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COMMENTARY

FDA's Fifth Draft Guidance on Biosimilars Sheds New Light on Approval Pathway

On May 13, the U.S. Food & Drug Administration ("FDA") issued a draft guidance, *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. The draft guidance is intended to assist biological product sponsors with the design and use of clinical pharmacology studies to support a showing that a proposed therapeutic biological product is "biosimilar" to its reference product under the Biologics Price Competition and Innovation Act of 2009 ("BPCI Act"). The draft guidance specifically relates to products such as therapeutic biologics, for which pharmacokinetic ("PK") and pharmacodynamic ("PD") data are required as part of a "stepwise" approach to developing the data and information needed to demonstrate biosimilarity. As the most detailed guidance yet on evidence needed to establish biosimilarity, the draft guidance adds further clarity to the cost of bringing a biosimilar to market.

In granular detail, the draft guidance covers overarching concepts related to clinical pharmacology testing for biosimilars, approaches for developing the appropriate clinical pharmacology database, and the utility of modeling and simulation for designing clinical trials. Notably, the draft guidance introduces the Agency's expectations for bridging data from products marketed outside of the United States and lays out key topics about which sponsors should meet with FDA early on in the biosimilar development process. The encouragement of early meetings with FDA echoes the Agency's stepwise approach to biosimilar approval, suggested in earlier draft guidance, which allows a sponsor to undertake research, identify areas of uncertainty, and then tailor future research to address those areas of uncertainty.

The draft guidance introduces four categories of similarity—not similar, similar, highly similar, and highly similar with fingerprint-like similarity—that will affect the extent to which further study is needed to establish biosimilarity. The category of "fingerprint-like similarity" may preview FDA's thought process on the concept of interchangeability, which is the level of biosimilarity necessary for possible substitution of a biosimilar for a reference product at the pharmacy level.

Once finalized, the draft guidance will be part of a series of guidance documents intended to implement the BPCI Act. These guidances are meant to help sponsors design clinical pharmacology studies needed to support an application for licensure of a biosimilar biologic. In February 2012, FDA released

the first three draft guidances on biosimilar product development, followed by a fourth guidance released in March 2013. Collectively, these previous draft guidance documents provided relatively general principles concerning the biosimilars application process, and this latest draft guidance adds a level of detail not previously provided. Additional guidance documents are expected on topics such as interchangeability, labeling, and exclusivity.

Biosimilarity and the Role of Clinical Pharmacology

The BPCI Act was enacted as a provision of the Patient Protection and Affordable Care Act and establishes an abbreviated route to FDA licensure of biological products shown to be "biosimilar" to and, possibly in addition, "interchangeable" with, an FDA-licensed reference product (the innovator, or brand-name, biological product). A biological product is a therapy used to treat a disease or health condition, such as vaccines, blood and blood components, gene therapies, tissues, and proteins. Biological products differ from small-molecule drugs in that they are made by cellular processes or biotechnology. In addition, as compared to small-molecule drugs, biologics are large, complex molecules that are relatively difficult to characterize and complex to manufacture. Biologics provide treatment for very serious diseases, including cancer and diabetes, but they are extremely expensive to develop. The intended effect of the BPCI Act is to increase competition for biologics, thereby reducing prices and expanding access to these drugs.

A biological product may be demonstrated to be "biosimilar" to a reference product if data shows that the product is "highly similar" to the reference product, notwithstanding minor differences in clinically inactive components, and that there are "no clinically meaningful differences" between the biological product and the reference product in terms of safety, purity, and potency.

To apply for the abbreviated licensure, the applicant must demonstrate in its biosimilar application ("351(k) application") that the product:

- Is a "biosimilar" to the reference product (as set forth above);
- Utilizes the same mechanism(s) of action for the proposed condition(s) of use;
- Has condition(s) of use proposed in labeling that have been previously approved for the reference product; and
- Has the same route of administration, dosage form, and strength as the reference product.

