FDA Publishes Draft Guidelines for Biosimilar Product Development

By James DeGiulio --

The U.S. Food and Drug Administration published its long-awaited draft guidance on the development of biosimilar products today (*see* FDA press release), taking a significant step toward the utilization of § 351(k) of the Public Health Service Act (amended by the Biologics Price Competition and Innovation Act (BPCIA)). Section 351(k) creates a biologics pathway that is reminiscent of the pathway set forth by the Hatch-Waxman Act for small molecule drugs. The FDA promised that it would release the guidance materials by the end of 2011, but failed to meet this deadline, most likely due to the complexities of the many issues surrounding biosimilar products. The agency indicates that these guidance documents provide the FDA's current thinking on key scientific and regulatory factors involved in submitting applications for biosimilar products. As expected, the FDA is seeking public comment on each of draft guidance documents within 60 days of the notice of publication in the Federal Register.

The BPCIA and section 351(k) have been in force since March 2010. However, without any indication as to how the statute will be implemented by the FDA, the pathway has not gained much traction as an alternative to filing a full Biologics License Application (BLA) for a biologic under the PHSA (42 U.S.C. § 262). Today's guidance documents provide some direction to companies involved in biosimilar development regarding the factors the FDA will use to evaluate whether to grant a license to their biosimilar products in the United States, despite the draft status of the guidance documents. Now the biologics industry awaits public notification of the first 351(k) application filing, which under the statute, would set in motion a complex exchange of documents pertaining to the biologic, eventually progressing to litigation between the reference drug BLA holder and the 351(k) biosimilar applicant.

The FDA published the following three draft guidance documents:

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

The first guidance document is intended to assist companies in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting a 351(k) application. As the FDA hinted last year, a stepwise approach to demonstrate biosimilarity is suggested, beginning first with structural and functional assays, and followed up with animal and clinical studies. The FDA intends to evaluate such a demonstration based on a "totality-of-the-evidence," focusing on the assessment of the effects of any differences in the products, rather than requiring an independent safety determination of the biosimilar product. Following this determination, if the differences in the two products are not "clinically meaningful," the FDA will require fewer or narrower human studies. Also discussed briefly are post-marketing safety monitoring considerations.

2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

The second guidance document provides an overview of the analytical factors the FDA will consider when assessing biosimilarity between a 351(k) product and a reference product. Specific analytical factors include functional activities, expression systems/cell types, manufacturing processes, physicochemical and immunochemical properties, quality and quantity of impurities, stability, and drug-specific reference standards based on the scientific literature. These factors need not be identical between the biosimilar and reference product.

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

The third guidance document provides answers to common questions about the BPCIA, many of which were raised at the FDA's public hearings on biosimilars on November 2-3, 2010. The question and answer format addresses primarily administrative questions that may arise during biologic product development, particularly in early stages leading up to BLA or 351(k) application filings. Questions are directed to the timing and content of FDA meetings, allowable differences in the formulation/delivery from the reference product, varying scope of the FDA licenses, the types of data that a biosimilar applicant can rely on in their application, and questions regarding exclusivity under 351(k)(7).

Patent Docs will provide a more detailed analysis of each of these guidance documents in future posts.