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FDA's Biosimilar Rules Will Provide Testing Clarity

Law360, New York (May 27, 2014, 3:43 PM ET) -- The U.S. Food and Drug Administration's biosimilars guidances provide some rules of the road for successfully navigating the highway to approval of a biosimilars application under Section 351. The FDA's newest draft guidance on demonstrating biosimilarity reiterates aspects of the agency's past guidance on the subject, but it also offers a bit more insight on its current thinking regarding the stepwise clinical testing approach that it expects to see from applicants. Early and frequent discussions with the FDA regarding planned clinical studies remain key in order to best position an application for approval.

FDA Biosimilars Guidances

The 2010 Biologics Price Competition and Innovation Act established a pathway for approval of biosimilar products when the sponsor of a biosimilar application can show that its proposed product is "highly similar" to a reference biologic product under Section 351(i)(2) of the Public Health Services Act.

A proposed product is highly similar if there is "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product." After public hearings in late 2010 and much debate, the industry keenly awaited further guidance from the FDA as to the type and extent of testing that would be needed to meet the statutory standard for biosimilarity.

In February 2012, the FDA issued a draft guidance, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," which was appreciated by the industry but left many wanting more substantive direction from the FDA. In the guidance, the FDA stressed that applicants would need

to use a “stepwise approach” to demonstrating biosimilarity and that the FDA would evaluate a biosimilar application using a risk-based, totality-of-the-evidence approach. The FDA also generally discussed the type of information that would be needed to demonstrate biosimilarity, including structural analyses, functional assays, animal data and clinical study data.

On May 13, 2014, the FDA issued another draft guidance, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." This guidance focuses on the clinical showing needed to demonstrate biosimilarity. The substantive information it provides is highly consistent with the earlier guidance issued in 2012. The 2014 guidance reiterates the FDA’s approach reflected in the 2012 guidance on demonstrating structural similarity between a proposed biosimilar product and the reference product. In some areas, however, the 2014 guidance provides further detail regarding the clinical testing needed to either demonstrate biosimilarity or to provide direction on the additional clinical testing needed.

Similarities between the FDA's 2012 and 2014 Guidance

Many of the substantive positions articulated by the FDA in the 2012 guidance are echoed and reiterated in the 2014 guidance, including:

- Applicants should take a stepwise approach to developing the data necessary to demonstrate biosimilarity and functional and clinical data can guide whether additional testing is needed and the design of that additional testing.

- The FDA will take a totality-of-the-evidence view of the data submitted in support of a biosimilar application.

- The use of animal and human immunogenicity, pharmacokinetic ("PK") and pharmacodynamic ("PD") data, including an emphasis on any clinically relevant PD measures and endpoints, as part of the totality of the evidence.

- A preference for crossover human-clinical studies where the product has a short half-life (e.g., shorter than five days) and low incidence of immunogenicity as well as a recommendation to use a parallel study design where the products have a longer half-life.

- The use of in-vivo and in-vitro functional assays to demonstrate bioequivalence, including bioassays, biological assays, binding assays and assays to elucidate the mechanism of action of the product.

- The potential availability of using data from a foreign reference product provided the sponsor provides adequate data or information to justify the relevance of such data and to establish a bridge to the U.S.-licensed reference product.

- The utility of comparing quality attributes of the proposed biosimilar product and the reference product using a “fingerprint-like analysis” that evaluates a large number of such attributes with high sensitivity using orthogonal methods.