The 351(k) application must be based on data derived from analytical studies, animal studies, and a clinical study or studies, including an assessment of immunogenicity, PK, and PD, unless FDA determines that such studies are unnecessary in the application. Clinical pharmacology studies—initial research done on small groups of human subjects—are of particular importance to support a showing of biosimilarity by demonstrating no clinically meaningful differences between the proposed biosimilar and the reference product. These studies are intended to act as a roadmap for the design of subsequent clinical testing needed to demonstrate no clinically meaningful differences between the biosimilar and the reference product.

Key Concepts in the Use of Clinical Pharmacology Studies to Support Biosimilarity

The draft guidance provides a detailed discussion of the concepts of exposure and response, assessment, evaluation of residual uncertainty, and assumptions about analytical quality and similarity, all of which are highly relevant to the development of proposed biosimilars. This section also examines bioanalytical methodology and the use of clinical pharmacology to acquire information on safety and immunogenicity.

Exposure and Response Assessment to Support a Demonstration of Biosimilarity. The draft guidance provides that a well-designed clinical PK and PD study evaluates the similarities and differences in the PK and PD profiles between the proposed biosimilar and the reference product. Exposure-response information can be used to determine safety, purity, and potency of any biologic, as well as to determine any potential clinically meaningful differences between the two products. However, determining the response to exposure to a biologic is challenging due to the complexity of these products that make up the active component. The draft guidance details the PD marker(s) and other biomarkers that should be used to provide maximum value to such studies.

Evaluation of Residual Uncertainty. FDA considers the totality of data and information submitted in evaluating a sponsor's data to support a demonstration of biosimilarity, including data from the structural and functional characterization, nonclinical evaluations, human PK and PD studies, clinical immunogenicity testing, and investigation of clinical safety. The draft guidance advises sponsors to collect such information in a stepwise manner and notes that PK, PD, and safety data obtained in conjunction with the clinical pharmacology studies is particularly pertinent to FDA's clinical pharmacology evaluation. Whether additional studies at each step are needed will be determined by the degree of residual uncertainty remaining with respect to the similarity of the products.

Assumptions About Analytical Quality and Similarity. Sponsors should perform extensive and robust comparative structural and functional studies, such as bioassays, binding assays, and studies of enzyme kinetics, to evaluate whether the proposed biosimilar and the reference product are highly similar. The draft guidance provides as an example that a meaningful assessment depends in part on the capabilities of analytical assays to assess the molecular weight of the protein, its higher order structure and post-translational modifications, heterogeneity, functional properties, impurity profiles, and degradation profiles denoting stability.

If the analytical characterization reveals differences between the proposed biosimilar and the reference product, the sponsor should clearly identify the type, nature, and extent of these differences and address their potential impact. The draft guidance suggests one of four results for a comparative analytical characterization, the outcome of which will inform the sponsor's next steps in the demonstration of biosimilarity:

- **Not Similar.** A proposed biosimilar that receives the characterization of "not similar" is not advised to undertake further steps in the 351(k) process, unless modifications can be made that are likely to lead to a highly similar biological product.
- **Similar.** If a proposed biosimilar receives the characterization of "similar," the sponsor needs to present additional information to determine whether the product is "highly similar" to the reference product.
- **Highly Similar.** Based on the results of the comparative analytical characterization, the proposed biosimilar meets the statutory standard for analytical similarity. A sponsor with this product characterization should next 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 proposed biosimilar meets the statutory standard for analytical similarity "based on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences." These results indicate "a very high level of confidence in the analytical similarity of the proposed biosimilar and the reference product," and sponsors should proceed with a more targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity.

Integrity of the Bioanalytical Methods Used in PK and PD studies. Sponsors should be sure to use the appropriate bioanalytical methods when evaluating the PK and PD properties of a proposed biosimilar and its reference product. The complex molecular structure of biologics may render conventional analytical methods for chemical drugs unsuitable. Thus, sponsors should ensure that the bioanalytical methods used for PK and PD evaluations are "accurate, precise, specific, sensitive, and reproducible." FDA further describes the requirements of bioanalytical methods in a separate guidance document, *Bioanalytical Method Validation.*

The draft guidance details three specific considerations for sponsors in designing bioanalytical methods for biosimilars:

General PK Assay Considerations. How sponsors should design or choose assays with regard to the mechanism of action and structural elements of the proposed biosimilar.

