US FDA Releases Draft Guidances for Biosimilars

The United States Food & Drug Administration (FDA) issued three highly anticipated draft guidelines for biosimilar products on 9 February 2012:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product ("**Scientific Considerations**")
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product ("**Quality Considerations**")
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 ("**Biosimilar Q&A**").

Background

The Biologics Price Competition and Innovation Act ("**BPCI Act**"), enacted as part of the Affordable Care Act on March 23, 2010, is intended to create an abbreviated approval pathway for biological products that can be demonstrated to be biosimilar to, or interchangeable with, a biological products previously approved by the FDA (called "**reference**" products). Under the BPCI Act, a proposed biological product that is demonstrated to be biosimilar to the reference drug can rely on existing scientific knowledge about the safety, purity, and potency of the reference product to support licensure through the streamlined approval pathway.

The FDA has now issued draft guidance documents describing its requirements for biosimilarity (but not for interchangeability). Highlights of the guidance documents are provided below.

Scientific Considerations Guidance

The Scientific Considerations Guidance is intended to assist applicants in demonstrating that a proposed product is biosimilar to a reference product for purposes of submitting a so-called "351(k)" marketing application for approval by the FDA.

The guidance presents an overview of the FDA's approach to determining biosimilarity, consistent with a longstanding Agency approach to evaluation of scientific evidence. The FDA will consider the ***totality of the evidence*** provided by a sponsor to support a demonstration of biosimilarity, and recommends that sponsors use a ***stepwise approach*** in their development of biosimilar products, encouraging applicants to meet early with the FDA to discuss their development plans.

Data supportive of a demonstration of biosimilarity include:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and

- Clinical studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

Quality Considerations Guidance

The Quality Considerations Guidance identifies analytical studies that may be relevant to assessing whether the proposed biosimilar protein product and a reference product are "highly similar." The guidance describes general principles of conducting a robust characterization of the proposed biosimilar product in assessing biosimilarity with the reference drug, identifying several factors for consideration in assessing whether products are highly similar:

- Expression system;
- Manufacturing process;
- Assessment of physiochemical properties;
- Functional activities;
- Receptor binding and immunochemical properties;
- Impurities;
- Reference product and reference standards;
- Finished drug product; and
- Stability.

The FDA specifically refrained from elaborating its approach to determining interchangeability since it is "continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product."

Biosimilar Q&A Guidance

The FDA also issued a series of questions and answers regarding implementation of the BPCI Act. This tool provides a general insight into the FDA's proposed approach to licensing biosimilar products. Three broad categories of information are addressed:

- Biosimilarity or interchangeability;
- Provisions related to the requirement to submit a BLA for a "Biological Product"; and
- Exclusivity.

Conclusion

This long-awaited development provides an initial roadmap to the FDA's current thinking on biosimilarity assessment for follow-on biological products. However, given the lack of detail, much is left to the FDA's discretion as it will assess biosimilar products on a case-by-case basis. Although more flexible for the FDA, it does not provide the regulatory certainty that a more detailed approach would have provided, such as, for example, the requirements issued by the European Medicines Agency.

Many questions about how the process will work in practice remain to be fully addressed, leaving industry participants to wait for the issuance of further guidelines (such as on interchangeability and exclusivity), and to closely watch how the FDA handles of the first applications to make use of the new approval pathway.

The FDA encourages industry stakeholders to provide comments on the draft guidance documents within **60 days** of 13 February 2012.

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