FDA Issues Highly Anticipated Draft Guidance on Biosimilars

On February 9, 2012, the US Food and Drug Administration (FDA) issued three draft guidance documents regarding biosimilars (a/k/a follow-on biologics). These documents reflect the agency's attempt to assist applicants seeking approval of a proposed biologic product under the abbreviated approval pathway set forth in the statute known as the Biologics Price Competition and Innovation Act (BPCI Act).

The BPCI Act was enacted on March 23, 2010, as part of the Patient Protection and Affordable Care Act (Affordable Care Act). It amends the Public Health Service Act (PHS Act) and creates an abbreviated pathway for biological products that are demonstrated to be “highly similar” or interchangeable with a reference biological product (e.g., antibodies, blood and blood components, proteins, vaccines) that has already been approved or “licensed” by the FDA. The relevant text of the BPCI Act can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf.

The three guidance documents describe key scientific and regulatory factors involved in submitting applications for biosimilar products for agency approval (351(k) applications). The FDA will formally notice the guidance documents in the Federal Register, and then the public can comment within 60 days.

Following the enactment of the BPCI, members of the pharmaceutical and biotechnology industries have anxiously awaited FDA guidance. Compared to the manufacturers of conventional small molecule drugs, biosimilar manufacturers face greater technical barriers to entry, more complicated manufacturing processes, and—without an analog to the “Orange Book”—significant uncertainty about the number of patents that may cover the reference biologic product. Consequently, the FDA's guidance has been heralded both as a set of rules for filing new applications and as the agency's attempt to implement a plan that strikes a balance among the competing goals of innovation, competition, affordable healthcare and patient safety.

The first guidance document, entitled, “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” focuses on therapeutic protein products and describes the FDA's risk-based approach in evaluating 351(k) applications. At the outset, the FDA's approach requires an evaluation of the “totality of the evidence.” Not surprisingly, the scale and content of the evidence that will pass muster will be determined on a product-specific basis.

The FDA further discusses a “stepwise approach” to demonstrating biosimilarity. Among other things, the FDA provides guidelines pertaining to the analysis of (i) structure, (ii) function, (iii) animal data (e.g., toxicity, PK and PD measures, and immunogenicity), and (iv) human data (e.g., pharmacokinetics, pharmacodynamics, clinical immunogenicity, clinical safety and effectiveness, clinical study design and the extrapolation of human data across indications). The FDA further mentions the significance of
postmarketing monitoring and consultation with the agency throughout the development process.

In addition, the FDA sets forth a listing of terminology. Among the list of terms are the agency’s definitions for the terms “protein” and “chemically synthesized polypeptide” as used in the BPCI Act to amend the definition of biologic product set forth in Section 351(i) of the Public Health Service Act (42 U.S.C. 262(i)). According to the FDA’s guidance:

- “Protein” means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.
- “Chemically synthesized polypeptide” means any alpha amino acid polymer that is (i) made entirely by chemical synthesis and (ii) less than 100 amino acids in size.

While the FDA notes that, in general, a sponsor must provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product (e.g., analytical studies and at least one human PK and/or PD study intended to support a demonstration of biosimilarity must include an adequate comparison to the reference product licensed under section 351(a)), the agency makes clear that, under certain circumstances, a sponsor may seek to use data comparing a proposed product with a non-US-licensed product. For example, data derived from animal or clinical studies of a non-US-licensed product might be used to address, in part, the requirements under section 351(k)(2)(A). To do so, the sponsor must further provide evidence establishing an acceptable bridge to the US-licensed reference product.


The third guidance document, entitled, “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,” attempts to answer questions from 351(k) applicants. The questions are grouped into the following categories: (i) biosimilarity or interchangeability, (ii) requirements for submitting a BLA for a “biological product” and (iii) exclusivity.
The first section addresses practical questions when seeking to obtain licensure for a biosimilar product. Representative questions include:

- Can a proposed biosimilar product have a different formulation than the reference product?
- Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?
- Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?
- Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?
- Can a sponsor use comparative animal or clinical data with a non-US-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?
- Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed?

The proposed answers to all of the preceding questions is “yes,” albeit with further qualifications and cautions from the FDA specific to each question. There are many other questions in this first section, each of which has a different answer and explanation.

In the second section, the FDA provides, among other things, insight into how it interprets terms such as the category of “protein (except any chemically synthesized polypeptide)” in the amended definition of “biological product” in section 351(i)(1) of the PHS Act and how it defines “product class” for purposes of determining whether an application for a biological product may be submitted under section 505 of the Food Drug and Cosmetic Act. Finally, the third section of this draft guidance discusses whether an applicant can include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS and how to determine whether there is an unexpired orphan exclusivity for an indication.


With some estimating biologics comprising more than half of the top-ten selling drugs by 2014, the FDA’s proposed scheme is far-reaching and will undoubtedly lead to further concerns and questions by industry over the next several months.

For more information about the Guidance or any other matter raised in this Legal Update, please contact any of the following lawyers.

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