The totality-of-the-evidence approach and the importance of evaluating many attributes using sensitive measures to provide a fingerprint-like analysis was not a new concept to the FDA’s 2012 guidance. These

concepts were suggested for biosimilars in an August 2011 article in the New England Journal of Medicine by the FDA's Drs. Kozlowski and Woodcock, who stated:

Such a totality[-]of[-]the[-]evidence approach can also be applied to assessing biosimilars, since it seems possible to exceed a current state-of-the-art analytic characterization by evaluating more attributes and combinations of attributes at greater sensitivity with multiple complementary methods. There may be strategies that allow a 'fingerprint'-like identification of very similar patterns in two different products. Such strategies were used in supporting the approval of a generic low-molecular-weight heparin product, enoxaparin — which, though it differs from proteins in important ways, is structurally complex. Although additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable future, the scope and extent of such studies may be reduced further if more extensive finger-print-like characterization is used.[1]

Additional Information from the FDA's 2014 Guidance

There are four areas where the FDA provided valuable additional information for companies looking to file a 351(k) biosimilar application.

First, the FDA stressed that three key concepts — exposure and response assessment, evaluation of residual uncertainty and assumptions about analytical quality and similarity — are particularly relevant to the agency's review. With respect to exposure (well-known PK variables such as Cmax, Cmin, and AUC) and response (PD, or the direct measure of pharmacological or toxicological effect of a drug), the FDA provided some detail regarding the design of PK and PD studies that will determine the extent and design of additional clinical studies that may be needed.

Presumably, more convincing PK and PD results will refine the design and extent of any additional clinical trials the FDA may require. The FDA's 2014 guidance provides additional detail on how to determine the appropriate PD markers to be measured. The guidance also states that the degree of uncertainty at each clinical step will dictate the need for further studies. Finally, in discussing the quality attributes analysis, the 2014 guidance again encourages the use of a fingerprint-like algorithm to compare the proposed and reference products. The 2014 guidance states that the comparative characterization data will be used to assess the proposed product as either: (1) not similar, (2) similar, (3) highly similar or (4) highly similar with fingerprint-like similarity. While the FDA provides a description of these categories, it is unclear precisely what information or data will ensure a proposed product falls in the third or fourth categories.

Second, the FDA discusses three specific assays it describes as "particularly important:" (1) ligand binding assays, (2) concentration and activity assays and (3) PD assays. The guidance suggests multiple assays may be necessary to provide meaningful information on the PK activity and PD effect of the proposed product. Sponsors should be prepared to provide supporting data for choice of assay and for any markers chosen for evaluation.

Third, with respect to the use of foreign-reference products and the need for a bridge study, the FDA's 2014 guidance states that the type of bridging data needed "will always include data from analytical studies (e.g., structural and functional data) that directly compares all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product and the non-U.S.-licensed product) and is likely to also include PK and, if appropriate, PD study data for all three products." This general criteria for bridging data is not surprising, though it is reassuring to have the FDA expressly articulate a criteria.

And fourth, the FDA's 2014 guidance states that modeling and simulation tools can be useful for designing PK and/or PD studies. Several creative companies were already investigating the use of modeling or simulation tools, and many have likely already submitted plans to use such data from such tools in prefiling meetings with the FDA as part of the agency's Biological Product Development Program ("BPDP") — the program that allows for preapplication meetings with the FDA to optimize product development and facilitate submission of biosimilar applications.

Preparing a Biosimilar Application in View of the FDA's 2014 Guidance

It is important to remember that the FDA is taking a risk-based approach to evaluating biosimilar applications — the agency wants to see data demonstrating that any clinical uncertainty is minimized as greatly as possible. To that end, we provide the following considerations for an applicant looking to file a biosimilar application.

Participate in the BPDP

The FDA is your friend! The agency is giving applicants an opportunity to discuss their applications, including their clinical plan-of-action, before filing an application. Participants in the BPDP can have no-fee initial advisory meeting with the FDA within 90 days of submitting the required information and the BPDP allows for four different types of additional meetings (meeting Types I-IV) where, for an additional fee, the agency can review and address various issues with an application.

Type I meetings are for programs that stalled, Type II meetings are to address specific issues with a program, Type III meetings are more substantive and entail an in-depth review of all data by the FDA, and Type IV meetings are for applications that are near-ready to be filed and focus on the format and content of an application. By the end of 2013, there were around 40 biosimilar development programs and the FDA held five initial meetings, and 32 meetings that were Type I-IV meetings. In addition to receiving valuable input regarding a proposed biosimilar product, the fees that an applicant pays to participate in the BPDP are applied toward the actual filing of a biosimilar application.

