March 8, 2017

Finally! FDA Issues a Draft Guidance on Interchangeable Biosimilars

In mid-January, the US Food and Drug Administration (FDA) issued a much-anticipated draft guidance on interchangeable biosimilars titled "Considerations in Demonstrating Interchangeability With a Reference Product" (January 2017).[1] In it, the FDA addresses standards for demonstrating interchangeability of biological products under the Biologics Price Competition and Innovation Act of 2009 (BPCIA).

The BPCIA created an abbreviated pathway for the FDA to license biologic products that are biosimilar to, or interchangeable with, a reference product. Under the BPCIA, a product is biosimilar if it is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and if there are no clinically meaningful differences between the two products in terms of safety, purity and potency. Further, a biosimilar is interchangeable if it is expected to produce the same clinical result as the reference product, and if the biosimilar poses no greater risk to the patient than the reference product with regard to safety or diminished efficacy of switching the two products in the same patient. An interchangeable biosimilar can be substituted for the reference product without the intervention of the prescribing health care provider.

To date, the FDA has issued a number of guidances addressing the standards for establishing biosimilarity, but this is the first guidance the FDA has issued addressing the higher standard for interchangeability. It should be noted that this draft guidance "focuses on therapeutic protein products" despite the BPICA applying generally to many different types of biologics. However, it does provide insight into the FDA's general approach to biosimilar interchangeability and provides an overview of important scientific considerations in demonstrating interchangeability. However, it must be stressed that this draft guidance is not binding on the FDA, and the final guidance may change (possibly significantly). Also, comments and suggestions regarding this draft are due to be filed with the FDA by March 20.

FDA's General Principles Regarding Interchangeability

This draft guidance begins by highlighting some general principles the FDA will apply to assessing interchangeability. For example, the FDA notes that, to be interchangeable, both the FDA (and the BPCIA) first require the follow-on product to be "biosimilar" to the reference product. Thus, a follow-on manufacturer should be prepared to follow the "totality of the evidence" and "residual uncertainty" approaches taken in its earlier series of guidances addressing biosimilarity under the BPCIA, including "Quality Considerations

[1] This draft guidance is available here.

For questions about the FDA's draft guidance on submitting comments or suggestions (due by March 20, 2017), or for more information on the BPCIA or biologic medicines, please contact your Katten attorney or the attorney listed below.

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in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" (April 2015), "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (April 2015), and "Biosimilarity: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (May 2015).[2]

To that end, the FDA expressly states that the type of data and information submitted to demonstrate interchangeability "may vary depending on the nature of the proposed interchangeable product." This data and information looks at factors 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" and may include:

- an evaluation of quality attributes,
- analytical differences in the drugs and the products,
- mechanisms of action,
- pharmacokinetics (PK),
- biodistribution, and
- immunogenicity risks in different patient populations and differences in expected toxicities.

Where there are differences in these parameters, the FDA will require the sponsor to provide a scientific justification for why such differences do not preclude a showing of interchangeability. However, the FDA will allow for extrapolation of certain data to demonstrate interchangeability in certain circumstances if the follow-on sponsor can provide a scientific rationale for it.

The FDA recommends that the sponsor seek a license for all such uses "when possible," but will also allow a biosimilar sponsor to seek an interchangeability finding for less than all of the approved uses of the reference product. But, the FDA also specifies that it will expect data from switching studies to support an analysis of the risks of switching, and that sponsors should account for the effects of any differences in the product's presentation on the appropriate use of the product.

Specific Issues Addressed in the FDA's Draft Guidance

In addition to these general principles, the FDA provided detailed comments on a variety of specific issues. On nearly all issues, the FDA stresses and recommends that a follow-on sponsor proactively discuss their plans with the Agency.

Factors Impacting the Amount and Type of Information Needed to Support Interchangeability

The FDA identifies multiple factors that may influence the data and information needed to support a demonstration of interchangeability, beyond what is needed to show biosimilarity.[3]

1. Product-Dependent Factors

   Similar to its recommendation for establishing biosimilarity, the FDA recommends that follow-on sponsors use a stepwise approach to assess interchangeability considerations, starting early in the process (i.e., during product development). At each step, the follow-on sponsor should evaluate whether there may be residual uncertainty about the interchangeability in an individual area and identify steps to address that uncertainty. Areas that may need to be addressed include the complexity of the molecule, activity in biological pathways, capabilities of current analytical techniques to characterize the molecule and product-specific immunogenicity risks. The FDA did note that "fingerprint-like characterization"[4] may reduce the uncertainty regarding interchangeability and may lead to "a more selective and targeted approach" to the clinical studies it requires to show interchangeability.

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[2] These, and other biosimilar, guidances are available here.

[3] For the FDA's position on data and information requirements for biosimilarity, see Section VII of its guidance titled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (April 2015).

[4] For the FDA's position regarding "fingerprint-like characterization," see its guidance titled "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" (April 2015) and its guidance titled "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" (December 2016).

