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Legal Update
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FDA Issues Guidance on Interchangeable Biosimilars

Introduction

The US Food and Drug Administration ("FDA") has issued long-awaited draft guidance addressing the standards for demonstrating interchangeability of biological products under the Biologics Price Competition and Innovation Act of 2009 ("BPCIA").

The BPCIA amended the Public Health Service Act to create an abbreviated pathway for FDA licensure of biologics 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 can be expected to produce the same clinical result as the reference product and if the risk—in terms of safety or diminished efficacy of switching the two products in the same patient—is no greater than when administering the reference product. Such a product may be substituted for the reference product without the intervention of the prescribing health care provider.

To date, FDA has issued a number of guidances addressing the standards for establishing biosimilarity, but this is the first guidance FDA has issued addressing the higher standard for interchangeability.

General Principles

In assessing interchangeability, FDA generally intends to follow the "totality of the evidence" and "residual uncertainty" approaches taken in its earlier series of guidances addressing Quality Considerations, Scientific Considerations and Questions and Answers for biosimilarity under the BPCIA.

To that end, FDA expressly recognizes that the type of data submitted "may vary depending on the nature of the proposed interchangeable product." Such information may include evaluation of quality attributes, analytical differences in the molecules, mechanisms of action, biodistribution in differing patient populations and toxicities. Where there are differences in these parameters, FDA will require the sponsor to establish a scientific justification for why such differences do not preclude a showing of interchangeability. FDA tempers that requirement by allowing for the possibility of extrapolation for certain of the data supporting a demonstration of interchangeability. FDA will also allow a sponsor to seek an interchangeability finding for less than all of the approved uses of the reference product but recommends that the sponsor seek licensure for all such uses "when possible." FDA also specifies that it will expect data from switching studies to support an analysis of the risks of switching and that sponsors should take into account the effects of any differences in the product's presentation on the appropriate use of the product.

FDA then discusses in detail a variety of issues related to the data a sponsor may generate and use to support the principal findings required to establish interchangeability.

Product-Dependent Factors

FDA recommends that sponsors use a stepwise approach to assess interchangeability considerations, beginning during product development. Specifically, at each step, the sponsor should evaluate whether and to what extent there may be residual uncertainty on an individual issue concerning interchangeability and should identify next steps to try to address that uncertainty. Areas in which residual uncertainty may need to be addressed may include the complexity of the molecule in question and capabilities of current analytical techniques to characterize the molecule, as well as product-specific immunogenicity risks. 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.

Impact of Biosimilar Product Postmarketing Data

FDA acknowledges that the tools for evaluating outcomes are continuing to improve, but, at this point, the agency believes that current techniques for assessing postmarketing data collected from products first licensed and marketed as a biosimilar would not be sufficient to support a demonstration of interchangeability in a number of areas. For example, the data would be insufficient for determining the pharmacokinetics (PK) and pharmacodynamics (PD) of switching between the proposed interchangeable product and the reference product. However, FDA notes that, in certain circumstances, postmarketing data from a licensed biosimilar product may be helpful as a factor when considering what data is necessary to support a demonstration of interchangeability. FDA cites, as an example, real-world data related to actual patient experiences in biosimilar switching scenarios. FDA also notes that postmarketing data on the actual use of a licensed biosimilar could help assess residual uncertainty involving immunogenicity. FDA encourages sponsors to discuss with the agency their plans for the possible use of such data.

Switching Study Design Considerations

FDA provides detailed observations and recommendations on multiple aspects of switching study design, including endpoints, sample size, sampling of PK/PD, population route of administration, number and duration of studies and integrated study design. Switching studies should evaluate changes in treatment that result in two or more switch intervals and, in the long course of therapy, should take into account dropouts and the scientific bases for addressing the possibility of missing data. An immune response or adverse event during a switching study could have a carryover effect, making it difficult to asses which product may have been the cause. Finally, FDA emphasizes that it takes a flexible approach to designing switching studies and that actual study designs should be assessed in consultation with FDA on a case-by-case basis.

