FDA Releases Additional Guidelines for Biosimilars

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Shortly after approving the first biosimilar under the abbreviated approval pathway created by the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), the FDA has recently issued 3 final guidances regarding biosimilars.

Background

Biological products, or "biologics," are pharmaceutical products created from biological sources. Unlike chemically synthesized pharmaceuticals, biologics are isolated from natural sources, and are typically more complex than conventional pharmaceutical drugs.

The BPCIA provides abbreviated pathways for the FDA to approve two types of follow-on biologics: biosimilar and interchangeable biological products. Similar to the 1984 Hatch-Waxman Act's abbreviated pathway for pharmaceuticals, the BPCIA allows a sponsor to seek approval of a "biosimilar" product under section 351(k) of the Public Health Service Act ("PHS Act") by relying on certain existing scientific knowledge about the safety, purity, and potency of the reference product. The BPCIA defines "biosimilar" as (1) "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and (2) having "no clinically meaningful differences between the biosimilar product and the reference biological product in terms of the safety, purity, and potency of the product." To meet the higher standard of "interchangeability," the application must further show (1) the biosimilar is expected to produce the same clinical result as the reference product and (2) a patient can switch back and forth between the biosimilar and the reference product with no adverse effects.

The FDA has been slow to accept and approve biosimilar applications, which has left open questions about how to establish biosimilarity and interchangeability under the statutory definitions. On April 28, 2015, the FDA finalized three draft guidances originally published in 2012:

- **Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009**
- **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**
- **Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product**

The new guidances provide insight into the FDA requirements for establishing biosimilarity.

**Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009**

This final guidance addresses three categories of commonly asked questions regarding FDA implementation of the BPCIA: (1) biosimilarity or interchangeability; (2) definitions relevant to the BPCIA; and (3) exclusivity.

With regard to biosimilarity or interchangeability, the guidance states that a proposed biosimilar may have a different formulation, delivery device, or container closure than the reference product under certain circumstances. Additionally, the guidance discloses conditions permitting an applicant to obtain licensure for fewer than all routes of administration, presentations, and conditions of use for which the reference product is licensed. Further, the guidance describes conditions in which a sponsor may support biosimilarity using comparative data with a non-U.S.-licensed product or extrapolated clinical data designed to support a different condition of use. The guidance additionally instructs applicants how to describe the "strength" of a proposed injectable biosimilar. Finally, the guidance states
that a biosimilar product that cites a reference product subject to the Pediatric Research Equity Act must include a pediatric assessment unless the applicant initially seeks approval as an interchangeable biological product.

With regard to the BPCIA’s definition of “biological product,” the guidance discloses the FDA’s regulatory definitions of “protein” and “chemically synthesized polypeptide.” Additionally, it defines when a proposed biological product is considered to be within the same “product class” as previously approved protein products.

With regard to exclusivity, the guidance instructs applicants and sponsor to search an online database, available here, to identify whether the reference product is subject to unexpired orphan exclusivity. The FDA will not approve a biosimilar during the 7-year exclusivity period.

**Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**

This final guidance provides an overview of the FDA’s recommendations for establishing biosimilarity and discusses in detail relevant scientific principles for designing data and information to show biosimilarity. The FDA stresses that it will apply a totality-of-the-evidence approach in its assessment of biosimilarity and will use a risk-based approach to evaluate all data and information submitted. The FDA further emphasizes that the information sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

The BPCIA requires an application to include analytical, animal, and clinical studies demonstrating that the biological product is “biosimilar” to a single reference product. As discussed above, the application must establish the product is “highly similar” to the reference product and has “no clinically meaningful differences.” Although the reference product must be U.S.-licensed, the application may rely on data from comparative studies with a non-U.S. licensed comparator product if the data is scientifically relevant. Because the FDA has discretion to determine what data is required to establish biosimilarity in a particular application, it encourages sponsors of the application to meet with the FDA early during product development to discuss adequate scientific justifications.

The FDA encourages sponsors to use a three step approach to develop evidence necessary to establish biosimilarity.

**First,** the sponsor should characterize the structural and functional aspects of both the proposed product and the reference product to identify potentially clinically relevant safety or efficacy risks. Structural analyses must use “state-of-the-art technology” to analyze multiple representative lots and show the proposed product will encode the same primary amino acid sequence as the reference product. Any minor modifications must be explained by the sponsor. The structural analyses for all relevant characteristics of the protein product (such as primary, secondary, tertiary, and quaternary structure; posttranslational modifications; and biological activities) must also be included. The FDA further recommends structural analysis of the finished dosage form to assess the effect of excipients or any other formulation effects. In vitro and/or in vivo functional assays must also be used to evaluate the pharmacologic activity of protein products.