Also, products with a history of detrimental immune responses may require more data than those with an extensive history where immunogenicity has not impacted clinical outcomes. However, the FDA emphasizes that these factors must be considered together to inform the consideration of residual uncertainty about the data, and provides illustrative examples of how the analysis may vary on a case-by-case basis.

2. Biosimilar Post-Marketing Data

   A follow-on sponsor may think that its post-marketing data for its previously approved "biosimilar" product may be sufficient to establish interchangeability. However, the FDA believes such data is generally not adequate for this purpose. The FDA's current thinking is that the biosimilar post-marketing data usually does not support interchangeability because it does not include a determination of the PK and pharmacodynamics (PD) of switching between the follow-on and reference products. Rather than using post-marketing data, the FDA has a preference for appropriately designed, prospective-controlled switching studies (at least for products that are intended to be administered to a patient more than once ("multi-administration products"), which are discussed below. However, certain post-marketing data may be helpful in certain circumstances, including actual patient experiences in biosimilar switching scenarios, as well as the immunogenicity data obtained from actual use of a licensed biosimilar. The FDA also highlights how it may use certain post-marketing data in conjunction with switching studies in their interchangeability analysis. Again, the FDA encourages follow-on sponsors to discuss their plans for using post-marketing data to address interchangeability with the Agency.

Switching Study Design and FDA's Recommendation to Use US Licensed Reference Product

The FDA will generally expect follow-on sponsors for multi-administration products to conduct one or more switching studies to address whether there is an increased risk in terms of safety or diminished efficacy when a patient alternates or switches from the reference product to the follow-on product.[5] In this draft guidance, the FDA provides detailed observations and recommendations on multiple aspects of switching study design, including proper endpoints, sample size, sampling of PK/PD and immunogenicity, study population (with a strong recommendation for using patients, not healthy volunteers), how many and which use/indication to study, route of administration, as well as number and duration of studies.

One of the more important aspects of this guidance is the FDA's expectation that interchangeability switching studies should use a US licensed reference product. This is different from what the FDA allows for a biosimilarity study, where comparisons to non-US products are acceptable. The FDA reasons that in biosimilarity studies the comparator serves only as a control, whereas in a switching study the reference product is used in both the active switching arm and the control switching arm, where a subtle difference in immunogenicity might prime the immune system over repeated switching, increasing the immune response. Nevertheless, the FDA allows for the possibility of using a non-US licensed product in a switching study, if the follow-on sponsor can provide adequate scientific justification.

In addition, the FDA's draft guidance describes how the primary endpoint of these switching studies should assess the impact of switching/alternating on clinical PK and PD (if available), and that such test methods and assays be developed and validated early in product development. Beyond PK/PD parameters, the FDA expects the switching studies to assess immunogenicity and safety. Also, the FDA expects that switching studies to evaluate changes in treatment that result in two or more switch intervals and, in products with a long course of therapy, would take into account dropouts and the scientific bases for addressing the possibility of missing data. In this regard, the FDA notes that an immune response or adverse event during a switching study could have a carryover effect, making it difficult to assess which product may have been the cause and would raise concerns about interchangeability of the two products. The FDA also discusses its expectation for integrated studies where the follow-on sponsor is using an single study to assess both biosimilarity (e.g., if there is "no clinically meaningful differences" between the products) and interchangeability (e.g., the effects of switching/alternating discussed above).

In the end, the FDA takes a flexible approach to designing switching studies that actual study designs will be assessed on a case-by-case basis and suggests that studies should be designed in consultation with the FDA, starting early in the product development process.

[5] Notably, for single-administration products, the "FDA expects that switching studies would generally not be needed." But the FDA expects the follow-on sponsor will provide a justification for not needing such a study and encourages sponsors to meet with the Agency to discuss their planned development approach.

Extrapolation of Data to Other Uses

As discussed above, there are certain instances when a follow-on sponsor may obtain approval for one of the multiple uses of the reference product by submitting the appropriate data and information and then seeking approval for additional uses by extrapolation. To do so, the follow-on sponsor would need to provide sufficient scientific justification that addresses a variety of areas including, but not limited to:

- mechanisms of action (which may include target receptor(s),
- binding, dose/concentration response and pattern of molecular signaling),
- the PK and biodistribution of the product in different patient populations, the immunogenicity and toxicity risks in different populations, and
- any other factor that may affect the safety or efficacy of the product in each use and patient population for which the reference product is licensed.

As a practical matter, the FDA suggests sponsors consider condition of use studies that would be adequately sensitive to changes to enable later extrapolation. Yet again, the FDA suggests interaction with the Agency early on in product development to discuss the sponsor's proposed extrapolation.

Product Presentation (i.e., Containers, Delivery Devices, and/or Labelling)

The draft guidance notes that the proposed product's container closure system, delivery device constituent part, and/or labelling (collectively referred to as the product's "presentation") may influence the amount and type of data and information needed to show interchangeability. According to the FDA, this is because administering a biologic generally involves injection or infusion into the body, which may be performed by health care providers, patients or caregivers. Thus, product administration could potentially vary depending on its presentation. The FDA does not expect all differences in presentation to negatively impact the interchangeability. Rather, presentation differences may be acceptable as long as there is data demonstrating the changes do not negatively impact the ability of end users to use the products appropriately when one is substituted for another.