Extrapolation of Data

If the proposed product meets the statutory requirements for interchangeability in a particular use, the sponsor may seek licensure for additional uses by extrapolation. The sponsor would need to provide sufficient scientific justification for extrapolation. FDA specifies a number of issues that should be addressed, including mechanism of action, biodistribution, immunogenicity and toxicity. To that end, FDA recommends that sponsors consider choosing a condition of use study that would enable later extrapolation.

Use of a Reference Product in Switching Studies

The reference product used in a switching study for the purpose of establishing interchangeability should be a biological product that is licensed in the United States. FDA distinguishes the situation in which a non-US product is used as a comparator in a study to establish biosimilarity, because, in that situation, the comparator product serves only as a control. In contrast, in a switching study, the reference product is used in both the active switching arm and the control switching arm. The repetitive administration necessary in a switching study could exacerbate a difference that might not rise to the level of consideration when the comparator is merely a control in a biosimilarity study. For example, a subtle difference in immunogenicity might prime the immune system over repeated switching, and the immune response could be increased in those circumstances. FDA ultimately states that sponsors would need to provide adequate scientific justification for using a non-US licensed comparator product in a switching study for the purpose of demonstrating interchangeability.

Presentations for Interchangeable Products

FDA acknowledges that the data necessary to support a demonstration of interchangeability may also be influenced by the proposed product's presentation, meaning the container closure system and/or delivery device constituent part of the product. As a threshold matter, FDA notes that the use of a biologic generally involves a sequence of steps because the products are injected or infused into the body, and they may be administered by health care providers, patients and/or caregivers. Thus, the tasks necessary to administer the product could vary considerably depending on the design of the presentation. FDA allows that differences in the design may be acceptable, provided that the differences are analyzed appropriately and there is data demonstrating that the changes do not negatively impact the ability of end users to use the products appropriately when one is substituted for another. To that end, FDA prescribes a series of analyses that should be undertaken to meet these goals, including a threshold analysis of any differences as well as studies to evaluate any such differences that may be found to be significant. FDA also states that in certain circumstances *in vitro* or *in vivo* performance testing may be necessary.

Postmarketing Safety Monitoring

FDA emphasizes the importance of "robust safety monitoring" for all biological products, including biosimilar and interchangeable products. Such monitoring should take into consideration concerns for safety and efficacy raised with respect to the reference product and its class, the proposed interchangeable product in development, the specific conditions of use and features of the target patient population. Adequate pharmacovigilance mechanisms should be in place, and FDA warns that, as with any biologic, the agency may require a postmarketing study or a clinical trial to evaluate such risks.

Conclusion

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 biosimilar as interchangeable. As noted by FDA, the general approach to the interchangeability analysis is conceptually similar to that for biosimilarity in that it examines the totality of the circumstances and analyzes residual risks. Not surprisingly, given the complexity and relative novelty of the subject, FDA repeats throughout the draft guidance that sponsors should consult with FDA on these issues early and often.

The draft is a significant step forward in FDA's progress toward full implementation of the regulations required by BPCIA. The subject remains one of first impression for most, if not all, stakeholders. To date, only four biosimilar products have been approved, and none has been found interchangeable. Indeed, many commentators have assessed that the possibility of finding interchangeability will be difficult to impossible given current technology. Nevertheless, the possibility of interchangeable biologics has captured the attention of many stakeholders, resulting in machinations such as scores of state legislatures passing various forms of legislation allowing for the substitution of interchangeable biosimilars under a variety of conditions. While the eventual licensure of biosimilars as "interchangeable" implicates many of the same hopes and fears as the first generics did in the small molecule industry, it appears that such licensing may remain far in the future.

Finally, interchangeability is not the only aspect of the BPCIA that is still in various stages of development and interpretation. As reported in a recent Mayer Brown Docket Report, the Supreme Court has granted *certiorari* in a case concerning the patent litigation provisions of the BPCIA, which many refer to as the "patent dance."

Thus, for the time being, the ultimate scope of the BPCIA remains to be decided.

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