

FDA Issues Draft Guidance on Biosimilar Interchangeability

Agency outlines flexible, case-by-case approach to demonstrating interchangeability to reference products; emphasizes role of “switching studies”

On January 18, 2017, the US Food and Drug Administration (FDA or Agency) issued its highly anticipated draft guidance on demonstrating interchangeability under the Biologics Price Competition and Innovation Act (BPCIA). The draft guidance, titled *Considerations in Demonstrating Interchangeability With a Reference Product*, provides FDA's thinking on the types of studies that biosimilar product sponsors should conduct and the data sponsors should provide to support a finding that a proposed biosimilar product is interchangeable with a reference biologic. The draft guidance marks an important milestone in FDA's ongoing efforts to implement the BPCIA. While the draft guidance is focused on therapeutic protein products, the principles it articulates may apply to demonstrations of interchangeability more broadly.

This *Client Alert* highlights key provisions in the draft guidance that are potentially significant both to manufacturers developing biosimilar products, and to holders of biologics license applications (BLAs) that may be referenced in a third party's application for licensure of an interchangeable biosimilar.

Background: Interchangeability under the BPCIA

The BPCIA, which was signed into law as a part of the Patient Protection and Affordable Care Act in 2010, amended the Public Health Service Act (PHS Act) to create an abbreviated pathway under section 351(k) for the licensure of biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference biologic. All biosimilar products must be highly similar to the reference product and have no clinically meaningful differences in terms of safety, purity and potency to be approved as a biosimilar under the section 351(k) pathway. However, a biosimilar can also be approved as “interchangeable” with the reference product, provided the biosimilar meets additional criteria to enable it to be substituted for the reference product without the prescribing health care provider's intervention.¹ Specifically, under section 351(k)(4) of the amended PHS Act, FDA will find a biological product interchangeable with the reference product if, in addition to meeting the standards for biosimilarity,² both:

- The proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient; and
- For a proposed interchangeable product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch³

FDA's determination that a proposed biosimilar product is interchangeable with the reference product may carry numerous benefits. Specifically, section 351(k)(6) of the PHS Act grants a period of exclusivity to the first-approved interchangeable product, during which time FDA is precluded from determining that a subsequent biosimilar applicant is also interchangeable for any condition of use. Moreover, the approval of interchangeable products may result in increased market competition for biologics that are licensed for the same condition of use and that may be substituted with one another. Yet, while FDA has approved a handful of biologics as biosimilar to their reference products, the Agency has not approved an interchangeable product — and, until the issuance of the new draft guidance, had not articulated how sponsors might demonstrate satisfaction of the statutory standard for interchangeability.

Demonstrating Interchangeability: Factors to Consider in Evaluating the Type and Amount of Data Needed to Support Interchangeability

Pursuant to the draft guidance, FDA plans to evaluate interchangeability based on the “totality of the evidence.”⁴ The draft guidance identifies a number of factors for sponsors to use in assessing the extent and type of data and information that should be collected to support an interchangeability determination.

As an initial matter, the Agency emphasizes that the evidence necessary to demonstrate interchangeability, beyond that needed to demonstrate biosimilarity, will hinge primarily on the characteristics of the given biological product, and thus may vary significantly product to product. FDA encourages sponsors to take a stepwise, iterative approach to demonstrating interchangeability, evaluating any residual uncertainty regarding interchangeability at each step in the data generation process, and identifying appropriate next steps accordingly.

FDA provides a list of product-dependent factors for sponsors to consider in determining the amount and type of data necessary to support a demonstration of interchangeability. These factors include:

- *Complexity of the product and extent of comparative and functional characterization:* FDA acknowledges that all relevant structural and functional differences between a proposed interchangeable product and the reference product may not be detectable using current analytical methodologies. However, the Agency suggests various means to reduce that residual uncertainty about interchangeability, thereby limiting the amount of additional data needed to demonstrate interchangeability. For example, FDA notes that data sets that include “highly sensitive analytics and/or sequential analytical methods” capable of identifying molecules with different attribute combinations (such as different glycoforms), along with a comprehensive assessment of the relationships between different attributes, may serve to hone in on the precise data and information required to support a finding of interchangeability.⁵

The degree of analytical similarity between the products, along with the evidence regarding the clinical relevance of the analytical data, will determine the extent to which residual uncertainty is reduced. The structural and functional complexity of the proposed interchangeable biosimilar and its reference product may also affect residual uncertainty. For example, FDA acknowledges that a product with a single target may have less residual uncertainty than a product that acts on multiple or less-defined biological pathways.

