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FDA Issues Draft Guidance Documents for Biosimilars

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On February 9, 2012, in a much anticipated press release, FDA announced the publication of draft guidance documents relating to the development of follow-on biologics for previously approved therapeutic proteins under the Biologics Price Competition and Innovation Act (the BPCIA). The guidance documents are general in nature and leave some questions unanswered, but represent the first step in removing uncertainties associated with the biosimilar approval pathway.

BACKGROUND

The BPCIA was signed into law on March 23, 2010, as part of the Patient Protection and Affordable Care Act (the Healthcare Reform Act), creating an FDA approval pathway for follow-on versions of biological products such as therapeutic proteins. It also provides exclusivity periods for reference biologic and certain follow-on products and a complex framework for resolving patent disputes between sponsors of the biosimilar product and the reference biologic product.

The BPCIA created a purportedly streamlined approval process and other similar provisions for follow-on biologics. Given the various complexities in structure and manufacturing processes, approval of a follow-on product under the BPCIA requires more than the showing of “bioequivalence” that is required for generic drugs. The sponsor of the follow-on biologic must demonstrate that it (i) is “*biosimilar*” to a reference product, (ii) uses the same mechanism of action, to the extent known for the reference product, and (iii) is being proposed for previously approved condition(s) of use. A biosimilar product may be deemed “*interchangeable*” if further requirements are met.

The BPCIA does not describe the necessary criteria for showing “high similarity” or “interchangeability,” or the nature of required clinical trials, analytical data, and animal studies. The BPCIA permits FDA to issue such guidance for individual products and product classes, including statements that certain products or entire product classes will not be approved under the pathway. Since the enactment of the BPCIA, the biotechnology industry has eagerly awaited the issuance of FDA guidelines on the approval requirements for follow-on biologics.

DRAFT GUIDANCE DOCUMENTS

The draft guidance documents issued on February 9, 2012, represent the first step by FDA in providing such guidelines. The documents are meant “to assist industry in developing [follow-on biologic] products in the United States.” They are publicly available on the FDA website. FDA is seeking public comment on the guidance documents within 60 days of the notice of publication in the Federal Register, which is expected to occur shortly.

Client Alert.

The three guidance documents are:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

SCIENTIFIC CONSIDERATIONS GUIDANCE

The draft scientific considerations 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 an application, called a “351(k)” application, to FDA.

The guidance recommends a stepwise approach for development of biosimilar products. It advises sponsors intending to develop biosimilar products to meet early with FDA to present their product development plans and establish a schedule of milestones to serve as landmarks for future discussions with FDA. The guidance recommends that the stepwise approach start with extensive structural and functional characterization of both the proposed product and the reference product, and then consider the role of animal data in assessing toxicity. In some cases, the applicant would need to provide additional support to demonstrate biosimilarity and contribute to immunogenicity assessment; conduct comparative human PK studies and PD studies, if there is a clinically relevant PD measure, in an appropriate study population; and compare the clinical immunogenicity, clinical safety, and effectiveness of the reference and follow-on biologic products.

The guidance describes a risk-based “totality-of-the-evidence” approach that FDA intends to use to evaluate the data and information submitted in support of a determination of biosimilarity of the proposed product to the reference product. Factors FDA may consider include:

- a) analytical studies that demonstrate that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- b) animal studies (including the assessment of toxicity); and
- c) a clinical study or 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 draft quality considerations guidance document provides an overview of analytical factors to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product for the purpose of submitting a 351(k) application. The document emphasizes the importance of extensive analytical, physico-chemical, and biological characterization in demonstrating that the proposed biosimilar product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components.

Client Alert.

According to the guidance, extensive, robust comparative physico-chemical and functional studies (which may include bioassays, biological assays, binding assays, and enzyme kinetics) should be performed to evaluate whether the proposed biosimilar product and the reference product are highly similar. It would allow, under certain circumstances, a sponsor to seek to use data derived from animal or clinical studies comparing a proposed protein product with a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the Public Health Service Act. In such a case, the sponsor would be advised to provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.

The draft guidance provides a number of factors manufacturers should consider, including: a) expression system; b) manufacturing process; c) assessment of physico-chemical properties; d) functional activities; e) receptor binding and immunochemical properties; f) impurities; g) reference product and reference standards; h) finishing drug product; and i) stability.

The guidance points out that advances in manufacturing science and Quality-by-Design approaches may facilitate production processes that can better match a reference product's fingerprint; these "fingerprint" approaches may be used to refine further animal or clinical studies.

BIOSIMILARS: QUESTIONS AND ANSWERS GUIDANCE

FDA has provided answers addressing questions from people interested in developing biosimilar products. The question-and-answer format addresses questions that may arise in the early stages of product development, such as how to request meetings with FDA, how to address differences in formulation in comparison to the reference product, how to request exclusivity, and other topics.

For example, FDA proposes regulatory definitions of "protein" and "chemically synthesized polypeptide." The term "protein" would mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size. The term "chemically synthesized polypeptide" would mean any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size. FDA considers any polymer composed of 40 or fewer amino acids to be a "peptide" and not a protein. Therefore, under the draft guidance, unless it otherwise meets the statutory definition of a "biological product" (e.g., a peptide vaccine), a peptide will be regulated as a drug under the Food, Drug and Cosmetic Act (FDCA). The statutory category of "protein" parenthetically excludes "any chemically synthesized polypeptide." Such molecules will be regulated as drugs under the FDCA, unless the chemically synthesized polypeptide otherwise meets the statutory definition of a "biological product."

According to the Q & A guidance, a proposed biosimilar product may have a different formulation than the reference product, use a different delivery device or container closure system, be directed to fewer than all of the routes of administration, be directed to fewer than all presentations (strengths, delivery device, or container closure systems), and be for fewer than all of the conditions of use than the reference product.

FDA addresses the question of whether an applicant can obtain an "interchangeability" determination in an original 351(k) application. Advantages to obtaining such a determination include substitution of interchangeable biologics without doctor intervention, and exclusivity for the first biosimilar deemed interchangeable with a given reference product. The BPCIA provides various general requirements for interchangeability, but does not provide clear criteria or guidance. The draft guidance document indicates that it is possible to obtain an "interchangeability" determination in the original application,

Client Alert.

but that “[a]t 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 and the sequential nature of that assessment. 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.”

IMPLICATIONS

Although the 351(k) pathway applies generally to biological products, the guidance documents focus on therapeutic protein products and provide an overview of scientific and analytical factors to consider in demonstrating biosimilarity between a proposed protein product and the reference product.

Companies looking to enter the follow-on biologics market might be disappointed by the lack of a categorical approach by FDA, and uncertainties surrounding the totality-of-the-evidence approach that FDA proposes to use to review applications for biosimilar products. The guidance documents do not address issues such as interchangeability standards, patent litigation procedures, and exclusivity standards for reference products, and do not provide clear guidance for any particular biologic products. Based on the draft guidance documents, companies looking to make follow-on biologics should engage FDA at an early stage, and throughout the entire biosimilar approval process.

Despite the draft status and their general nature, the guidance documents are the first step towards removing the uncertainties surrounding the biosimilar approval pathway. As expected, it appears that the FDA evaluation and approval process will occur on a case-by-case basis, and will be tailored to specific products.

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