The FDA then provides what it refers to as a "clear and flexible" framework for a follow-on sponsor to determine what data and information may be necessary, which is intended to reduce potential uncertainty during product development. As part of its proposed framework, the FDA recommends that all follow-on sponsors undertake threshold analyses to identify any differences between the end-users' (e.g., patients or caregivers) use the follow-on and the reference products. The three types of threshold analyses the FDA recommends includes:

- a side-by-side labeling comparison;
- a comparative task analysis of the manual and intellectual activities for end users interacting with both follow-on and reference products; and
- a physical comparison of the products and their container closure systems and/or delivery devices.

If there are no differences in presentation, the FDA believes it is likely that additional data will not be necessary to demonstrate interchangeability. If there are "minor design differences" (i.e., they do not affect an external critical design attribute), they will likely be viewed by the FDA as acceptable provided the data and information submitted to the FDA demonstrates the differences are, in fact, minor. If there are significant differences, the FDA recommends that the follow-on sponsor consider modifying the design to minimize the differences. If the product presentation is not redesigned, the threshold analyses results can be used to determine the need for additional data and information, if any, from additional studies, such as comparative use human factors studies.[6] In such circumstances, the FDA may require additional tests (e.g., *in vitro* or *in vivo* performance testing) and beyond what is described in the guidance depending on "a risk-based analysis" and will be determined on a case-by-case basis. Again, the FDA recommends early communication between the sponsor and the Agency on these issues.

[6] It is worth noting that the FDA considers comparative use human factor studies for interchangeability purposes to be different than human factor validation studies described in its Guidance for Industry and FDA staff tilted "Applying Human Factors and Usability Engineering to Medical Devices," with the FDA going so far as to state that validation studies "generally do not apply when evaluating interchangeability."

The FDA recommends that the follow-on sponsor carefully consider the presentation of the reference product and "generally should not seek licensure for a presentation for which the reference product is not licensed." As an example, the FDA provides that if the reference is marketed as a vial and a prefilled syringe, a follow-on should not seek approval for an auto-injector. While not outright prohibiting such large changes to presentation, the FDA further recommends that the follow-on sponsor who seeks to do so discuss the proposed presentation with the Agency early in product development and be prepared to show how such a change could still support interchangeability.

Post-Marketing Safety Monitoring

The FDA emphasizes the importance of "robust postmarketing safety monitoring" for all biological products, including biosimilar and interchangeable products. Such monitoring should evaluate the safety and effectiveness of the follow-on product with respect to the reference product and its class, previous studies of the follow-on product during development or clinical use in other countries, and the specific conditions of use and features of the target patient population. The FDA also requires that adequate pharmacovigilance mechanisms be in place for interchangeable products. Finally, the FDA warns that, as with any biologic product, the Agency may require a post-marketing study or a clinical trial to evaluate such risks.

Implications

While the FDA (and the courts) has delved into the issue of bioavailability and other aspects of the BPCIA (e.g., the patent litigation process) in the six years since Congress passed the law, the issue of interchangeability has not substantively been addressed until now with this draft guidance.

The FDA's draft interchangeability guidance provides a detailed, yet relatively flexible, set of observations and recommendations with respect to the process by which a sponsor can establish a follow-on product is interchangeable with a reference product. Generally speaking, the FDA's approach to interchangeability is conceptually similar to that for biosimilarity as it examines the totality of the circumstances and analyzes residual risks. Unsurprisingly, the FDA repeatedly encourages discussion between the follow-on sponsor and the Agency early and often throughout the development process of a follow-on biologic product. As was the case for biosimilarity, the FDA is likely to provide additional guidances that clarify and expand upon interchangeability.

The draft is a significant step forward in the FDA's progress toward full implementation of the regulations required by BPCIA. However, the subject remains one of first impression for all involved in biologics. As of March 2017, only four biosimilars have been approved, and none have been deemed interchangeable. Even in the EU, where a biosimilars approval system has been in place for years, there are no interchangeable products on the market. Indeed, many are concerned that interchangeability will be difficult, if not impossible, to demonstrate because of deficiencies in the current analytical technology.

While biosimilars and interchangeable biologics have been touted as an effective means for significantly lowering drug costs, the jury is still out. The small molecule generic industry had similar growing pains when the Hatch-Waxman Act was first enacted three decades ago, and the hope is the interchangeable biologics will rise to the same level of savings achieved as in the generic industry. However, such benefits of follow-on biologics may not be realized until years from now.

Practitioners in this area have been advising a "wait and see" approach to how the ultimate scope of the BPCIA will be determined. This guidance has not changed that overall message, but does provide a start in the right direction. This could be the year more certainty is provided related to the application of the BPCIA, which could provide a more efficient and cost-effective pathway to market for follow-on biologics.