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FDA Issues Draft Guidance on the Development of Biosimilar Products

On May 14, 2014, the Food and Drug Administration (FDA or Agency) issued a draft guidance entitled "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." The draft guidance is intended to "assist sponsors with the design and use of clinical pharmacology studies to support a decision that a proposed therapeutic biological product is *biosimilar* to its reference product."

Background

Enacted in 2010, the Patient Protection and Affordable Care Act established an abbreviated pathway for FDA licensure of biological products that are demonstrated to be "biosimilar to" or "interchangeable with" an FDA-licensed reference product. 42 U.S.C. § 262(k)(3)(A) (section 351(k)(3)(A) of the Public Health Service Act). To implement the law, FDA has enacted a series of draft guidances related to biosimilar product development:

- "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (Feb. 2012).
- "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" (Feb. 2012).
- "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (Feb. 2012).
- "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants" (Mar. 2013).

FDA now has issued five draft guidances on the biosimilar approval pathway, though the Agency has not yet addressed issues related to interchangeability, labeling or exclusivity.

Under the Act, a proposed biological product is "biosimilar" to the reference product if (1) it is "highly similar … notwithstanding minor differences in clinically inactive components" and (2) "there are no clinically meaningfully differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." 42 U.S.C. § 262(i)(2). Sponsors can demonstrate biosimilarity based upon data derived from analytical studies, animal studies and "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics)." *Id.* § 262(k)(2)(A)(i)(I).

Demonstrating Biosimilarity With Clinical Pharmacology Studies

The draft guidance emphasizes that clinical pharmacology studies are "a critical part of demonstrating biosimilarity." Clinical pharmacology studies are small, early-stage studies in human subjects; these types of studies may include pharmacokinetic (PK) and pharmacodynamic (PD) studies; absorption, distribution, metabolism and excretion (ADME) studies; dose-ranging studies; and drug-drug interaction (DDI) studies. According to the draft guidance, clinical pharmacology studies — if done well — "can add

to the totality of the evidence, reduce residual uncertainty, and thus guide the need for and design of subsequent clinical testing to successfully support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity."

Three Key Concepts

According to FDA, three key concepts are especially relevant to biosimilar product development: exposure and response assessment, evaluation of residual uncertainty and assumptions about analytical quality and similarity.

Exposure and Response Assessment. The draft guidance acknowledges that determining "the response to exposure to a biological product is particularly challenging, because the active product is not a single chemical … ; rather, it is a mixture of closely related, complex biological substances that, in aggregate, make up the active component." Accordingly, it is imperative that sponsors design clinical pharmacology studies that can evaluate effectively the similarities and differences in the PK and PD profiles of the proposed biosimilar product and the reference product. A well-designed PK and PD study can operate to refine "in both design and extent" the "additional clinical trials necessary to assess whether there are clinically meaningful differences between the proposed biosimilar product and the reference product."

Evaluation of Residual Uncertainty. The draft guidance states further that, in evaluating the data submitted by a sponsor to support a demonstration of biosimilarity, "clinical PK and PD data and safety data obtained in conjunction with the clinical pharmacology studies" are "[e]specially pertinent." That said, the Agency makes clear that it will take "a risk-based approach" and "consider the totality of the data and information submitted, including, for example, data from the structural and functional characterization, nonclinical evaluations, human PK and PD studies, clinical immunogenicity testing, and investigation of clinical safety and when necessary clinical effectiveness." In any case, data should be collected in a so-called "stepwise" manner, i.e., research should be conducted, residual uncertainty should be identified and additional studies should be conducted to resolve the uncertainty — and, per FDA, the Agency should be consulted throughout the process.

Assumptions About Analytical Quality and Similarity. The draft guidance notes that, in a stepwise assessment of biosimilarity, a sponsor's ability to take a selective and targeted approach to animal and/or clinical studies will often depend on a structural and functional comparison of the proposed biosimilar product and the reference product that quantifies, in some measure, their "overall similarity." According to FDA, the result of such a comparative analytical characterization will lead to one of four assessments of a proposed biosimilar product:

- Not similar. Further development through the abbreviated biosimilar pathway is "not recommended."

- Similar. Additional analytical data or other studies are necessary. "Comparative PK and PD studies of the proposed biosimilar product and the reference product," for example, may "help resolve that some differences … would be within an acceptable range [so as] to consider the proposed biosimilar product to be highly similar to the reference product."

- Highly similar. The sponsor may "conduct targeted and selective animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity."

- Highly similar with fingerprint-like similarity. The sponsor may "use a *more* targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity" (emphasis added).

Other Topics

The draft guidance also describes FDA's current thinking on bioanalytical methodology; the use of clinical pharmacology studies to gain safety and immunogenicity information; critical study design issues; and the utility of simulation tools in study design and data analysis.

How Hunton & Williams LLP Can Help

FDA is accepting comments on this draft guidance through August 12, 2014. Our lawyers have extensive experience advising clients on drug and biological product approval strategies involving new drug applications, 505(b)(2) applications, biologics license applications and 351(k) applications. If you would like to know how this draft guidance may affect your biosimilar product development or FDA-licensed biological product, or if you need assistance preparing comments on this draft guidance, please contact us.

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