- *Product-specific immunogenicity risk:* FDA explains that the level of clinical experience with the reference product and comprehensive risk assessments may have an impact on the data and information needed to support a finding of interchangeability. As an example, the Agency notes that products with a history of immunogenicity risks might require more data to show interchangeability as

compared to products with a documented history showing the immunogenicity does not affect clinical outcomes.

In addition, FDA acknowledges in the draft guidance that post-marketing data from a licensed biosimilar product may be useful in considering the data necessary to support a finding of interchangeability with the reference product. FDA notes that post-marketing data absent corresponding data from appropriate switching studies (as discussed in more detail below) would generally be *insufficient* to support a finding of interchangeability; however, the Agency acknowledges that such data may help to address the residual uncertainty about interchangeability and thus help to characterize the data needed to support a finding of interchangeability. Moreover, FDA indicates that in certain cases, post-market surveillance data from the licensed biosimilar may be *required* to address the residual uncertainty regarding the demonstration of interchangeability, in addition to data from an appropriately designed switching study. FDA thus anticipates that in certain cases, a sponsor may first need to obtain licensure of a product as a biosimilar and collect post-marketing data before interchangeability can be established.

Demonstrating the Product “Can Be Expected to Produce the Same Clinical Result as the Reference Product in Any Given Patient”

As noted above, one of the elements to demonstrate interchangeability, beyond a general showing of biosimilarity, is that the product can be expected to produce the same clinical result as the reference product in any given patient. FDA highlights that the data and information provided to FDA to satisfy this element may include, but may not necessarily be limited to, an evaluation of the data and information that was generated to support a demonstration of biosimilarity in the first instance. Specifically, FDA notes that such data and information may include:

- Identification and analysis of critical quality attributes
- Identification of analytical differences between the products, and an analysis of the associated potential clinical impacts
- Analysis of the mechanism(s) of action and differences in expected toxicities in each condition of use for which the reference product is licensed
- Pharmacokinetics, biodistribution, immunogenicity risk and differences in expected toxicities of the product in different patient populations
- Any other factors that may affect safety or efficacy in each condition of use and patient population for which the reference product is licensed

Interchangeability can be demonstrated notwithstanding the existence of differences between the proposed interchangeable product and the reference product with respect to the factors listed above. However, FDA encourages sponsors to scientifically justify why those differences do not preclude an interchangeability determination.

Demonstrating the Risk of Switching Between Products Is Not Greater Than the Risk Associated With Use of the Reference Product Alone

A proposed interchangeable product intended to be administered to an individual more than once must meet the statutory requirement that alternating or switching between the proposed product and the reference product carries no greater risk compared to use of the reference product alone. To demonstrate that this requirement has been met, sponsors are expected to provide data from one or more switching

studies, which evaluate the effect of alternating or switching between the proposed interchangeable product and the reference product.⁶

The draft guidance includes considerable discussion of the suggested design and analysis of switching studies. Among other considerations, a switching study should evaluate at least two exposure periods to each of the proposed interchangeable product and the reference product (constituting at least three switches between the proposed product and the reference product). Additionally, the primary endpoint should assess the impact of switching or alternating on clinical pharmacokinetics and pharmacodynamics (if available). FDA notes that the anticipated use of the proposed interchangeable product in clinical practice should inform the design of the switching study, accounting for scenarios in which alternating products may cause the most concern. The draft guidance also provides the following suggestions:

- FDA strongly recommends that sponsors enroll patients, rather than healthy subjects, in switching studies.
- Sponsors should provide adequate justification to FDA regarding any dropout rates or missing data rates that differentially affect study treatment arms.
- The combination of factors that would be expected to cause the greatest concern regarding immune response and the resulting safety and efficacy impact — specifically, the condition to be treated, dosing, and duration of exposure interval to each product — should be considered when determining the number and duration of switches between the proposed interchangeable product and the reference product.
- During the last switch interval following the dose after which at least three half-lives of the reference product have elapsed, intensive pharmacokinetics sampling should be conducted to capture the full pharmacokinetics profile.
- FDA asserts that sponsors should use a US-licensed comparator reference product in switching studies to support a determination of interchangeability. This is in contrast to FDA’s guidance on demonstrating biosimilarity,⁷ in which FDA has advised that sponsors can seek to use data derived from studies comparing their proposed biosimilar products to non-US licensed comparators to show biosimilarity.

Notably, FDA contemplates that sponsors can also pursue an “integrated study design,” intended for studies that are meant both to evaluate the impact of switching or alternating between the proposed interchangeable product and the reference product, and to support a demonstration that there are no clinically meaningful differences between the products. In addition, while FDA expects that switching studies will generally not be needed for biological products intended to be administered to an individual only once, the Agency nonetheless expects sponsors to justify why such data are unnecessary.

