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Biosimilars: Draft Guidance Documents Issued by FDA[1]

The new abbreviated regulatory approval pathway for "biosimilar" and "interchangeable" types of biologic drug products was implemented in the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) as part of the Patient Protection and Affordable Care Act of 2010. The details about the use of this pathway were left for further development through Food & Drug Administration ("FDA") action. While the details were initially expected to be determined through federal agency rulemaking, the FDA promptly indicated it would issue such details in the form of "industry guidance," which does not have the force and effect of law but does provide an indication of how the FDA would handle such biologics applications. On February 9, 2012, the FDA issued three draft guidance documents on biosimilar product development. A link containing the three guidance documents can be found here. As was widely expected, the guidance documents emphasize a case-by-case approach to biosimilar approval, although they did not address the other more rigorous pathway of "interchangeable" products.

The first draft guidance document, *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product,* gives an overview of the FDA's approach to determining biosimilarity specifically for therapeutic protein products. The first guidance document stresses the FDA's use of a *totality of the evidence* approach when considering data that supports biosimilarity. The first guidance document recommends that sponsors (*i.e.*, biosimilar applicants) use a stepwise approach to develop evidence of biosimilarity, wherein at each step sponsors "should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty."[2] The guidance document further provides information on the types of studies that may be required to show biosimilarity.

The second draft guidance document, *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*, provides a summary of analytical factors and studies that may be relevant to a determination that a proposed biosimilar and reference product are highly similar. These include a determination of: (a) the differences between the chosen expression system(s); (b) quality assessments, such as Quality-by-Design, quality risk management and effective quality systems as these affect the manufacturing process; (c) physicochemical properties such as heterogeneity and the ranges of variability of different isoforms; (d) differences in functional assays between the proposed biosimilar and the reference product; (e) receptor binding and immunochemical properties; (f) the characterization, identification and quantification of impurities; (g) a comparison of the proposed product to reference standards; (h) comparison of the finished biosimilar and reference drug products, and (i) stability of the proposed biosimilar and reference product. Thus, demonstrating biosimilarity to a reference drug product under the proposed FDA guidelines will require a wider and far more complicated set of studies compared to the relatively fewer and less complicated studies (e.g., bioequivalence and dissolution tests) required for a generic small-molecule pharmaceutical under the long-standing Hatch-Waxman regime.

The final draft guidance document, *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, provides answers to common questions regarding the development of a biosimilar program, such as whom to contact at the FDA and when. The guidance document provides that an initial meeting between the FDA and a sponsor should occur after manufacturing plans have been made and preliminary comparative analytical data has been collected. This final guidance document also provides for some agency flexibility in licensing (i.e., a sponsor can "license" by seeking FDA approval for a different number of routes of

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[2] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, page 7, lines 234-236.

administration, strengths, conditions, etc., than a reference product) and exclusivity options similar to those present in the previously existing Biologics License Application ("BLA") process.

All three guidance documents define a "protein" as any amino acid polymer having greater than 40 amino acids, a "peptide" as any amino acid polymer having less than or equal to 40 amino acids, and a "chemically synthesized polypeptide" as any amino acid polymer that is made by chemical synthesis and has less than 100 amino acids. Therefore, proteins are classified as "biological products" subject to the BCPI Act regulatory pathway, while peptides (excluding those that are included within the definition of "biological product," i.e., a peptide vaccine) and chemically synthesized polypeptides are not. Chemically synthesized polypeptides will thus be regulated as drugs, likely because it appears the FDA has taken the position that such products are easily replicated and need fewer studies to confirm equivalency to a reference product as are small molecule pharmaceuticals. Although the final guidance document attempts to explain the rationale for these size demarcations, products that do not meet the definition of a biological product under the BCPI Act will not be able to take advantage of this new regulatory pathway and will need to pursue FDA approval through the older BLA process.

Once the FDA approval hurdles have been overcome, sponsors will still have to address the complicated patent dance, set forth in the BCPI Act, required to resolve any patent challenges by the reference drug product owner.

The FDA is seeking public comment on the guidance documents and instructions on how to submit comments will be announced soon. If you have specific questions regarding the implications of the guidance documents, please contact us.

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