.[5] The FDA's objectives while reviewing the IND are to ensure the safety of clinical subjects and to assure the quality of the scientific evaluations of the investigational drug for its intended use.[6] Unless the FDA issues a clinical hold, clinical trials may commence 30 days after the FDA receives the IND.[7]

Next, the sponsor submits a BLA, which contains data derived from preclinical and clinical studies that establishes the product is safe, pure and potent (in other words, effective for its intended use), to obtain marketing approval for a biologic.[8] Compared with small molecules, biologics are structurally complex and difficult to characterize, so even minor manufacturing changes may alter the safety or efficacy of the drug. Therefore, BLA approval (and approval through 351(k) Application) is also predicated on the biologic's manufacturing, processing, packaging or storage facility meeting standards designed to assure the biologic remains safe, pure, and potent.

An abbreviated 351(k) Application must include information demonstrating that the biologic is biosimilar to the reference product based on:

a) analytical studies showing that the product is highly similar to the reference product;
b) animal studies assessing toxicity; and
c) clinical studies sufficient to demonstrate safety, purity, and potency in one or more condition for use for which the reference product is licensed.[9]

The FDA may decide that any of the above elements are unnecessary in the application. Additionally, the biologic must:

a) use the same mechanism of action for the condition(s);
b) seek approval for the same condition in the proposed labeling;
c) use the same route of administration, dosage form and strength; and
d) be manufactured, processed, packaged or held in a facility that meets the same standards designed to assure the biologic remains safe, pure, and potent as the reference product.[10]

A sponsor seeking approval for an interchangeable must also file a 351(k) Application. In addition to meeting the requirements for biosimilarity, the application must establish that the proposed product "can be expected to produce the same clinical result as the reference product in any given patient."[11] Additionally, if the product is administered more than once, the safety and reduced efficacy risks of alternating or switching between the proposed interchangeable and the reference product cannot be greater than the risks of repeated use of the reference product without alternating or switching.[12]

FDA guidance for establishing biosimilarity

The FDA recently issued four pieces of draft guidance[13] to assist sponsors in preparing and submitting 351(k) Applications. The purpose of the development program for a 351(K) Application is to establish that the proposed product is biosimilar to the reference product, which includes assessing the effects of any observed differences between the products.[14] However, unlike small molecules which can be exactly replicated, it is currently impossible to make a precise copy of a biologic. For example, proteins can differ based on their primary amino acid sequence, post-translational modifications (e.g., glycosylation), and three-dimensional structure (e.g., protein folding and protein-protein interactions), each of which can be altered by the use of different cell lines, manufacturing process or storage conditions. Therefore, the applicant or "sponsor" must establish that these structural differences do not have a clinically meaningful impact on the safety, potency or purity of the drug, which the sponsor establishes through analytical, animal and human studies.

Rather than specifying studies that need to be conducted from the outset, FDA currently recommends the sponsor participate in early discussions with the FDA regarding its development plan and establish a step-wise approach with milestones for future discussions. Following completion of each step, the applicant should identify the next steps to address any remaining uncertainty about biosimilarity. For example, if a sponsor conducts a comprehensive array of analytical testing, which establishes that the proposed product is 99% structurally and functionally identical to the reference product, the FDA might reduce the scope or number of, or deem unnecessary, subsequent animal and clinical studies than if the product is only 90% structurally and functionally identical. Thus, a sponsor must prepare for an unpredictable development plan, in which the results of the previous step inform the strategy for the next step.

Moreover, the FDA anticipates utilizing a totality-of-the-evidence approach to evaluate the data supporting the 351(k) Application. This fact-specific evaluation creates additional uncertainty about what is necessary to establish biosimilarity. In particular, the Scientific Guidance provides that "[a] sponsor **may** be able to demonstrate biosimilar" despite minor formulation and structural difference, so long as the sponsor demonstrates "the differences are not clinically meaningful."[15] The Guidance explains that "clinically meaningful" may include "a difference in the expected range of safety, purity or potency of the proposed and reference products," which is simply a restatement of the BPCIA's definition of biosimilarity.[16] Therefore, the FDA's totality-of-the-evidence approach merely mirrors statutory requirements and increases uncertainty due to its fact-specific nature, rather than providing practical requirements for establishing biosimilarity.

Incentives and regulatory exclusivities

Similar to the *Hatch-Waxman Act,* the BPCIA provides incentives to the brand manufacturer to continue innovating new biologics and to the manufacturer of the first interchangeable to promote early filing of 351(k) Applications. An innovator BLA sponsor enjoys a 12-year exclusivity after BLA approval, and the first biosimilar determined to be interchangeable receives one year of marketing exclusivity.[17] However, this one-year period may be shortened depending on the timing of an underlying patent litigation.[18] Moreover, the interchangeable exclusivity does not prevent the approval of biosimilars.[19] Biosimilars that are not interchangeable receive no marketing exclusivity.[20]

Biosimilars vs biobetters

Although development of biosimilars has the potential to be a lucrative enterprise, with estimated sales between $1.9-2.6 billion by 2015[21], there are still significant hurdles the manufacturers of biosimilars will face that may not be adequately overcome by the incentives set forth in the BPCIA. In contrast, the significant regulatory and marketing advantages a manufacturer will enjoy by developing and filing a BLA for an improved version of a biologic (a "biobetter") may better offset the additional costs.

