Cooley

February 16, 2012

On February 9, 2012, the Food and Drug Administration released three long-awaited "draft" industry Guidances concerning Biosimilars, also known as Follow on Biologics. The draft Guidance documents provide in broad strokes the FDA's proposal for its implementation of the Biologics Price Competition and Innovation Act (BPCIA) of 2009, which created an abbreviated pathway for approval of biosimilar products. The Guidances generally address quality and scientific data considerations to demonstrate biosimilarity to Innovators' Reference Products.

The BPCIA was enacted as part of the Patient Protection and Affordable Care Act (Affordable Care Act) (Pub. L. 111–148) on March 23, 2010. The BPCIA amended the Public Health Service Act (PHS Act) and other statutes to create an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product. The objectives of the BPCIA are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the ‘‘Hatch-Waxman Act''), which established abbreviated pathways for the approval of generic drug products under the Federal Food, Drug, and Cosmetic Act. However, the regulatory pathway created by the BPCIA is notably different from the Hatch-Waxman Act, in large part due to the recognition that, unlike the drugs covered by Hatch-Waxman, Biosimilars will not be identical to the reference product. In brief, the FDA revealed in its Guidances its flexibility in implementing standards for biosimilarity, as well as its willingness to work with parties closely during the application process. Interesting highlights from each Guidance are summarized below.

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

As stated by the FDA: "This guidance provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA's interpretation of the [BPCIA]."

The draft (non-binding) Guidance provides questions and answers on a variety of topics related to implementation of the BPCIA. Highlights of the questions and answers include:

Planning meeting with the FDA—FDA recommends that Biosimilars sponsors request an initial meeting with the FDA at the time the sponsor can provide a description of its Biosimilars plan, the manufacturing process and preliminary comparative analytical data with the reference product.

Formulations, Routes of Administration, and Indications—In what may develop as a counterpart to the "skinny label" (i.e. "carve-out") provision of the Hatch Waxman Act, the FDA proposes that an applicant may seek a license for a biosimilar product (1) for a different formulation than the reference product, provided there are no clinically meaningful differences between the Biosimilar and the reference product in terms of safety, purity, and potency; (2) for fewer than all routes of administration for which an injectable reference product is licensed, provided there are no clinically meaningful differences between the proposed product and the reference product; and (3) for fewer than all indications for which the reference product is licensed.

Interchangeability—FDA indicates that it can make determinations of interchangeability but cautions that "at this time it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability." The FDA acknowledges that it is continuing to assess information to enable a determination that a biological product is interchangeable with the reference product.

New regulatory definitions—FDA also provides new regulatory definitions of *"protein"* and *"chemically synthesized polypeptide"* to assist in defining a "biological product." Biological product is defined to include a "protein (except any chemically synthesized polypeptide)." A *"chemically synthesized polypeptide"* means "any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in

size." Compounds greater than 99 amino acids will be scrutinized to determine whether they are related to shorter natural peptides. Accordingly, chemically synthesized compounds less than 100 amino acids in length would appear presumptively to fall under the Hatch-Waxman abbreviated pathway for Drugs.

Reference product exclusivity—FDA also acknowledges that a BLA applicant can include a request for reference product exclusivity but that FDA is continuing its review of reference product exclusivity provisions and there is a request for public comment to consider FDA's construction of the statutory provisions (see Docket No. FDA-2010-N-0477).

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

This draft Guidance provides an overview of the analytical factors that a sponsor should consider when assessing "biosimilarity between a proposed therapeutic protein product and a reference product." The Guidance also describes the FDA's current thinking on the scientific and technical information of the chemistry, manufacturing, and controls (CMC) section of the marketing application.

The Guidance provides a useful list of factors that a sponsor should consider when assessing the similarity of its proposed products including:

- Expression system
- Manufacturing process
- Physicochemical properties
- Functional activities
- Receptor binding and immunochemical properties
- Impurities
- Characterization of the reference product and reference standards
- Characterization of the finished drug product
- Stability

Importantly, the Guidance makes clear that FDA is *not* providing an overview of its approach to determining interchangeability (contrasted with biosimilarity) because "FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product."

