More on FDA Draft Guidelines for "Follow-on" Biologic Drug Approval Pathway

By Kevin E. Noonan -- February 14, 2012

Last Thursday, the U.S. Food and Drug Administration issued draft guidances pursuant to its authority under the Biologics Price Competition and Innovation Act of 2009 (*see* "FDA Publishes Draft Guidelines for Biosimilar Product Development"). The draft guidances are intended by the agency to implement the follow-on biologic drug pathway mandated by the statute, and are set forth in three separate guidances directed to:

1) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

2) Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

3) Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

The first draft guidance, directed to scientific considerations concerning biosimilarity, is "focused" on therapeutic polypeptides and uses a "step-wise," "totality of the evidence" approach." As set forth in detail in the draft guidance, this approach addresses the question of biosimilarity using various analytical method "step-by-step," where the results of one assay are interpreted and used to select additional assays that will provide additional information missing or unclear from earlier assays. The first step is always "rigorous" comparisons of the physicochemical characteristics and functional properties of a candidate biosimilar drug, performed in comparison with the reference drug product. From these results, the draft guidance recommends animal toxicity testing (as expressly required by the statute), human pharmacokinetic and pharmacodynamics studies, immunogenicity studies, and clinical safety and effectiveness trials. The draft guidance also recommends postmarketing safety monitoring for biosimilar products having a reference drug product known to be associated with significant risks of adverse events. This guidance also defines the use of the term "should" as meaning "recommended" rather than "required" by the agency.

The second draft guidance, related to quality considerations, is specifically concerned with chemistry, manufacturing, and controls (CMC) of biosimilar products. This draft guidance references almost two dozen earlier FDA and International Conference on Harmonization (ICH) guidances relating to biologic drug regulations, particularly relating to the production of recombinant protein products (like the first draft guidance, this draft guidance is specifically directed to therapeutic proteins, albeit acknowledging that the suggestions in the guidance might also apply to proteins and peptides used with diagnostic methods). The draft guidance also advocates a "risk-based" approach, which will permit variances in biologic drug properties and characteristics (including primary amino acid sequence) if justified by the biosimilar applicant. Assessments will be made under a "totality of the analytical data" standard, intended to take into account interactions between various measured parameters. Specific aspects of biologic drug production falling within the scope of this guidance includes the expression system,

manufacturing processes, assessments of physicochemical properties, functional assays, receptor binding (when appropriate) and immunochemical properties, impurities (both product- and process-related), reference product and reference standards, the finished drug product and stability studies.

The final draft guidance is presented as a response to questions raised during pubic hearings on FDA rulemaking. The gist of the answers given is that the agency will take a permissive approach to changes in formulation, delivery device or container and fewer than all the routes of administration, presentations or conditions of use of the reference biologic drug, provided that the biosimilar applicant provides the statutorily mandated evidence that the product is "highly similar" to the reference drug product and has equivalent safety, purity, and potency. The FDA also indicates in this draft guidance that animal or clinical data from non-U.S. licensed biosimilar products will be considered in support of a biosimilars application under Section 351(k) but only under specific circumstances set forth in the guidance. The guidance specificly states that agency has not yet established requirements for interchangeability.

Finally, each draft guidance carries a disclaimer that the guidance represents the agency's "current thinking" and that applicants can use "alternative approach[es]" if the approach satisfies the statutory requirements. No rights are created or conferred nor is the agency bound by the terms of these guidances (presumably even when promulgated in final form).

The guidances are merely provisional in nature, and are subject to revision based on public comments received by the agency within 60 days of publication (*i.e.*, April 9, 2012).

And yet. . .

At first blush the draft guidances are a little disappointing to anyone looking for clear guidelines for biosimilar applications. While it is perhaps the case that the "correct" path to biosimilar licensure will only be developed by working through the issues as they arise, in the main the guidances merely recite well-known concepts (that therapeutic proteins are more chemically complex than small molecule drugs, for example). The types of analytical methodologies are recommended to be "rigorous" and "state-of-the–art" with but a few examples of what the agency has in mind. The draft guidances are also strictly limited to theraoeutic proteins (although the quality guidance suggests that similar approaches may be used for proteins utilized in diagnostic assays). The agency has adopted a "totality of the evidence" standard which, like Supreme Court "totality of the circumstances" tests provides utmost agency flexibility and a minimum of information on the metes and bounds of acceptable evidence. The draft guidances also suggest a "stepwise" or "step-by-step" approach, wherein the quality (and perhaps quantity) and persuasiveness of the evidence presented from each analytical methodology informs the type of evidence necessary in succeeding analytical methods; in this way "selective and targeted" application of successive analytical testing can be preformed to remove "residual uncertainty." While reciting the requirement for the statutorily-mandated testing (for example, comparisons of the physicochemical characteristics and functional properties of a candidate biosimilar drug, performed in comparison with the reference drug product, and animal toxicity testing) the guidances provide little more than general recommendations regarding what a biosimilars applicant must submit to satisfy the agency that the biosimilar is "highly similar" to the reference biologic drug. The provisional nature of the draft guidances is emphasized by the qualifying language throughout that the requirement for almost all

the suggested types of evidence can be waived upon an adequate showing of the absence of differences between the biosimilar and the reference biologic drug.

The most specific advice comes from the third draft guidance, which is presented as a response to questions raised during pubic hearings on FDA rulemaking. But the guidance specificly states that agency has not yet established requirements for interchangeability.

Maybe it was unrealistic to expect anything more specific from the agency in view of the short timeline for producing the draft guidances and the complete lack of (U.S.) experience with biosimilar drug approval. The second guidance references more than a dozen other FDA and International Conference on Harmonization (ICH) guidances relating to biologic drug regulations, particularly relating to the production of recombinant protein products. Going forward, it may be profitable to compare these guidances with the experiences in Europe and elsewhere regarding biosimilar drugs, and to provide suggestions during the comment period for changes in the draft guidances consistent with successful biosimilar drug approvals abroad