WSGR ALERT

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FDA PUBLISHES PROPOSED IMPLEMENTATION GUIDELINES FOR BIOSIMILAR APPROVALS

After almost no movement in the last year on the biosimilar regulatory front, the Food and Drug Administration (FDA) and the White House both have weighed in this past week, proposing significant changes and implementation guidelines for this important regulatory pathway. The new guidelines outline the process through which the FDA will approve biologics based on the demonstration that they are biosimilar to, or interchangeable with, already approved reference biological products. Although far from perfect, these guidelines will help biosimilar manufacturers meet rapidly expanding patient needs and open the door to less expensive versions of approved biological products, which accounted for $138 billion in U.S. sales in 2010 alone.

Biosimilars include a large variety of biological products, including vaccines, blood and blood components, gene therapies, tissues, and proteins (such as antibodies). In contrast to producers of traditional chemical-based therapies, manufacturers of biological products face greater technical barriers-to-entry as a result of more complicated manufacturing processes. The three guidance documents issued by the FDA on February 9, 2012, reflect the agency's attempt to assist applicants seeking approval through the abbreviated biosimilar pathway (or 351(k) application) set forth in the Biologics Price Competition and Innovation Act (BPCI). The FDA will formally publish the guideline documents in the Federal Register, at which point the public will be invited to comment within 60 days.

Of the recently issued draft guidance documents, the director of the FDA's Center for Drug Evaluation and Research, Janet Woodcock, M.D., commented:

> "When it comes to getting new bio-similar products on the market, FDA has taken an innovative approach to supporting their development at every step of the process. These draft documents are designed to help industry develop bio-similar versions of currently approved biological products, which can enhance competition, and may lead to better patient access and lower cost to consumers."

The three draft guideline documents include:

1) **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**
This draft guidance document provides details of a risk-based, case-by-case approach encompassing a "totality-of-the-evidence" analysis procedure through which the FDA will assess biosimilarity between the proposed and referenced products. Guideline measurements include, among other considerations, analysis pertaining to: i) structure, ii) function, iii) animal data (e.g., toxicity, PK and PD measures, clinical immunogenicity), and iv) clinical data (e.g., pharmacokinetics, pharmacodynamics, clinical immunogenicity, clinical safety and effectiveness, clinical study design, and extrapolation of human data across indications). The FDA also will include post-marketing safety monitoring considerations as an important component of the entire biosimilar development process.

Although the FDA recognizes that direct comparison of information and data between the proposed biosimilar and reference products should be provided to demonstrate biosimilarity, the agency makes clear that, under certain circumstances, a sponsor may seek to use data comparing a proposed product with a non-U.S.-licensed product. For example, animal or clinical data from studies on a non-U.S.-licensed product may be used to address, in part, biosimilar application requirements under Section 351(k)(2)(A) of the BPCI. As with all studies, the FDA encourages applicants to consult with them and establish early milestone schedules to facilitate the biosimilar development process.

The draft guidance also includes a list of terminology and definitions proposed to be used by the FDA, including the amendment of the term "biological product" as it currently is defined in the BPCI act, and the addition of the terms "protein," "product," and "chemically synthesized polypeptide." Under the guidelines, the term "protein" is proposed to mean "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size." In addition, the

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term "chemically synthesized polypeptide" is proposed to mean "any alpha amino acid polymer that is a) made entirely by chemical synthesis and b) is less than 100 amino acids in size."

2) **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product**
The second draft guidance document offers an overview of analytical factors that may be considered by the FDA in a 351(k) application when evaluating the biosimilarity between a proposed biosimilar product and a reference product. Such factors include: i) the expression system used; ii) manufacturing processes; iii) physiochemical properties; iv) functional activity, receptor binding, and immunochemical processes; v) impurities; vi) stability; vii) finished product characterization; and vii) physiochemical and biological assessment of the reference product and reference standings, including "a thorough analytical comparison between the proposed biosimilar product and the reference product." While recognizing that the ability to discern relevant differences may be dependent upon the current analytical technology available and the complexity of the product, the FDA concludes that a 351(k) application for a biosimilar product must contain both animal and clinical studies, demonstrating biosimilarity with regard to assessment of toxicity, immunogenicity, and pharmacokinetics or pharmacodynamics, among other considerations.

3) **Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009**
The last draft guidance document attempts to answer anticipated questions from biosimilar developers, addressing concerns that potentially could arise in the early stages of product development. The questions are grouped into the following categories: i) biosimilarity or interchangeability; ii) requirements for submitting a BLA for a "biological product"; and iii) exclusivity. The first section addresses practical questions on seeking licensure for a biosimilar product. The last two sections provide insights into the FDA's interpretation and definition of specific terms used in the biosimilar development process, as well as the process required for requesting reference product exclusivity under Section 351(k)(7).

The documents can be accessed on the FDA's website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm.

The introduction of the new biosimilar guidance documents comes on the heels of another agency effort—the creation of the Biosimilar and Interchangeable Products User Fee program. This program would charge fees to biosimilar applicants to cover the FDA resources needed to support the developmental processes mandated in the BPCI. The FDA has submitted user fee program guidance documents to Congress for review and approval.

While the FDA has pressed on with its agenda of moving forward with biosimilar development, other governmental agencies have provided input that may influence those contemplating entry into the biosimilar development field. For example, President Barack Obama's 2012 budget put back on the table a proposal that seeks to reduce from 12 to 7 years the amount of data exclusivity protection offered to "innovator" biologics against biosimilar products. This proposed reduction, if approved, may help biosimilar development companies decide between pursuing a BLA or biosimilar route for approval of their biological products.

With the publication of these guidelines, it is clear that the FDA remains committed to developing a pathway for biosimilar product approval in the near future. The guidelines represent increased assurance and stability from the FDA that may help to overcome the initial high costs of entering the biosimilar market and navigating the intellectual property and regulatory complexities that exist for biosimilar developers. For additional information, please contact Jeffrey Guise or another member of Wilson Sonsini Goodrich & Rosati's intellectual property practice.

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