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Beyond Biosimilarity: Draft Guidance for Demonstrating Biologic Interchangeability

BY HA KUNG WONG AND SEAN MCDONAGH

The primary focus of the Food and Drug Administration, industry and counsel preparing for the advent of follow-on biologics in the United States has been the legal and regulatory framework governing the approval of such products as biosimilars under the Biologics Price Competition and Innovation Act of 2009 (''BPCIA''). However, the BPCIA further provides that the FDA may determine that a biologic product is also interchangeable with (and thus, under Federal law, freely substitutable for) its reference product. As stakeholders anticipate the potential for ''generic biologics,'' the FDA has released a Draft Guidance outlining considerations for applicants seeking to demonstrate interchangeability. This Draft Guidance sheds some light on the burdens sponsors of proposed interchangeable biological products (''interchangeables'') will (and will not) face along the path to interchangeable licensure.

About the Authors:

- Ha Kung Wong is a partner based in Fitzpatrick, Cella, Harper & Scinto's New York office. He practices general IP law with an emphasis on complex patent and trade secret litigation, as well as IP due diligence, in pharmaceuticals, biologics and chemistry.
- Sean McDonagh is an associate in the firm's New York office. His practice is focused on Hatch-Waxman litigation and transactional IP due diligence.

On Jan. 18, 2017, the FDA released *Considerations in Demonstrating Interchangeability With a Reference Product* (''the Draft Guidance''),[1] outlining the FDA's recommendations to sponsors seeking to demonstrate interchangeability under the BPCIA. The Draft Guidance is focused on therapeutic protein products, and is intended to provide an overview of the scientific considerations and information the FDA will evaluate when determining interchangeability. Most notably, as discussed below, the Draft Guidance indicates that sponsors will likely be required to conduct a clinical study assessing the risks associated with switching between the proposed interchangeable and the reference product.

Interchangeability Under the BPCIA

The BPCIA establishes an abbreviated pathway to licensure for biological products shown to be either biosimilar to, or interchangeable with, an FDA-licensed biological reference product.[2] In contrast to biosimilars, an interchangeable may be substituted by a pharmacist for its reference product without the intervention of the prescribing health care provider (i.e., even if the reference product is prescribed).[3] The BPCIA further provides significant exclusivity incentives for the first approved interchangeable for a given reference product.[4]

A product may be designated as interchangeable under the BPCIA if it is sufficiently shown that the product is biosimilar[5] to the reference product and further ''can be expected to produce the same clinical result as the reference product in any given patient.''[6] Additionally, where the product is administered more than once

[1] *Available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf.

[2] *See* §§ 7002-7003, amending Section 351(k) of the Public Health Service Act, *codified at* 42 U.S.C. 262(k).

[3] 42 U.S.C. 262(i)(3).

[4] *See* 42 U.S.C. 262(k)(6).

[5] Biosimilarity is defined in the BPCIA to mean ''the biological product is highly similar to the reference product'' and ''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.'' *See* 42 U.S.C. 262(i)(2).

[6] *See* 42 U.S.C. 262(k)(4)(A).

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to an individual, it must be shown that ''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.''[7]

Interchangeability Under the Draft Guidance

The Draft Guidance outlines the data the FDA expects will generally be required to demonstrate that a proposed interchangeable is clinically equivalent to the reference product and has no switching risk. Consistent with prior industry guidance for demonstrating biosimilarity,[8] the Draft Guidance recommends a stepwise approach to progressively identify and address ''residual uncertainty'' about clinical outcomes and switching risk.[9]

To show clinical equivalence ''in any given patient,'' the Draft Guidance indicates that sponsors are expected to demonstrate that the proposed interchangeable product should produce the same clinical result in all of the reference product's licensed conditions of use.[10] Notably, the Draft Guidance states that such showing ''will likely not involve additional clinical studies'' beyond those required to support the other elements of interchangeability.[11] Rather, the Draft Guidance contemplates that evidence in support of this element can include an evaluation of the evidence generated to support biosimilarity, such as identification and analysis of structural and immunogenic differences between the reference product and the proposed interchangeable product. Sponsors are recommended to include a scientific justification as to why any differences ''do not preclude'' a determination of clinical equivalence in any given patient.[12]

With respect to switching risk, however, the ''FDA expects that applications generally will include data from a switching study or studies in one or more appropriate conditions of use.''[13] The Draft Guidance provides fairly specific input on the design of such studies, as discussed below.

