Key FDA Officials Signal Approach to Review of Biosimilar Products

Agency Will Rely on a Risk-Based and "Totality of the Evidence" Standard

In an article published in yesterday's *New England Journal of Medicine ("NEJM")*, several key officials with the Food and Drug Administration ("FDA") outlined an approach to review and approval of biosimilars in the United States. While this approach does not represent the official position of the agency, it does signal how the agency will likely review applications for biosimilar products under the Biologics Price Competition and Innovation Act. That statute, which was adopted last year, authorized FDA for the first time to approve biosimilars pursuant to an abbreviated pathway where applicants may rely on FDA's previous approval of a "reference product."

Specifically, in a publication entitled "Developing the Nation's Biosimilars Program" in the August 4, 2011 edition of the *NEJM*, Dr. Steven Kozlowski (Director, Office of Biotechnology Products), Dr. Janet Woodcock (Director, Center for Drug Evaluation and Research), Dr. Karen Midthun (Director, Center for Biologics Evaluation and Research), and Dr. Rachel Behrman Sherman (Associate Director for Medical Policy) make the following key observations:

(1) FDA must, as a matter of initial priority, develop scientific criteria to evaluate how similar a biosimilar must be to a reference product to be close enough for approval. This will be challenging since most biologic products are complex and can not be easily characterized.

(2) Given the complexity of biologics, a "one size fits all" approach will not work. Rather, depending on the particular product, FDA scientists will consider various types of information or the "totality of the evidence" to assess biosimilarity.

(3) A totality of the evidence approach contemplates the use of multiple, complementary methods that allow for the evaluation of more attributes of a product at greater sensitivity. The authors point out this strategy was used to support approval of generic enoxaparin.

(4) Under this approach, animal and clinical studies will "for the foreseeable future" be required for approval of protein biosimilars. But, the scope and extent of such studies may be reduced where detailed "fingerprint-like characterization" is utilized.

(5) The totality of the evidence approach will require applicants to "carefully tailor" animal and human testing to address, what the article refers to as, any "residual uncertainty." Applicants will also need to select appropriate source materials and "tune their processes" carefully.

(6) To provide helpful advice on the type of animal and human testing required for a biosimilar, an extensive product review (exceeding a typical pre-IND meeting) will be required early on. The agency is currently considering how such interactions will be structured.

(7) The potential for immunogenicity presents critical questions for biosimilars. The agency intends to evaluate immunogenicity in a risk-based manner, and will consider protein aggregation and whether the product stimulates immunity to nonredundant self-proteins.

(8) Since even small changes to a biologic may affect safety and efficacy, and such changes are frequently made by manufacturers, FDA will need to establish a robust pharmacovigilance program that allows for ready identification of each biosimilar product and manufacturer.

(9) For products seeking a designation of "interchangeability," FDA will enunciate regulatory standards outlining data requirements. This designation reflects FDA's judgment that a biosimilar may be substituted for the reference product without the prescriber's intervention.

(10) Finally, the agency will also develop standards to ensure that biosimilar products, which have not been deemed interchangeable, are not inadvertently substituted for a reference product without the prescriber's consent.

This approach to the evaluation of biosimilars will likely be further elaborated as more formal FDA policy later this year. The agency has previously indicated that it intends to issue a guidance document by the end of the year which will clarify, from a substantive perspective, the agency's thinking on various issues surrounding biosimilars. Those issues include how to define a biosimilar product, what standards should govern biosimilarity and interchangeability, how to name products and accompanying pharmacovigilance issues, and the types of exclusivity that apply to biosimilars. In November 2010, FDA sponsored a two day public hearing where it invited stakeholders to express their views on these and other issues. The information generated as part of that hearing will undoubtedly help shape FDA's forthcoming guidance document on biosimilars.

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