The Guidance further directs that all applications should "contain a complete and thorough CMC section" and that other companion Guidances should be consulted for information to include in the CMC section. Additionally, FDA advises that "robust" comparative physicochemical and functional studies be performed and a detailed description of the methods used (and their limitations) accompany the application.

The Guidance also provides insight on the use of data derived from animal or clinical studies comparing a proposed product with a non-U.S. licensed product to address regulatory requirements. Specifically, FDA suggests that a sponsor provide "adequate data or information" to justify the relevance of the data in assessing biosimilarity and to establish an "acceptable bridge" to the U.S. reference product while further noting that the bridge is likely to include comparative physicochemical characterizations, bioassays/functional assays, and comparative clinical and/or nonclinical pharmacokinetic and/or pharmacodynamic data and any differences in primary packaging. Here and in other portions of the Guidances, FDA encourages early and ongoing discussions with the FDA to shepherd the process.

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

This guidance describes the FDA's proposed framework to determine biosimilarity using its longstanding approach of evaluating scientific evidence. The guidance indicates that the FDA will consider the "totality of the evidence" submitted by a sponsor and "recommends" that sponsors "use a stepwise approach" in developing products.

According to the FDA, by following a stepwise approach, a sponsor should include:

Structural analysis—FDA recommends using "state-of-the-art" technology showing, for example, primary and higher order structures, post-translational modifications, and intentional chemical modifications. As part of this analysis, FDA recommends that sponsors "analyze the finished dosage form of multiple lots of the proposed product and the referenced product" and assess excipients and formulation effect on purity, product- and process-related impurities and stability. FDA also notes that if a product cannot be adequately analyzed using state-of-the-art technology that the sponsor should consult FDA for guidance on whether the proposed product is suitable for submission under section 351(k).

Functional assays—FDA provides several examples of appropriate studies including bioassays, biological assays, binding assays and enzyme kinetics. FDA recommends that any functional assays performed should be comparative "so they can provide evidence of similarity, or reveal differences, in the performance of the proposed product compared to the reference product, especially differences resulting from structural variations that cannot be detected using current analytical methods."

Animal data—FDA suggests that an applicant perform toxicity studies, pharmacokinetic and pharmacodynamic measurements, and immunogenicity studies. FDA provides several suggestions that may narrow the scope of animal studies. For example, the Guidance notes that animal toxicity studies are not useful if there is no animal species that can provide pharmacologically relevant data for the protein product. Additionally, the Guidance details the scope and extent of any animal toxicity studies will depend on the body of information available and that if toxicity studies are not warranted, additional comparative in vitro testing, using human cells or tissues may be warranted. The Guidance also notes that nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not warranted when the proposed protein product has been demonstrated to be highly similar to the reference product through structural and functional characterization and animal toxicity studies.

Human Clinical studies—FDA also recommends that an applicant include as part of the application pharmacokinetic and pharmacodynamic measurements, immunogenicity results, and safety and efficacy data. FDA notes that clinical studies should be "designed to demonstrate that the proposed product has neither decreased nor increased activity compared to the reference product." The Guidance indicates that, unless justified otherwise, FDA expects that a sponsor will present comparative human pharmacodynamic studies. FDA also recommends that sponsors provide scientific justifications for the size and length of their clinical trials to demonstrate sufficient exposure to the proposed product and the reference product along with the detection of relevant safety signals and clinically meaningful differences in effectiveness and safety between the proposed and referenced products.

Additional details are described in the Guidance that will help shape the scope and extent of the scientific data necessary to place the sponsor in a position to support its scientific application and request for market approval.

The newly released draft FDA Guidances provide substantial information regarding the FDA's current view regarding implementing the BPCIA. The Guidances are not meant to provide answers or solutions to the myriad issues that a Biosimilars sponsor or Reference Product Sponsor will face. Nonetheless, the Guidances provide a useful insight into how the FDA intends to implement the statutory requirements of the BPCIA.

The FDA has solicited comments and suggestions by April 16, 2012.

Please contact Cooley for additional information or assistance incorporating these Guidances into your biosimilar product strategies.

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