Analytical Framework and Key Considerations

Several factors that may influence the data needed to support a demonstration of interchangeability within this framework are emphasized.

Extent of Comparative Characterization: The Draft Guidance contemplates that comparative analytical evidence generated to support biosimilarity will also be relevant to the determination of interchangeability.[14] While noting that ''there is a continuum of comparative analytical data'' that could support a demonstration of biosimilarity, the Draft Guidance states several times that clinically relevant ''fingerprint-like'' analytical similarity may permit a ''more selective and targeted approach'' to demonstrating interchangeability, including required clinical studies.[15]

Product Complexity: The degree of structural and functional complexity of the proposed interchangeable may also influence the sponsor's burden; as an example, the Draft Guidance states that ''products expected to have a single target'' may pose less uncertainty regarding interchangeability than ''those acting on multiple or less-defined biological pathways.''[16]

Immunogenicity Risk: The Draft Guidance also states that risk assessments for the proposed interchangeable and clinical experience with the reference product regarding immunogenicity can affect the data required to support a demonstration of interchangeability, noting that ''products with a documented history of inducing detrimental immune responses may require more data to support interchangeability than products with an extensive documented history that immunogenicity does not impact clinical outcomes.''[17]

Considering the foregoing factors together, the FDA will determine whether ''residual uncertainty'' remains with respect to clinical equivalence. If so, the FDA may determine that, for example, postmarketing data of the product as a licensed biosimilar will also be required to support a demonstration of interchangeability.[18]

Postmarketing Data: While postmarketing data may be considered or required to support interchangeability, the Draft Guidance indicates that postmarketing data will not be accepted as a substitute for a switching study. The Draft Guidance acknowledges that ''in certain circumstances, postmarketing data from a licensed biosimilar product may be helpful as a factor when considering what data is necessary.''[19] However, the ''current thinking'' of the FDA ''is that postmarketing data collected from products first licensed and marketed as a biosimilar, without corresponding data derived from an appropriately designed, prospective, controlled switching study or studies, generally would not be sufficient to support a demonstration of interchangeability.''[20]

Switching Studies

As noted, for those products intended to be administered to an individual more than once, a suitable switching study or studies will likely be required. Fairly detailed recommendations for the design and analysis of such studies, including endpoints, sample sizes, patient populations and analytical parameters, are provided at Section VI.A. of the Draft Guidance.

Whereas sponsors may rely in part on studies comparing a proposed product to a non-U.S.-licensed com-

[7] 42 U.S.C. 262(k)(4)(B).
[8] *See, e.g.*, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.
[9] Draft Guidance at 5.
[10] *Id.* at 3.
[11] *Id.* at 3-4.
[12] *Id.* at 3.
[13] *Id.* at 4.
[14] *Id.* at 5-6.
[15] *Id.* at 6.
[16] *Id.* at 7.
[17] *Id.* at 7.
[18] *Id.* at 7-8.
[19] *Id.* at 8.
[20] *Id.* at 8.

