FDA Publishes Draft Biosimilars Guidance

February 16, 2012

The Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, a U.S. Food and Drug Administration (FDA)-licensed biological reference product. On February 9, 2012, FDA published the first three in a series of highly anticipated draft guidance documents that describe the agency's approach to making the determination that two biological products are "biosimilar" or "interchangeable." In this newsletter, we provide a summary of these guidance documents and discuss some of their implications.

On February 9, 2012, the U.S. Food and Drug Administration (FDA) published three draft guidance documents that begin to describe the agency's interpretation of the biosimilar approval pathway created by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). A biological product is "biosimilar" to an FDA-licensed biological (the "reference product") if it is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the products in terms of safety, purity and potency. *See* BPCI Act § 7002(b)(3).

The draft guidance documents, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," and "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," address a broad range of issues. Following are some highlights from these documents.

Information Required to Establish Biosimilarity

- *Biosimilar sponsors should be prepared to provide a range of data, including comparative clinical safety and effectiveness data (as necessary), to support the biosimilarity of the proposed product.* FDA states it intends to consider the "totality of evidence" submitted by a sponsor to support a demonstration of biosimilarity. The agency recommends that sponsors use a "stepwise approach" to develop the evidence

necessary to demonstrate that the proposed product is biosimilar to a reference product. Recommended steps include extensive structural and functional characterization of the proposed product and the reference product; animal data for the assessment of toxicity and, in some cases, for the provision of additional support for demonstrating biosimilarity and contributing to an immunogenicity assessment; comparative human pharmacokinetic (PK) and pharmacodynamic (PD) studies conducted in an appropriate study population; comparison of clinical immunogenicity of the two products; and comparative clinical safety and effectiveness data.

At each step, sponsors should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to address that uncertainty. FDA intends to use a risk-based, totality of the evidence approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product. Although it is clear FDA may require a sponsor to furnish clinical data to support the safety or effectiveness of the biosimilar in some cases, the guidance does not make clear how frequently the agency will require biosimilar sponsors to furnish such data.

- *The amount and type of data necessary to support a biosimilar application will be determined on a case-by-case basis.* Consistent with public statements that preceded the publication of these guidance documents, FDA states the "type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis."

- *In all cases, however, biosimilar sponsors will be expected to produce "extensive" analytical data comparing the proposed biosimilar and the reference product using "state-of-the-art technology."* In assessing the extent to which a proposed biosimilar is "highly similar" to a reference product, the biosimilar sponsor should consider a number of factors, including: the expression system used to produce each product; the manufacturing system used to produce each product; physicochemical properties (*e.g.*, primary, secondary, tertiary and quaternary structure, post-translational modifications); performance in functional assays; receptor binding and immunochemical properties; impurities; compliance with reference standards for the reference product; and stability. Biosimilar sponsors should perform such comparisons on multiple lots of the proposed product and reference product, as well as multiple lots of the finished dosage form of each. The biosimilar sponsor should provide this comparative information in addition to a complete chemistry, manufacturing and controls data submission.

- *Insofar as a reference product cannot be adequately characterized with "state-of-the-art" technology, biosimilar sponsors should meet with the agency to determine whether such a product is appropriate for submission under the biosimilar pathway.* Presumably, such products may be required to apply for licensure under a full biologics license application.

- *FDA encourages sponsors of proposed biosimilar products to meet with the agency at various points during the biosimilar development process.* FDA states biosimilar sponsors should request an initial meeting with FDA when they are able to provide the agency with an overview of its proposed development program, manufacturing information and preliminary comparative analytical data with the reference product. The agency intends to review this information and provide individualized feedback. FDA anticipates this initial dialogue will enable the applicant and the agency to establish a schedule of product development milestones that will serve as landmarks for future discussions. In this regard, FDA "encourages sponsors to consult extensively" with the agency throughout development as needed.

Extrapolation of Clinical Data

- *An applicant may be permitted to extrapolate clinical data intended to support a demonstration of biosimilarity in one indication to support licensure of the proposed product in one or more additional indications for which the reference product is licensed, provided there is sufficient scientific justification for such reliance.* Applicants will need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each additional indication for which licensure is sought. Scientific justification for such application should address the mechanism(s) of action for each indication, the pharmacokinetics and biodistribution of products in different patient populations and differences in expected toxicities for each indication, among other items. This suggests that where a reference product has multiple indications for use with different mechanisms of action for different uses, FDA may limit the approval of a biosimilar to an indication for which the mechanism of action is well-established and for which the agency can infer that the biosimilar would be expected to be effective and safe.

- *A sponsor may use data derived from animal or clinical studies comparing a proposed biosimilar with a non-U.S.-licensed product to establish biosimilarity, provided the sponsor provides adequate data to scientifically justify the relevance of this comparative data.* Biosimilar sponsors are encouraged to discuss with FDA the adequacy of the scientific justification and bridge to the U.S.-licensed reference

product early in the proposed product's development program. The scientific bridge between the non-U.S.-licensed product and the U.S.-licensed product is likely to include comparative physico-chemical characterization, bioassays/functional assays and comparative clinical and/or non-clinical PK and/or PD data, to address any differences in formulation or primary packaging. A final determination of the adequacy of this information will be made by FDA during review of the 351(k) application.