For example, Glycotype GmbH is conducting clinical studies of TrasGEX™, which purportedly has better therapeutic outcomes and less immunogenic reactions compared to the originator, Herceptin®. Not only would TrasGEX™ receive 12 years of marketing exclusivity, the actual marketing and sales of the drug will not be limited to that of Herceptin®, and, in fact, it may be marketed as a better alternative.

The lack of clarity, detailed above, regarding what is necessary to receive FDA approval for a biosimilar may discourage manufacturers from filing 351(k) Applications. Moreover, the FDA so far has provided minimal guidance for establishing interchangeability. In addition, the recommendations set forth in the Scientific Guidance and Quality Guidance only applies to therapeutic protein products, rather than the broad array of biologics defined in the statute. In contrast, the BLA approval process is significantly more developed. Approvals for biologics have been provided for products exhibiting continued safety, purity and potency since 1944, and the current evidentiary standard for establishing effectiveness has been in effect since 1972.[22]

Development costs of biosimilars are expected to be significantly less than innovator biologics ($75-250 million vs. $800 million).[23] However, despite requiring full clinical data to support a BLA, the development costs for a biobetter may not be considerably higher than pursuing an interchangeable or, perhaps, even a biosimilar. Although the 351(K) Application is intended to be an abbreviated process, the FDA's lack of clarity and experience may increase clinical trial costs, especially while the process is being developed and perfected. Moreover, there has been no guidance on what is required to establish interchangeability, so it is possible that the costs may be commensurate with a BLA. In addition, a biobetter will have substantially less early stage R&D expenditures compared to an originator biologic, thereby reducing the total costs for development.

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A manufacturer that files a BLA for a biobetter will not be blocked by the 12-year exclusivity period, and in fact, will enjoy its own 12-year marketing exclusivity. Although a biobetter manufacturer will incur additional expenses marketing its product, the advantages over the originator biologic should make it easier to market. In theory, a sponsor does not need to market an interchangeable because it is freely substitutable at the pharmacy. However, several states are considering, or have passed legislation, that restricts the pharmacy's ability to substitute interchangeables by allowing doctors or patients to refuse substitution of interchangeables and/or requiring notification of the substitution to the prescribing doctor.[24] Thus, manufacturers will need to convince the public that interchangeables are safe, effective and cheaper alternatives to reference products. Moreover, if the product merely obtains FDA approval as a biosimilar, the product cannot be substituted for the reference drug, and thus must be separately marketed to doctors and patients.

In light of the regulatory exclusivities and certainty in the approval process, it is anticipated that several biologic manufacturers may choose to file a BLA for a biobetter rather than a 351(k) Application for a biosimilar.

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[1] *U.S. Pharmaceutical Sales – 2012,* DRUGS.COM, http://www.drugs.com/stats/top100/2012/sales (last updated August 2013).
[2] 42 U.S.C. § 262(i)(1).
[3] 42 U.S.C. § 262(i)(2).
[4] 42 U.S.C. § 262(i)(3).
[5] 21 CFR §§ 312.20, 312.23.
[6] 21 CFR §§ 312.22(a).
[7] 21 CFR §§ 312.40(b).
[8] 21 CFR §§ 601.2(a).
[9] 42 U.S.C. § 262(k)(2)(A)(i)(I).
[10] 42 U.S.C. § 262(k)(2)(A)(i)(II)-(V).
[11] 42 U.S.C. § 262(k)(4)(A).
[12] 42 U.S.C. § 262(k)(4)(B).
[13] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (February 2012) (hereinafter "Scientific Guidance"); Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (February 2012); Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (February 2012); and Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (March 2013).
[14] Scientific Guidance, at 7.
[15] Scientific Guidance, *supra* note 13, at 8 (emphasis added).
[16] *Compare Id., with* 42 U.S.C. § 262(i)(2)(B).
[17] 42 U.S.C. § 262(k)(6)-(7).
[18] 42 U.S.C. § 262(k)(6)(B)-(C).
[19] 42 U.S.C. § 262(k)(6).
[20] 42 U.S.C. § 262.
[21] *Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape,* IMS HEALTH, at 1 (December 2011), http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf
[22] FDA Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, at 4 (May 1998).
[23] Andrew Fischer Bourgoin and Beth Nuskey, *An Outlook on US Biosimilar Competition,* THOMSON REUTERS, at 9 (April 2013), http://thomsonreuters.com/products/ip-science/04_013/anoutlookonusbiosimilarcompetition-cwp-en.pdf
[24] Fisher Bourgoin & Nuskey, *supra* note 23, at 6.