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FDA Finalizes Key Guidance Documents on Biosimilars

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On the heels of its approval of the first biosimilar product in March, FDA has just released final versions of three key biosimilar guidance documents under the Biologics Price Competition and Innovation Act (BPCIA). The newly finalized documents update draft guidance documents published in February 2012. Together, the three final guidance documents present FDA's approach for determining biosimilarity and the critical scientific and quality issues that sponsors will need to address in their so-called "351(k) applications" (named after the new section added to the Public Health Service Act by the BPCIA).

Scientific Considerations in Demonstrating Biosimilarity

The first finalized guidance document, **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**, lays out the approach that sponsors should take when developing the evidence needed to demonstrate biosimilarity to a reference product, as well as FDA's "totality-of-the-evidence" approach for reviewing biosimilar applications. In addition, it discusses general scientific principles for sponsors to consider when performing:

- structural and functional analyses of the proposed biosimilar;
- animal toxicity studies;
- human pharmacokinetic and pharmacodynamic studies;
- clinical immunogenicity assessments; and
- clinical safety and effectiveness studies.

The substantive information in this final guidance mirrors what the Agency presented in the 2012 draft guidance document, although some changes were made to clarify and reorganize the recommendations. Notably, the Agency continues to encourage sponsors to consult with FDA early and often during the biosimilar development process because "the type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis."

Quality Considerations in Demonstrating Biosimilarity

The second guidance document addresses **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product** and deals with the technical aspects of "chemistry, manufacturing, and controls" (CMC) information for a proposed biosimilar application. Significant changes in the finalized version of this guidance include a more detailed discussion about the need for "bridging data" when a non-U.S.-licensed comparator biologic is used in certain studies supporting a demonstration of biosimilarity to a U.S.-licensed reference product, as well as expanded descriptions on characterizing impurities in the biosimilar product that may be different than impurities in the reference product. The take-home message of this guidance continues to be that "proteins are very sensitive to their environment" – thus, for example, even the primary packaging for the product should to be analyzed in comparison to the reference product's packaging to determine whether product stability or clinical performance is adversely affected.

Questions and Answers

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 is the third guidance document, organized (as evident from the title) into a question and answer (Q&A) format. FDA has positioned this as a living document that will be updated with new Q&As as necessary. The recently released iteration finalizes many of the Q&As that were presented for comment in the February 2012 draft version, but it omits several questions (presumably due to an inability to finalize the Agency's answers at this point in time) and also indicates that a few of the draft Q&As are in the process of being revised and will be released again for public comment. Of particular note, a draft Q&A regarding whether a sponsor can request a determination from FDA on

interchangeability as part of the original 351(k) application has been omitted.

Significant Questions Remain

Despite the publication of this final guidance for industry, many of the more contentious questions surrounding the new regulatory pathway for biosimilars remain unanswered by FDA. Draft guidance on biosimilar "naming" reportedly was sent last year to the Department of Health and Human Services for review and approval before FDA releases the draft for public comment. The two sides of the naming issue continue to disagree about whether a biosimilar's nonproprietary name should be the same as that of the reference product, and whether and to what degree this will affect product tracking and post-market safety surveillance. A final decision on naming conventions may also have practical implications for pharmacy, PBM, and payor operations, including formulary development.

In addition, the Agency has yet to provide any guidance on what will be necessary to establish the interchangeability of an approved biosimilar. As noted in our **recent blog post** regarding state activity on biosimilar substitution laws, the sponsor of the recently approved biosimilar product, Zarxio, did not seek an interchangeability decision from FDA. Whether or not a biosimilar is "interchangeable" will be critical in determining whether pharmacists may substitute the biosimilar for its prescribed reference product, given that most states acting to impose limits on such substitution are requiring the biosimilar first to be approved by FDA as interchangeable.

Other scientific and technical questions for which industry is seeking more specific guidance from FDA include what standards must be met for indication extrapolation and labeling requirements. The Zarxio approval provides some insight into FDA's thinking on these issues. The Agency approved Zarxio for use in all five of the labeled indications of its reference product (Neupogen), even though the sponsor did not study the biosimilar for each indication, and the labeling for Zarxio is almost identical to that of its reference product. Accordingly, FDA did permit indication extrapolation for this well-characterized protein product. Indication extrapolation may be more difficult to obtain from the Agency for a product with a less well-characterized mechanism of action. This would track the trend observed so far with biosimilars approved for marketing in Europe.

We will continue to keep our readers apprised of any developments from FDA, CMS, or the states on these important issues and others related to biosimilars.

Authors

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