Educate the FDA

Unlike in the small molecule context, the FDA does not yet have a template of the information that it wants to see to determine the biosimilarity of a proposed product. It is up to the applicant to educate the FDA about the information that it needs to make that determination and why that information is valuable to the analysis.

Consider Biosimilarity from Different Angles

The FDA’s totality-of-the-evidence approach should be met with a broad spectrum of supporting information. In addition to addressing the FDA’s key clinical data with appropriate PK and PD data, be sure to support such data with appropriate additional data and information, especially analytical characterization data.

Choose Assays and Biomarkers Wisely

The clinical testing endpoints that were used to develop a reference product may not be the appropriate ones to consider in demonstrating bioavailability. Any assays, biomarkers or endpoints that are under consideration should be particular to the proposed biosimilar and should be vetted with the FDA in

advance. And take note of the assays the FDA referred to as being of “critical importance.”

Be Justifiably Creative

Demonstrating biosimilarity can be a costly endeavor. Consider the use of statistical analyses, simulation or predictive data and foreign data to obtain approval of your proposed product overseas. In addition, strong characterization information using, for example, mass spectrometry, capillary isoelectric focusing and peptide mapping, is a must in order to demonstrate a fingerprint-like approach.

Have a Flexible Plan

The FDA has dictated that applicants should take a stepwise approach to demonstrating biosimilarity. Don’t fight it. Have your plan of action and be prepared to justify it, but also be prepared to adjust your plan based on the data that you compile and your conversations with the FDA.

Finally, in addition to preparing to make a regulatory showing of biosimilarity, applicants should not forget to consider the patent barriers that may be encountered after your application is on file. Applicants should consult with counsel to understand the patent landscape for a reference biological product during the product development stage. In addition, applicants should also have an early discussion regarding whether to avail themselves of the ability to challenge patents using the inter partes review ("IPR") procedure created by the America Invents Act.

IPR petitions can be filed one year after a patent has issued and are focused solely on challenging the validity, anticipation or obviousness under Sections 102 and 103, respectively, of the Patent Act, of a patent based on prior art references. IPRs are potentially faster and more cost-effective than district court patent proceedings, are presided over by a panel of administrative law judges with technical backgrounds, do not recognize a presumption of patent validity and have a lower burden for proving patent invalidity. In addition, in about two years of IPR proceedings, the patent challengers have been relatively successful: 80 percent of the petitions to institute an IPR proceeding have been granted, about 95 percent of the challenged claims have been invalidated and over 120 IPR proceedings have been settled.

Future Considerations

It is unclear if or when the FDA will provide any additional comment or guidance regarding what is needed to demonstrate biosimilarity. With the incremental approach the FDA has taken thus far, it is reasonable to think that the FDA may issue a guidance on the structural data that it would like to see as part of a biosimilar application. However, we do not expect to see such a guidance soon. In addition, with the number of products and companies engaged in the BPDP, the first wave of biosimilar applications are expected soon. After the first wave of biosimilar applications are filed and eventually approved, we may see some product-specific biosimilar guidances. The European Medicines Agency has developed a practice of issuing such product-specific guidances.

Conclusion

The FDA's 2014 guidance reinforces the main teachings from the agency's 2012 guidance, but also provides some additional detail regarding the clinical data and information needed to demonstrate that a proposed product is “highly similar.” The additional teachings in the 2014 guidance will be helpful in formulating a clinical study plan of action. Open and early communication with the FDA remains key for

preparing biosimilars applications along with enrolling and participating in the agency's BPDP to discuss and improve any clinical study plan of action.

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[1] S. Kozlowski et al. (2011) Developing the Nation’s Biosimilars Program, N. ENGL. J. MED.; 365[5], 385-388, 386.