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parator product to demonstrate biosimilarity,[21] the Agency ''strongly recommends'' that sponsors use a U.S.-licensed reference product in any switching study to support a determination of interchangeability.[22] The Draft Guidance further provides recommendations for integrated studies of biosimilarity and switching risk for sponsors considering a single study to establish interchangeability.[23]

Product Presentation—Container Closure Systems and Delivery Devices

In addition to the analyses outlined above, the Draft Guidance recommends that sponsors undertake a comparative analysis of the proposed interchangeable product's ''presentation,'' defined to refer to the ''container closure system and/or delivery device constituent part of the product.''[24] Noting repeatedly that biologic products are administered to a variety of end users, that the tasks involved in administration ''can vary considerably depending on the type of presentation and its design characteristics,'' and that interchangeable products can be substituted without health care provider intervention or additional training, the Draft Guidance states that ''it is important that sponsors carefully consider the presentation of the proposed interchangeable product relative to the reference product'' to address the potential risk of ''use-related error.''[25]

In particular, the Draft Guidance recommends that sponsors generally should not seek licensure for a presentation for which the reference product is not licensed. ''For example, if the reference product is only marketed in a vial and a prefilled syringe, a sponsor should not seek licensure for the proposed interchangeable product for a different presentation, such as an auto-injector.''[26]

The Draft Guidance further outlines a ''threshold'' presentation analysis to evaluate the potential for errors in product use.[27] Sponsors are advised to conduct a line-by-line labeling comparison, a visual and tactile physical comparison and a comparative task analysis to identify differences in ''external critical design attributes''—those features that directly affect the performance of critical tasks.[28] If such differences are found in the final design of the proposed interchangeable product, the Draft Guidance recommends that sponsors conduct a ''comparative use human factors'' study to assess differences in the use error rate between the reference product and the proposed interchangeable product.[29] Although considerations for such studies are outlined in the Appendix to the Draft Guidance, the FDA ''expects that such additional studies will likely not be needed for many interchangeable products.''[30]

[21] *Id.* at 15.
[22] *Id.* at 16.
[23] *Id.* at 12.
[24] *Id.* at 16-18.
[25] *Id.* at 17.
[26] *Id.*
[27] *Id.* at 19-20.
[28] *Id.* at 20.
[29] *Id.* at 22-23.
[30] *Id.* at 17.

Discussion

Based on the Draft Guidance, it appears that the FDA will generally expect sponsors to provide:

- a comparative analysis of the data generated to establish biosimilarity;
- a switching study;
- scientific justification for extrapolating supporting data from the studied condition of use to any additional conditions of use for which the reference product is licensed; and
- a comparative threshold analysis of product presentation.

The most notable feature of the Draft Guidance is the switching study requirement for products intended to be administered more than once. The FDA has apparently concluded that ''the risk in terms of safety or diminished efficacy of alternating or switching between use'' of the proposed interchangeable and the reference product will generally only be adequately assessed by a clinical trial. The suggested design of the switching studies provided in the Draft Guidance is relatively robust and potentially resource intensive for sponsors. Going forward, sponsors may be incentivized to conduct an integrated study of biosimilarity and switching risk to reduce the overall burden of interchangeable licensure, or, if required clinical studies are extensive, to simply work towards its own Biologic License Application (''BLA'') to take advantage of longer exclusivity.

Conversely, the Draft Guidance indicates that additional clinical trials (beyond those required to establish biosimilarity) likely will not be required to establish that a proposed interchangeable product ''can be expected to produce the same clinical result as the reference product in any given patient.'' Although the Draft Guidance contemplates analysis of clinical outcomes in various patient populations, one could interpret the recommendations to emphasize clinical parity in each of the reference product's licensed conditions of use. The recommendations provided in this regard appear largely coextensive with those provided to establish biosimilarity. Some stakeholders may have expected or appreciated further clarity on the extent of analyses required in different patient populations and subpopulations.

In contrast to the arguably limited recommendations provided for demonstrating clinical equivalence, the Draft Guidance places substantial emphasis on presentation, providing a relatively detailed template for sponsors to identify and minimize risks of use-related error arising from external critical design attributes. This element of interchangeability may not have been readily apparent from the statute, and may represent an opportunity for innovators and reference product manufacturers to implement additional barriers (including so-called ''soft IP'' barriers, such as trademarks and design patents) to interchangeable licensure and competition.

The Draft Guidance is subject to public comment before finalization by the FDA. Comments should be submitted by March 20, 2017, and should be identified with reference to the following Docket Number: FDA-2017-D-0154.