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FDA Issues Highly Anticipated Biosimilar Draft Guidance

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On Thursday, February 9, Food and Drug Administration issued three draft guidance documents related to the §351(k) approval pathway for biosimilars under the Biologics Price Competition and Innovation Act of 2009, a law that amended the Public Health Service Act to create an approval pathway for biosimilar and interchangeable versions of reference products (i.e. §351(k) applications). The issued guidance does not contain any surprises as most of the concepts have been aired in public meetings and other communications to and from FDA.

The BPCIA was enacted as part of the Affordable Care Act on March 23, 2010. It creates an abbreviated licensure pathway for biological products demonstrated to be biosimilar to, or interchangeable with, a reference product. Section 351(k) of the PHS Act (42 91 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) of the PHS Act defines biosimilarity to mean "*that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components*" and that "*there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product*." The BPCI Act also amended the definition of biological product to include "protein (except any chemically synthesized polypeptide)."

The draft guidance issued is: 1) Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, 2) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, and 3) Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. The draft guidance documents provide a general roadmap and an approach, but FDA will assess each proposed biosimilar on a case-by-case basis. The approach taken in the guidance documents is a "totality of evidence" approach, where all data will be considered, and multiple types of data may be required to be gathered, in assessing whether a proposed biosimilar product is sufficiently "similar" to a reference product to warrant approval.

The FDA is seeking public comment on each of the draft guidance documents within 60 days of the notice of publication in the Federal Register. To date, the notice has not been published. Comments may highlight crucial aspects of a particular technology or molecule and may be incorporated in the final guidance. One should review the issued draft documents carefully and consider the impacts it will have on the proposed biosimilar, and what data will need to be generated to meet the FDA requirements.

Summaries of the three guidance documents

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

This is the longest of the three guidance documents and addresses the issues that will be of greatest concern to companies, i.e. what is required scientifically to demonstrate that a proposed therapeutic protein product has met the threshold of "similarity" to a reference product.

This guidance discusses among other issues the following three key considerations in demonstrating biosimilarity:

- The FDA will take a stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness;

- The FDA will use a totality-of-the-evidence approach to review applications for biosimilar products; and

- The guidance document discusses the general scientific principles in conducting comparative structural and functional analysis, animal testing, human PK and PD studies, clinical immunogenicity assessment, and clinical safety and effectiveness studies (including clinical study design issues).

As noted above, the FDA intends to consider a "totality of evidence" approach when the Agency evaluates the sponsor's demonstration of biosimilarity, consistent with a longstanding Agency approach to evaluating scientific evidence. It should be noted that the guidance for industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998) provides insight to the concept of the totality-of-the-evidence approach in a different context (i.e., considerations of both the quantity and quality of the evidence to support effectiveness for drugs and biological products). Some of the principles discussed in the 1998 guidance may also be relevant in the design of a development program to support a demonstration of biosimilarity.

For both owners of the reference product and companies proposing a biosimilar product the discussion in Sections VI and VII of the guidance document will be of particular interest.

Section VI of the document concerns the FDA recommendations on a sponsor's use a stepwise approach to develop the evidence needed to demonstrate biosimilarity. That is, in evaluating a sponsor's demonstration of biosimilarity, the FDA will consider the totality of the data and information submitted in the application, including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and clinical safety and effectiveness data. It may be possible for a sponsor to demonstrate biosimilarity even though there are formulation or minor structural differences, provided that the sponsor provides sufficient data and information demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity.

Section VII of the document discusses scientific considerations in the stepwise approach to developing data and information needed to support a demonstration of biosimilarity, i.e. structural analysis, functional assays, animal data, and clinical studies. To demonstrate biosimilarity, a sponsor must provide sufficient data and information to show that the proposed product and the reference product are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency. Not all studies in all areas will necessarily be required to demonstrate biosimilarity, rather the type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

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

This guidance is essentially an FAQ concerning common questions for proposed biosimilar products. In addition this guidance document provides a brief background to the BPCIA.

The format of the document is a series of questions with proposed answers of "yes" or "no," along with further explanation or modification. The questions and answers are grouped in three categories: 1) Biosimilarity or Interchangeability; 2) Provisions Related to Requirement to Submit a BLA for a "Biological Product;" and 3) Exclusivity. For example, the FDA answers "yes" to each of the following from the first section:

- Can a proposed biosimilar product have a different formulation than the reference product?
- Can a proposed biosimilar product have a delivery device or container closure system that is different from its 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-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?

The second section of the guidance document addresses two questions:

- How does FDA interpret the category of "protein (except any chemically synthesized polypeptide)" in the amended definition of "biological product" in §351(i)(1) of the PHS Act?
- How is "product class" defined for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period?

The definition of "protein" provides the FDA's interpretation of this term as it applies to the amended definition of "biological product" in PHS Act §351(i)(1). In this context, the FDA defines "protein" as meaning any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size. The guidance indicates that "compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product." In contrast, the term "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. It should be noted that A chemically synthesized polypeptide, as defined, is not a "biological product" and will be

regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory definition of a "biological product."

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

This document provides recommendations on the scientific and technical information for the Chemistry, Manufacturing and Controls (CMC) section of a §351(k) application, as well as an overview of the analytical factors to consider in an assessment of biosimilarity between a proposed product and a reference product.

Per standard practice, those individuals and companies interested in providing comments and suggestions regarding the draft guidance should submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD, 20852. Comments must be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance, and comments should be identified with the docket number listed in the notice of availability.

Links:

FDA Press Release:
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf