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Opening the Door for Generic Biologics: FDA Releases the First Guidance Documents Implementing the Biosimilar Approval Pathway

Therapeutic biologic products are at the forefront of medical research and provide promising treatments for a variety of medical conditions. Unlike traditional pharmaceutical drugs, which generally are chemically synthesized, well-characterized molecules, biological drugs (or biologics) are derived from natural sources, including humans, animals and microorganisms. As a result, biologics are generally complex mixtures of molecules that are not easily isolated, identified and characterized, and they may differ as a result of seemingly minor variations in the manufacturing process. This complexity has, until recently, presented a barrier to the development of a framework for the review and approval of generic alternatives to biologic drugs.

In light of recent advances in technology and an increasing call for generic alternatives to biologic drugs, Congress enacted the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) as a component of the Patient Protection and Affordable Care Act (PPACA), which was signed into law by President Obama on March 23, 2010.[1] The BPCI Act amended the Public Health Service Act (PHSA) to create an abbreviated approval pathway for biological products that are demonstrated to be highly similar (biosimilar) to, or interchangeable with, an FDA-licensed biological product. On February 9, 2012, the Food and Drug Administration (FDA) released three long awaited draft guidance documents on biosimilar product development that are intended to implement provisions of the PPACA. The three FDA guidance documents include:

- 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

Although they leave a number of questions unanswered, these three documents are a significant step in FDA's implementation of the PPACA and provide important guidance to the budding biosimilar product industry, which promises to grow rapidly with further regulatory certainty.[2]

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The Biologics Price Competition and Innovation Act of 2009

The BPCI Act amended the PHSA to add section 351(k), allowing sponsors

to submit applications for licensure of biosimilar products that references information regarding FDA's previous determination on a licensed biological product (reference product). Under the exclusive provisions of the BPCI Act, applications may be submitted four years following the date of the first licensure of the reference product.[3] However, in order to utilize this abbreviated pathway, an applicant must show that a proposed biological product is biosimilar to a reference product based on data from analytical studies that demonstrate the product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.[4] In addition, the applicant must submit data, including data from animal and clinical studies, sufficient to demonstrate that the proposed biosimilar product continues to be safe, pure and potent, and that the product's mechanism of action, conditions of use and route of administration are the same as the reference product.[5] However, FDA may not approve a 351(k) application until the expiration of a 12-year exclusivity period from the date of first licensure of the reference product.[6]

Under the BPCI Act, approved biosimilars are considered to be comparable to branded biologics, and are expected to be less expensive to produce and sell based on reduced development costs. However, biosimilars are not considered to be true "generic" versions of the branded product and, unlike generic drugs, may not be substituted for the branded product without medical review. Due to the molecular complexity of biologics, the BPCI Act requires additional evidence in order to establish that a proposed biosimilar product is "interchangeable" with a reference product, thus allowing substitution of the biosimilar without medical review.

In order to demonstrate interchangeability, an applicant must prove that a proposed product is biosimilar to a reference product and also demonstrate that the proposed product can be expected to produce the same clinical result as the reference product in any given patient, and that alternating or switching between the reference product and the proposed product entails no greater risk than using the reference product alone.[7] Although FDA has stated that a single application may be submitted to demonstrate both biosimilarity and interchangeability, FDA makes clear in its three draft guidance documents that such a showing in a single application is likely not possible at this time, as the Agency is still in the process of developing guidance on interchangeability. The three draft guidance documents, and thus the only guidance available on the biosimilar approval pathway, address biosimilarity only.

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

The first draft guidance, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,"[8] is intended to assist applicants in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting a 351(k) application to FDA. It provides an overview of FDA's approach to determining biosimilarity, which the Agency considers to be consistent with its longstanding approach to the evaluation of scientific evidence. Although this draft guidance focuses on therapeutic protein products, it states that the scientific principles may be applied to other types of proposed biosimilar products as well.

In the draft guidance, FDA first discusses the complexities of protein products, explaining that, unlike small molecule drugs for which the structure can usually be completely defined and entirely reproduced, proteins

are typically more complex and it is unlikely that they can be shown to be structurally identical to a reference product. Advances in analytical sciences have enabled some protein products to be extensively characterized; however, current analytical methodologies may be unable to fully detect all relevant structural and functional differences between two proteins. Moreover, protein structures may also be affected by environmental conditions, such as formulation, light, temperature, moisture and packaging materials. Because, as FDA cautions, even minor structural differences can significantly affect a protein's safety, purity and potency, it is important to fully evaluate these differences in reaching a determination of biosimilarity. Thus, 351(k) applications must include data derived from analytical studies, animal studies, and one or more clinical studies, as well as detailed manufacturing information, in order to demonstrate biosimilarity, unless FDA determines otherwise.

FDA's guidance recommends that sponsors take a "stepwise approach" to developing the evidence needed to demonstrate biosimilarity, and it discusses the scientific considerations applicable to each of the required steps: structural analysis, functional assays, animal data, and clinical data. Under this approach, a sponsor should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product at each step in the process and identify the next steps to try to address that uncertainty. FDA states that the foundation of this process starts with an extensive structural and functional characterization of both the proposed biosimilar product and the reference product, which may involve a "fingerprint-like" analysis algorithm that covers a large number of product attributes and their combinations to quantify the similarities or differences between the two products. FDA believes that this approach may reduce the possibility of undetected structural differences between the products and lead to more selective and targeted animal and clinical testing. After the initial characterization, FDA urges sponsors to consider the role of animal data to assess toxicity and, in some cases, to provide additional support for demonstrating biosimilarity. The sponsor should then conduct comparative human pharmacokinetic and pharmacodynamic studies (if there is a clinically relevant pharmacodynamic measure), and compare the clinical immunogenicity of the two products. Finally, if uncertainties as to biosimilarity remain after both animal and human testing, the sponsor should then consider what comparative clinical safety and effectiveness data may be required to support the application.

Under FDA's totality-of-the-evidence approach, a sponsor may be able to demonstrate biosimilarity even though there are formulation or minor structural differences between the two products, provided that the sponsor submits sufficient information demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity. According to FDA, the type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

According to FDA's guidance, robust postmarket safety monitoring is an important component of biologic product approval, and the same principles apply to biosimilars. Further, the labeling of a biosimilar product must state that the product is approved as biosimilar to a reference product for one or more stated indications and routes of administration and that the product has or has not been determined to be interchangeable with the reference product. FDA encourages sponsors to meet early with FDA, and to establish a schedule of milestones

that will serve as landmarks for future discussions with the Agency to facilitate biosimilar development and review.

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

The second draft guidance, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product,"[9] provides an overview of analytical factors that may be relevant to assessing whether a proposed therapeutic protein product and a reference product are biosimilar. Although the draft guidance applies specifically to therapeutic proteins, it states that the general scientific principles may be informative for the development of other types of products.

According to FDA, advances in manufacturing science and production methods may enhance the likelihood that a product will be highly similar to a reference product by better targeting the original product's physiochemical and functional properties. FDA emphasizes the importance of an extensive analytical characterization, stating that the body of knowledge will serve to support product quality during development, at approval, and over the post-approval life cycle. Thus, in addition to a complete chemistry, manufacturing and controls (CMC) section, a 351(k) application should also include robust comparative physicochemical and functional studies assessing the analytical similarity of the proposed biosimilar to the reference product. Sponsors should also identify and determine relative levels of protein variants that may alter the biological properties of the expressed protein through comparative analytical characterization studies, and should evaluate any differences in higher order structure through functional assays.

FDA addresses nine factors for consideration in assessing whether products are highly similar.

These include the following:

- **The expression construct** for a proposed biosimilar product should encode the same primary amino acid sequence as its reference product. Although minor modifications that will not have an effect on safety, purity or potency may be justified, the differences must be carefully considered because the type of expression system will significantly affect the types of process- and product-related substances and impurities that may be present.
- **Manufacturing processes** using Quality-by-Design approaches, along with effective risk management and quality systems, will facilitate the consistent manufacturing of a biosimilar product.
- **Physicochemical assessment** of the proposed and reference products should consider all relevant characteristics of the proteins, including the primary, secondary, tertiary and quaternary structures, post-translational modifications and functional activities, in order to maximize the potential for detecting differences in quality attributes.
- **Functional assays** complement physiochemical analyses and serve as a quality measure of the function of the protein product. Depending on the structural complexity of the protein and available analytical technology, the physiochemical analysis may be unable to confirm the integrity of the higher order structures, but a confirmation may be inferred from the product's biological activity as measured through functional assays.
- **Receptor binding and immunochemical properties** should be analyzed and characterized when they are part of the activity attributed to the protein product.

- **Product- and process-related impurities** should be identified, characterized and quantified in both the proposed and reference products. If the biosimilar manufacturing process introduces different or higher levels of impurities than those present in the reference product, additional pharmacological, toxicological or other studies may be necessary.
- **Reference products and standards** should be employed in analytic studies to characterize the proposed biosimilar as part of a broad comparison that includes the reference product, any available reference standards and relevant publicly available information.
- **Finished drug products** should be characterized based on the most downstream intermediate best suited for the analytical procedures, and the attributes evaluated should be stable through any further processing steps, keeping in mind that proteins are very sensitive to their environment and differences in excipients or primary packaging may affect product degradation and possibly clinical performance.
- **Stability** should be assessed using accelerated and stress stability studies or focused degradation studies to establish degradation profiles and provide a direct comparison of the proposed biosimilar with the reference product.