Data Extrapolation to Support Additional Conditions of Use

While FDA acknowledges that sponsors of proposed interchangeable biologics can seek licensure for fewer than all of the reference product’s licensed conditions of use, when possible, the Agency expects (and recommends) that sponsors will seek licensure for all such conditions of use. The draft guidance states that, with sufficient scientific justification, sponsors may be able to extrapolate data to support licensure for one or more additional conditions of use beyond the condition covered by the submitted studies. The scientific justification should address the following issues for the tested and extrapolated conditions of use, among others:

- Analysis of the mechanism(s) of action and differences in expected toxicities in each condition of use for which the reference product is licensed
- Pharmacokinetics, biodistribution, immunogenicity risk and differences in expected toxicities of the product in different patient populations
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which the reference product is licensed

Consistent with the flexibility articulated in the guidance generally, differences in conditions of use with respect to the factors above may not foreclose the possibility of extrapolation. However, FDA expects sponsors to provide sufficient scientific justification for such differences considering the totality of the evidence.

The Impact of Product Presentations on Interchangeability Determinations

The draft guidance generally advises sponsors not to seek licensure for product presentations for which the reference product is not licensed. However, differences in container closure systems or delivery devices may be acceptable as long as sponsors provide data to show that the changes do not negatively affect end users' appropriate use of substituted interchangeable products. FDA recommends that sponsors analyze the presentations of proposed interchangeable products by conducting three types of threshold analyses: a line-by-line labeling comparison; a comparative task analysis; and a physical comparison of the products and their container closure systems and/or delivery device constituent parts.

If these analyses identify presentation differences between the proposed interchangeable product and the reference product that FDA does not consider minor, sponsors should either modify the presentation design or provide FDA with data to demonstrate that the differences will not negatively impact appropriate use of the substituted interchangeable product. Such evidence may be gathered in a focused comparative use human factors study, the potential design for which FDA discusses in an appendix to the draft guidance.

Conclusion

Coming nearly seven years after the BPCIA was signed into law, FDA's new draft guidance may be seen as a first step for biosimilar product sponsors looking to develop and market interchangeable biosimilar products. However, certain aspects of the draft guidance may pose significant hurdles that sponsors will need to clear before being able to bring an interchangeable product to market. Most notably, the draft guidance reflects FDA's expectation that sponsors will provide data from one or more switching studies to support a demonstration of interchangeability for a proposed product that is intended to be administered more than once. Moreover, FDA's position that sponsors should use a US-licensed comparator in such studies may present a challenge for sponsors of proposed interchangeable products for which the reference product is subject to a risk evaluation and mitigation strategy (REMS), if that REMS places restrictions on access to the reference product. In addition, FDA asserts that, in some cases, a proposed interchangeable product may need to be licensed first as a biosimilar to enable the sponsor to gather appropriate post-market data before the product can be licensed as an interchangeable.

If FDA ultimately finalizes this guidance to implement the interchangeability standards as described in the draft guidance, industry may be required to make significant investments in resources and time to bring an interchangeable to market. In addition, while the flexible, case-by-case approach in the draft guidance may give sponsors leeway to gather data tailored to their proposed products, the approach may also make it difficult to predict the specific information needed to demonstrate interchangeability in particular

cases. Accordingly, FDA urges sponsors to consult with the Agency regarding sponsors' plans for demonstrating the interchangeability of their proposed products , and to do so early in the development process. Until both FDA and industry gain more familiarity applying the interchangeability standards, such meetings may be critical to building a successful development program for an interchangeable product.

Parties interested in submitting comments to FDA on the draft guidance are advised to do so by March 19, 2017, to ensure that FDA considers those comments prior to preparing the final version of the guidance.

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Endnotes

¹ 42 U.S.C. §§ 262(i), 262(k)(4).

² Although a demonstration of biosimilarity is a prerequisite to demonstrating interchangeability, this *Client Alert*, like FDA's draft guidance, focuses on the additional criteria that must be met to demonstrate interchangeability. The alert is not intended to discuss the biosimilarity standard itself.

³ 42 U.S.C. § 262(k)(4).

⁴ FDA, *Draft Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product*, at 2 (Jan. 2017), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>.

⁵ *Id.* at 6.

⁶ *Id.* at 4.

⁷ See FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at 6 (Apr. 2015), available at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>; FDA, *Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, at 8 (Apr. 2015), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf>.