**Second,** the sponsor should demonstrate safety and biosimilarity through animal studies. These studies generally do not establish safety, but are relevant to support the demonstration of biosimilarity through evidence of PK and PD measures. Nevertheless, animal toxicity and immunogenicity studies may be useful where uncertainty about safety remains after the initial structural and functional characterization.

**Third,** the sponsor should conduct comparative human PK and PD studies and a clinical immunogenicity assessment of the two products in an appropriate study population. The sponsor should discuss study proposals and overall clinical development plan with the FDA before initiating such studies. A sponsor should provide adequate scientific justification for choices in study design, population, endpoints, and other parameters. Human PK and PD measures comparing the proposed product to the reference product are typically fundamental to demonstrate biosimilarity. Even where relevant PD measures are not available, sensitive PD endpoints may be assessed. The FDA further expects at least one comparative clinical study regarding immunogenicity in order to assess the safety and effectiveness of the proposed product. The overall immunogenicity assessment should consider the nature of the immune response, the clinical relevance and severity of consequences, the incidence of immune responses, and the population being studied. Generally, the FDA expects studies to present statistical evidence that the proposed product is neither
significantly inferior nor superior to the reference product. An applicant may provide sufficient scientific justification to extrapolate clinical data to support a determination of biosimilarity for various indications.

If there is uncertainty at each step, the sponsor should evaluate the uncertainty and consult with the FDA to adequately address it.

Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product

This guideline relates to the biosimilarity of therapeutic protein products and describes nine factors that are relevant in developing analytical studies to show a proposed product is “highly similar” to a reference product.

1. **Expression System.** The application should seek to minimize differences between the proposed and referenced expression systems. The FDA expects the expression construct for a proposed product encodes the same primary amino acid sequence as its reference product. However, minor modifications (such as N- or C-terminal truncations) that are not expected to change the product performance may be justified.

2. **Manufacturing Process.** The application should demonstrate its manufacturing process does not result in significant differences between the proposed product and its reference product.

3. **Assessment of Physiochemical Properties.** Physicochemical assessments are designed to maximize the potential for detecting differences between the proposed and reference products. The sponsor should consider all relevant characteristics of the protein product and design tests to account for the heterogeneity of the proposed product and the reference product as well as the ranges of variability for each.

4. **Functional Activities.** Functional assays are designed to complement physicochemical analyses and evaluate the function of the protein product. Sponsors should perform appropriate assays to evaluate the range of relevant functional activities for a product.

5. **Receptor Binding and Immunochemical Properties.** Sponsors should analyze specific binding or immunochemical properties when they are part of the activity attributed to the protein product.

6. **Impurities.** Sponsors should characterize, identify, and quantify impurities in the proposed product and reference product. Sponsors should further perform a risk-based assessment regarding any differences in process-related impurities between the proposed and reference products.

7. **Reference Product and Reference Standards.** Sponsors should provide a broad comparison of the proposed product to the reference product that is not strictly limited to analysis of each product in isolation. For example, the biosimilarity analysis may further consider applicable reference standards and relevant publicly available information.

8. **Finished Drug Product.** Product characterization studies should be performed on the most downstream intermediate best suited for each analytical procedure. Thus, sponsors should analyze the finished drug product if it is best suited for a particular analysis. If the analysis is performed on an earlier intermediate, sponsors should provide additional information. Additionally, sponsors should clearly identify excipients used in the proposed product that differ from those in the reference product.

9. **Stability.** Sponsors should include comparative studies conducted under multiple stress conditions to establish degradation profiles of the proposed and reference product.

Conclusion

The recently issued final guidances provide insight into how the FDA will evaluate biosimilarity and directions for sponsors throughout product development. However, many additional questions surrounding the BPCI Act remain. For example, the currently issued guidances do not address how the FDA will determine “interchangeability.” Interchangeable drugs are likely to be more profitable than mere biosimilars because they can be sold in place of the reference drug without a prescribing doctor’s approval.
Upcoming draft guidances plan to provide additional information regarding the required scientific requirements for establishing biosimilarity and interchangeability as well as naming and labeling requirements for approved biosimilars. In January, the FDA’s Center for Drug Evaluation and Research (CDER) announced plans to publish five draft guidances on biosimilars in 2015:

- Considerations in Demonstrating Interchangeability to a Reference Product
- Labeling for Biosimilar Biological Products
- Nonproprietary Naming for Biological Products
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity

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