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

The third draft guidance, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,"[10] provides answers to common questions FDA has received from sponsors interested in developing biosimilar products, manufacturers of licensed biologics and other interested parties, including comments received in response to the November 2–3, 2010 public hearing and the public docket established to obtain input on implementation of the BPCI Act. The question-and-answer format is intended to facilitate development programs by addressing questions that may arise in the early stages of biosimilar product development. FDA intends to update the guidance to include additional questions and answers as appropriate.

In the draft questions and answers, FDA addresses several administrative issues, explaining, for example, that the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) share regulatory responsibility for biologic products, and that sponsors should request an initial meeting with FDA when they can provide a proposed development plan, manufacturing process information and preliminary comparative analytic data. FDA also addresses more substantive issues that expand upon the requirements of the BPCI Act, explaining, for example, the circumstances under which a sponsor may use a non-U.S.-licensed reference product for comparative analyses, those under which a proposed biosimilar product may have a delivery device or container closure system different from the reference product, and those under which an applicant may obtain licensure for fewer than all routes of administration, presentations or conditions of use for which a reference product is licensed. The document also explains certain provisions of the BPCI Act related to exclusivity and the amendment to the definition of "biological product" in the PHSA.

What Is Next for Biosimilars

Industry has expressed relief that the FDA has released guidance on the biosimilar approval pathway; however, many have complained that the

Agency left several important questions unanswered. Particularly, industry is still left wondering whether the biosimilar approval pathway will result in sufficient development cost savings to make biosimilars worth pursuing. Although the guidance documents discuss necessary studies, including clinical trials, which will be required to support a 351(k) application, the Agency's strong emphasis on evaluating data needs on a case-by-case basis leaves significant uncertainty.

Although the guidance documents also explicitly exclude from their scope any discussion of the interchangeability pathway for biologics, they suggest that FDA currently contemplates a two-step pathway, with biologics first being approved as biosimilars and then reviewed for interchangeability. In light of this, industry has expressed some disappointment in the lack of any further guidance from FDA on what will be the true generic form for biologics. Industry also has expressed lingering concern that physicians may be hesitant to prescribe biosimilars because, even if they are less expensive to produce and sell, they lack generic-like interchangeability, which also prevents pharmacies from substituting biosimilars for licensed biologics outside physician control.

As of February 3, 2012, FDA reported that it has received nine investigational new drug applications (INDs) to pursue clinical testing on potential biosimilar products, and 35 requests for pre-IND meetings. However, FDA has yet to receive a 351(k) application in the two years since the enactment of the PPACA, and only time will tell how industry will proceed in light of the new guidance.

To facilitate the biosimilar approval pathway, FDA and industry recently negotiated a package of recommended user fees to help cover the Agency's cost of reviewing biosimilar applications. The proposed user fee program is currently awaiting approval in Congress.[11] FDA is also seeking public comment on the draft guidance documents, and urges interested parties to submit comments by April 16, 2012.[12] As of yet, however, there is no clear indication as to when industry can expect issuance of final guidance documents. Given this unclear timeframe and the remaining areas of uncertainty, biosimilars are likely to be a focus of scrutiny in both the industry and Agency for several years to come.

Endnotes

[1] Pub. L. No. 111–148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010).

[2] In 2010, seven of the top 20 selling drugs in the U.S. were biologics, and biologics with $30 billion in U.S. sales are expected to lose patent protection by 2020. Thomas M. Burton, *FDA Sets Path for Biotech Drug Companies*, WSJ.com (Feb. 10, 2010), http://online.wsj.com/article/SB10001424052970204642604577213143424515820.html.

[3] PHSA §§ 351(k)(2)(A)(iii)(I), 351(k)(7)(B), 42 U.S.C. §§ 262(k)(2)(A)(iii)(I), 262(k)(7)(B) (Supp. IV 2010).

[4] PHSA § 351(k)(2)(A)(i)(I)(aa), 42. U.S.C. § 262(k)(2)(A)(i)(I)(aa).

[5] PHSA § 351(k)(2)(A)(i)(I)(bb)–(IV), 42 U.S.C. § 262(k)(2)(A)(i)(I)(bb)–(IV).

[6] PHSA § 351(k)(7)(A), 42 U.S.C. § 262(k)(7)(A).

[7] PHSA §§ 351(k)(2)(B), 351(k)(4), 42 U.S.C. §§ 262(k)(2)(B), 262(k)(4).

[8] FDA, "Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Draft Guidance" (February 2012), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

[9] FDA, "Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product: Draft Guidance" (February 2012), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf.

[10] FDA, "Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Draft Guidance" (February 2012), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf.

[11] Generic Drug and Biosimilar User Fee Act of 2012, H.R. 3988, 112th Cong. (2012).

[12] Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Availability, 77 Fed. Reg. 8883 (Feb. 15, 2011); Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; Availability, 77 Fed. Reg. 8884 (Feb. 15, 2011); Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; Availability, 77 Fed. Reg. 8885 (Feb. 15, 2011).

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