May 14, 2014

FDA Releases New Guidance for Biosimilar Applications

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Yesterday, the U.S. Food and Drug Administration provided further clarity as to how it will evaluate applications for approval of biosimilars when it released a draft guidance document outlining the types of clinical pharmacology data it wants to see to support a finding that a therapeutic biological product is highly similar to a reference product. This most recent guidance document comes more than one year after the last guidance document from the FDA specifically addressing biosimilars, and continues the agency's slow and cautious implementation of the Biologics Price Competition and Innovation Act that was enacted in March of 2010.

The guidance is focused primarily on the pharmacokinetic (PK) and pharmacodynamic (PD) data necessary to demonstrate biosimilarity. While the guidance is intended to assist biosimilar applicants in designing clinical pharmacology studies that can support an application submitted under 351(k), it is nonbinding and a biosimilar applicant may use an alternative approach to demonstrate biosimilarity provided it satisfies the requirements of the applicable statute and regulations. The FDA has established a 90-day period for public comment on the draft guidance.

Critical Considerations for Biosimilar Applicants

The FDA identifies three "critical considerations" that it will take into account in evaluating the use of clinical pharmacology studies to support a biosimilar application: 1) exposure and response assessment; 2) evaluation or residual uncertainty; and 3) analytical quality and uncertainty.

- **Exposure and response assessment** – The FDA uses the term exposure to refer to PK variables, including drug input (i.e., dose), peak concentration (Cmax), lowest concentration (Cmin), concentration prior to next dose (Ctrough ss), and area under the plasma/blood concentration-time curve (AUC). The term response refers to PD, and is a direct measure of the pharmacological and toxicological effect of a drug in humans. The guidance emphasizes that to the extent applicants are able to submit convincing PK and PD results, the overall clinical development program needed to show biosimilarity can be refined (i.e., narrowed) in both design and extent of additional clinical trials needed.

- **Evaluation of residual uncertainty** – The FDA will use a "risk-based approach" in evaluating the biosimilar applicant's data, and will consider the totality of the data and information submitted. Data should be collected in a stepwise manner and meetings between the applicant and FDA should occur after each step. The need for additional data and/or clinical studies will be determined by the degree of "residual uncertainty" regarding the similarity of the products after each step.

- **Assumptions about analytical quality and similarity** – The guidance makes clear that the FDA expects that, as a first step, "extensive and robust" comparative structural and functional studies (e.g. bioassays, binding assays, and studies of enzyme kinetics) will be performed by the 351(k) applicant to demonstrate that the proposed biosimilar product and the reference product are highly similar. State-of-the-art analytical assays, to the extent available, should be used to assess molecular weight of the protein, higher order structure, post-translational modifications, heterogeneity, functional properties, impurity profiles, degradation profiles, etc.

The guidance sets forth a four-tier assessment that the FDA will use to grade a biosimilar applicants analytical data:

- **Not similar** – substantial differences apparent from the analytical studies indicate that the products are "not similar' and further progression through the 351(k) pathway is not recommended;
- **Similar** – additional analytical data or other studies are needed to determine if the products are indeed highly similar;
- **Highly similar** - the proposed biosimilar product meets the statutory standard for analytical similarity, and moving forward with targeted and selective animal and/or clinical studies it resolve residual uncertainty is appropriate;

- **Highly similar with fingerprint-like similarity** – the proposed biosimilar meets the statutory standard for analytical similarity based on integrated, multi- parameter approaches that are extremely sensitive. More targeted and selective animal and/or clinical studies are appropriate.

Key Takeaways

- The FDA considers a clinical pharmacology study or studies (i.e., PK and PD studies) to be critical to demonstrating that the biosimilar product and the reference product are "highly similar" as required by the statute. By submitting convincing PK and PD data, a biosimilar applicant can focus (i.e., limit) the design and extent of additional clinical trials that might be needed to demonstrate to the FDA that there are no clinically meaningful differences between the two products.

- The FDA will implement a stepwise approach to the collection and evaluation of biosimilarity data generated from structural and functional characterization, nonclinical evaluations, human PK and PD studies, clinical immunogenicity testing, and investigation of clinical safety and, when necessary, clinical effectiveness. The FDA encourages meetings after each step. Before a biosimilar applicant can progress to the next step, the FDA will determine the degree of residual uncertainty that remains regarding the similarity of the products and whether any additional studies are needed to reduce that uncertainty.

- As a first step in the process, biosimilar applicants should perform extensive and robust comparative structural and functional studies to evaluate whether the reference product and the biosimilar product are highly similar. The onus is on the biosimilar applicant to identify and utilize available state-of-the art analytical assays for this assessment. If the analytical studies are not sufficiently rigorous, or show significant differences between the two products, then the FDA may conclude that the biosimilar product is not similar, and further progress down the 351(k) pathway is not warranted, or that it is similar, but more extensive analytical characterization is required before any clinical studies should be initiated. Conversely, if the analytical studies are extensive and robust, and result in a high level of confidence that the products are highly similar, then the biosimilar applicant can proceed with more targeted and selective animal and/or clinical studies.

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