General PK and PD Assay Considerations. How sponsors should employ the most suitable assays and methodologies with the goal of obtaining data that reflects drug exposure, biological activity, and/or the PD effect of the proposed biosimilar and reference product.

Specific Assays. Sponsors should keep in mind three types of assays of particular importance for biosimilar development:

- **Ligand Binding Assays.** Ligand binding assays are currently used to measure the concentration of most biological products in circulation. These assays are analytical methods in which quantification is based on macromolecular interactions with assay reagents.
- **Concentration and Activity Assays.** Bioanalytical methods that are not based on ligand binding can be used to quantify the concentrations of the proposed biosimilar and reference products. For some biologics, these measurements may rely on activity assays.
- **PD Assays.** If PD markers are not available to support a proposed biosimilar's development through clinical pharmacology studies, but the PD assessment is a piece of the biosimilarity evaluation, sponsors are advised to provide FDA with a rationale for the selection of PD endpoints and/or markers, along with data to demonstrate the assay quality.

Safety and Immunogenicity. The draft guidance defines "immunogenicity" in this context as "an immune response to the biological product that may result in immune-mediated toxicity and/or lack of effectiveness." Sponsors should collect and evaluate safety and immunogenicity data from the clinical pharmacology studies, although FDA does recognize that such studies may need to be supplemented by additional evaluations either pre- or post-approval. FDA nonetheless stresses that clinical pharmacology studies may suggest "clinically meaningful differences" between the two products, which may indicate the need for further investigation.

Sponsors should also consider the reference product's publicly available safety and immunogenicity profile when designing clinical pharmacology studies for the proposed biosimilar. FDA provided recommendations for immunogenicity assay development in a previous draft guidance document, *Assay Development for Immunogenicity Testing of Therapeutic Proteins*.

Developing Clinical Pharmacology Data for Supporting a Demonstration of Biosimilarity

The draft guidance encourages sponsors to discuss "the crucial aspects of their clinical pharmacology development plan" with FDA early on. Specifically, sponsors should discuss the following design topics with FDA early in the development of the biosimilar program:

Study Design. The draft guidance describes two study designs of particular importance for evaluating clinical PK and PD similarity for proposed biosimilars:

- **Crossover Design.** Crossover designs are single-dose, randomized studies recommended for PK similarity assessments for a product with a short half-life (e.g., shorter than five days), a rapid PD exposure (e.g., onset, maximal effect, and disappearance in conjunction with drug exposure), and a low incidence of immunogenicity. The draft guidance recommends multiple doses for PD similarity assessments when the PD effect is delayed or otherwise not parallel to the single-dose drug PK profile.
- **Parallel Design.** Parallel designs are appropriate for biologics with a long half-life that elicit immunogenetic responses that can affect PK and/or PD similarity assessments.

Reference Product. The BPCI Act defines a "reference product" for a proposed biosimilar as the single biological product licensed under section 351(a) of the Public Health Service Act against which a proposed biosimilar is evaluated in a 351(k) application. To support biosimilarity, a sponsor must include analytical studies and at least one clinical PK and, if appropriate, PD study to adequately compare the proposed biosimilar to the U.S.-licensed reference product. Additionally, the draft guidance indicates that for certain studies, a sponsor may use a non-U.S. licensed comparator product to support a demonstration of biosimilarity, noting that the sponsor must then provide sufficient data to scientifically justify use of the non-U.S. licensed product and "establish an acceptable bridge to the U.S.-licensed reference product." The draft guidance further explores the requirements for the bridging data. The FDA statements regarding foreign data usage represent welcome

progress to many in the industry, although it is too soon to evaluate their practical significance in product development.