Permissible Differences Between Reference and Biosimilar Products

- *A proposed biosimilar may be permitted to have a different formulation or a different delivery device/container closure system than the reference product.* Applicants will be expected to provide clinical data illustrating that such changes do not lead to clinically meaningful differences in terms of safety, purity and potency.
- *A biosimilar applicant may obtain licensure of a proposed biosimilar for fewer than all routes of administration, presentations (e.g., strengths or delivery device or container closure systems) and indications for use for which a reference product has been licensed.* Applicants must demonstrate such differences will not produce any clinically meaningful differences between the proposed biosimilar and the reference product in terms of safety, purity and potency. FDA states it will consider a proposed biosimilar product that is in a delivery device to be a combination product that may require a separate device application.
- *FDA (generally) expects the units of activity for a proposed biosimilar product to be the same as the units of activity for the reference product.* The guidance explicitly states: "If the total content of drug substance is expressed in units of activity (*e.g.*, international units (IU) or units per total volume in a container closure), the units of the proposed biosimilar product should be the *same* as the reference product" (emphasis added).

Interchangeability

- *The guidance documents do not address the requirements for determining if a proposed product is interchangeable with a reference product, other than to say that the agency would be unlikely to determine that a proposed product is interchangeable with a reference product in an original application.* The FDA explicitly states, "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original [biosimilar] application given the statutory standard for interchangeability and the sequential nature of that assessment." This

suggests that, at least initially, biosimilar products will not be eligible for automatic substitution under state generic substitution laws.

Impact of Biosimilar Pathway on Reference Manufacturer's Ability to Make Manufacturing Changes

- *Demonstrating that a proposed product is biosimilar to a reference product will typically require more data than that required for the reference product's manufacturer to establish the comparability of the reference product before and after manufacturing changes.* FDA states the demonstration of biosimilarity to a reference product is more complex for a manufacturer of a biosimilar product because it will likely have a different manufacturing process (*e.g.*, different cell line, raw materials, equipment, processes, process controls and acceptance criteria) without direct knowledge of the manufacturing process for the reference product. In contrast, the reference product manufacturer has "extensive knowledge and information" about the product and its existing manufacturing process, including establishing controls and acceptance parameters.

Labeling of Biosimilar Products

- *FDA expects biosimilar labeling to include clear statements advising (1) that the biosimilar product has been approved as a biosimilar to a reference product for stated indication(s) and route(s) of administration; and (2) whether the product has been determined to be interchangeable with the reference product.* The agency does not, however, indicate whether it will require a proposed product to adopt unique non-proprietary nomenclature. Guidance on non-proprietary nomenclature for biosimilars is expected to be released at a future date.

Definition of "Protein"

- *FDA defines the term "protein" to mean "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size."* The BPCI Act amends the definition of the term "biological product" to include a "protein." FDA indicates 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.

Post-market Safety Considerations

- *FDA states that because some aspects of post-market safety monitoring are "product-specific," a post-market safety monitoring program should consider any particular safety concerns associated with the use of the referenced product "and its class," in addition to the proposed product in its development and clinical use if marketed outside of the United States.* FDA also states the monitoring program should have "adequate mechanisms" to differentiate between adverse events associated with the proposed biosimilar product and the referenced product, including the ability to identify adverse events that have not been previously associated with the reference product.

Intellectual Property Considerations

The multiplicity of factors and analyses suggested by the guidance will inevitably require biotechnology companies to carefully balance the regulatory requirements against intellectual property (IP) considerations. In this regard, it will be important for companies pursuing the biosimilar pathway to ensure communication and coordination between research and development and regulatory teams, and regulatory and patent counsel.

Special consideration and planning will be needed when a company is weighing the risks of prosecuting a patent to cover their biosimilar and applying for biosimilar approval with FDA. For example, the applicant may be faced with the prospect of arguing to the U.S. Patent and Trademark Office that a biologic is novel and non-obvious compared to an approved, branded product, but later presenting data and statements to FDA that their product is biosimilar and/or interchangeable with the branded product and uses the same active ingredient, in the same way, to produce the same result.

Implications

The biosimilars approval pathway has been the subject of intense industry interest since it was created as part of the Patient Protection and Affordable Care Act. (FDA has stated that, to date, it has received 35 pre-investigational new drug (IND) meeting requests for proposed biosimilars to 11 reference products, held 21 pre-IND sponsor meetings and received 9 INDs.) The draft guidance documents represent the agency's

first formal expression of its intentions regarding the implementation of this new approval pathway.

Consistent with the *public statements* that preceded the publication of these guidance documents, the agency proposes to take a robust, nuanced and individualized approach to the evaluation of proposed biosimilar products. Throughout the guidance documents, FDA notes the presence of unique scientific issues that may complicate the agency's ability to approve a biosimilar product—especially as compared to the agency's evaluation algorithm for a small molecule drug under an abbreviated new drug application. In taking this approach, FDA indicates it will balance the BPCI Act's mandate to improve patient access to biological products with the desire to ensure biosimilar products be used effectively and safely. While this approach may be reasonable, it does not provide the type of clarity manufacturers may be seeking as they undertake expensive business strategies predicated on biosimilars. Notably, the agency pointedly defers until a later time providing guidance on the interchangeability market pathway.

Although the guidance documents cover a range of issues, a number of items, such as the requirements for interchangeability, are not addressed. Given this fact, the important issues outlined above and the robust expectations set forth in these draft guidance documents, manufacturers would be well-advised to consider providing the agency with comments and suggestions for clarifying the pathway standards and areas where more guidance would be helpful.

FDA is accepting comments on these draft guidance documents until April 16, 2012.