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FDA Biosimilar Policy: 3 Documents, 1 Key Theme

Law360, New York (May 12, 2015, 12:42 PM ET) --

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On April 28, 2015, three years after the initial draft biosimilar guidance documents were issued, the U.S. Food and Drug Administration released final biosimilar guidance documents. The final biosimilar guidance documents mirror the initial drafts and consist of the following three documents: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; and a Q&A Regarding Implementation of the Biologics Price Competition and Innovation Act ("BPCI Act") of 2009.

Throughout each of the three guidance documents, the FDA emphasizes its recommendation that potential biosimilar applicants meet early and often with the FDA during their development of a biosimilar.

1. Scientific Considerations Guidance Document

The Scientific Considerations Guidance Document provides an overview of the FDA's approach to determining biosimilarity and discusses the important scientific considerations needed to demonstrate this biosimilarity. These scientific considerations include: (1) a stepwise approach to demonstrating biosimilarity; (2) the totality-of-the-evidence approach that the FDA will use to review applications; and (3) general scientific principles in conducting different analyses and studies.

The FDA highly recommends the use of a stepwise approach to show biosimilarity. According to the FDA, such an approach should include the following: (1) extensive structural and functional characterization of the proposed product and the reference product; (2) animal studies; (3) comparative human pharmacokinetics (PK) and pharmacodynamics (PD) studies; (4) clinical immunogenicity assessment; and (5) additional clinical data needed to address any uncertainty about biosimilarity. Each of the above should preferably be performed in a stepwise manner instead of in parallel "to better address residual uncertainty about biosimilarity that might remain at each step." (Scientific Considerations at 8.)

The FDA anticipates that the biosimilar applicant will evaluate the existence of any residual uncertainty about biosimilarity of its proposed product after each step and will identify ways to address any such uncertainty. Further, the FDA stresses the importance of consulting with it after the performing structural and functional characterization studies and before finalizing the clinical program. The FDA encourages biosimilar applicants to continue to discuss the development of their biosimilar and any related experimental data with the agency throughout the process.

The FDA elaborated on the structural and functional studies, animal studies and clinical studies it would expect to be included in a successful biosimilar application. A few of the structural tests the FDA highly recommends include the following comparisons of the proposed product and the reference product: primary structures, such as amino acid sequence; higher order structures; and enzymatic post-translational modifications. Functional studies should evaluate the pharmacologic activity of protein products by in vitro and/or in vivo functional assays, which include biological assays, binding assays, enzyme kinetics and animal models of disease to evaluate functional effects on pharmacodynamics markers or efficacy measures.

The FDA also discussed the role of animal studies in the biosimilar application and discussed some animal studies that may be useful, including animal toxicity studies, animal pharmacokinetic and pharmacodynamics measures, and animal immunogenicity assessments. Finally, the FDA provided information regarding clinical studies. "As a scientific matter, the FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s)) and a clinical immunogenicity assessment." (Scientific Considerations at 14.)

In addition to setting forth the experimental data that should be included in a biosimilar application, the FDA further described how it will assess whether the data provided demonstrates biosimilarity by using a totality-of-the-evidence approach. The totality-of-the-evidence approach requires a risk-based evaluation of all of the data and information submitted by the sponsor. The critical analysis is whether the evidence shows no clinically meaningful differences between the proposed product and the reference product.

2. Quality Considerations Guidance Document

The Quality Considerations Guidance Document provides guidance regarding the relevant studies needed to assess whether the proposed product and reference product are highly similar to support the claim of biosimilarity. The FDA expects biosimilar applicants to "use appropriate analytical methodology that has adequate sensitivity and specificity to detect and characterize differences between the proposed product and the reference product." (Quality Considerations at 6.) Specifically, the FDA highly recommends the use of widely available state-of-the-art technology. Further, the FDA encourages submission of comprehensive analytical similarity data to the FDA early in the development process, so the FDA can provide input on the extent and scope of any necessary animal and clinical studies.

The FDA also addresses how a biosimilar applicant should handle a comparison between the proposed product and a non-U.S.-licensed comparator product in place of the reference product. The FDA requires that the biosimilar applicant establish a "bridge" to the reference product. To do so, a biosimilar applicant should conduct analytical studies that directly compare all three products: (1) the proposed product, (2) the reference product and (3) the non-U.S.-licensed comparator product.

Again, the FDA highly recommends that a biosimilar applicant choosing to rely on such comparative data to meet early with the FDA to discuss the adequacy of the bridge to the reference product. It is interesting to note that the FDA offer of recommendations on how a biosimilar applicant should handle a comparison between the proposed product and a non-U.S.-licensed comparator product is a vast departure from its rigid view on the use of a non-U.S.-licensed comparator product in small molecule abbreviated new drug applications. In those small molecule ANDA cases, the FDA has generally declined to allow comparisons with non-U.S.-licensed comparator products.

Finally, the Quality Considerations Guidance Document lists a number of factors a biosimilar applicant should consider when assessing whether products are highly similar. The biosimilar applicant should contemplate the following: expression system, manufacturing process, assessment of physiochemical properties, functional activities, receptor binding and immunochemical properties, impurities, reference product and reference standards, finished drug product and stability. The FDA lays out key points that should be considered when assessing each individual factor.

3. Q&A Guidance Document

Those who read the draft versions of these guidance documents will note that the Q&A Regarding Implementation of the BPCI Act is substantially revised from its earlier version. For example, the final document includes an extensive discussion of the use of bridging studies to use data from outside the United States as part of a biosimilar applicant's showing of biosimilarity. The FDA encourages that, in such cases, studies should directly compare the biosimilar, the US reference product, and the foreign comparative reference product. Like the other documents, the Q&A encourages extensive communication with the FDA to resolve issues, including the proper scope of bridging studies.

Another category in the Q&A document that has undergone substantial revision is the section on extrapolation of clinical data. The FDA has expanded the issues that need to be addressed prior to justifying extrapolation and also has suggested that biosimilar applicants not try to extrapolate from indications approved under the accelerated approval subpart.

Additionally, there are four questions in the draft that are not in the final Q&A document. The FDA has indicated that these questions will be finalized and added at a later date. The most contentious of these is the question regarding interchangeability. The FDA has not provided any timeline as to when it will provide clarification on the process of demonstrating interchangeability for a biosimilar product with its biologic reference product. To date, the FDA has not had to address this topic, since the first approved biosimilar application for Zarxio did not request a finding of interchangeability. However, it is likely that as the biosimilar application process is clarified, more applicants will seek a finding of interchangeability.

Conclusion

One key theme that did arise from the guidance documents is the FDA's willingness to advise biosimilar applicants during the development process. Throughout all three documents, the FDA encourages biosimilar applicants to meet with the FDA early and often throughout the development process. In fact, the "FDA anticipates that early discussions with the FDA about product development plans and about the approaches to providing adequate scientific justifications will facilitate biosimilar development." (Scientific Considerations at 23.)

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