Study Population. The draft guidance describes two study populations of particular importance for evaluating clinical PK and PD similarity for proposed biosimilars:

- **Healthy Volunteer vs. Patient.** The chosen study population should be that which best detects and evaluates differences in PK and PD profiles between the proposed biosimilar and the reference product. Human PK and PD studies should ideally be conducted in healthy volunteers, provided the sponsor can safely administer the product, because such studies are more sensitive in evaluating biosimilarity. If safety or efficacy concerns prevent the use of healthy volunteers, sponsors should conduct the clinical pharmacology studies in patients.
- **Demographic Group.** Sponsors should conduct clinical pharmacology studies in the subject or patient demographic group most capable of providing a sensitive measure of the differences between the proposed biosimilar and the reference product. Sponsors must also provide justification for the chosen demographic.

Dose Selection. The selected dose should be the most sensitive to detecting and evaluating the differences in the PK and PD profiles between the proposed biosimilar and the reference product. For example, for studies conducted in patients, the most suitable choice may be the approved dose for the reference product, as it may best demonstrate the pharmacological effects in a clinical setting. The draft guidance provides variations to this general suggestion based on other circumstances, such as healthy subjects or measuring PD.

Route of Administration. Sponsors should conduct human PK and PD studies with the same route of administration as that used for the reference product. For a reference product with more than one approved route of administration, sponsors should select the route most sensitive for detecting clinically meaningful differences (typically the subcutaneous or other extravascular routes).

Pharmacokinetic Measures. Sponsors should obtain all PK measures for the proposed biosimilar and the reference product. Specifically, the draft guidance provides details as to how sponsors should obtain C_{max} and total exposure.

Pharmacodynamic Measures. In some circumstances, human PK and PD data showing similar exposure and response between a proposed biosimilar and a reference product may be enough to assess clinically meaningful differences between the products. The draft guidance describes when such circumstances occur and notes that full safety and immunogenicity evaluations are nonetheless required either before or after approval. If human PK and PD data is insufficient to completely assess for clinically meaningful differences, a targeted approach to gather additional data may be needed. The draft guidance describes what criteria will determine such subsequent targeted steps.

Defining the Appropriate Pharmacodynamic Time Profile. The best sampling strategy for determining PD measures may not be the same as that used for PK measures. PK sampling may require frequent sampling at early time points after administration, with decreased frequency later on. In contrast, PD sampling may differ, and sponsors should explain these differences.

Statistical Comparison of PK and PD Results. FDA's recommended clinical pharmacology similarity assessments rely on: (i) a criterion to allow the comparison, (ii) a confidence interval for the criterion, and (iii) an acceptable limit. Sponsors should perform log-transformation of the exposure measures prior to statistical analysis. FDA's earlier guidance, *Statistical Approaches to Establishing Bioequivalence*, can provide sponsors with an average equivalence statistical approach to comparing PK and PD parameters for both replicate and nonreplicate design studies. This section provides the confidence interval for the ratios between the means of the parameters of the proposed biosimilar and the reference product. If results of the PK and/or PD study fall outside the predefined limits, and such results may indicate underlying differences between the two products, sponsors should explain such differences. Notably, however, the draft guidance states that "[i]f such differences do not translate into clinically meaningful differences and the safety, purity, and potency of the product are not affected, it may be possible to continue developing under the 351(k) pathway."

Utility of Simulation Tools in Study Design and Data Analysis

The draft guidance suggests the usefulness of modeling and simulation tools for designing PK and PD studies. Specifically, for biomarker-based comparisons, sponsors should select a dose on the steep portion of the dose-response curve of the reference product and provide data to support the claim that the selected dose falls on this steep curve. Sponsors may use publicly available data for the dose-response relationship of the reference product to analyze using simulations in order to justify the selected dose for the PK and/or PD study. If such data is not available for the reference product, the sponsor may generate this information using a small study.

Conclusion

The draft guidance concludes by reiterating the critical role of clinical pharmacology studies in the development of biosimilars. Specifically, these studies are "part of a stepwise process for demonstrating biosimilarity between a proposed biosimilar product and the reference product and add to the *totality of the evidence* to support an overall demonstration of biosimilarity…."

Comments Should Be Submitted by August 12

To ensure that FDA considers comments before issuing the final version of the draft guidance, FDA encourages industry to submit comments on the draft guidance by August 12. Comments can be submitted electronically to http://www.regulations.gov [Docket No. FDA–2014–D–0234].

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