

FDA Issues Three Draft Guidances for Biosimilars

Initial guidance provides insights on regulatory pathway for biosimilars, but does not address many critical issues.

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After much anticipation, the Food and Drug Administration (FDA) today issued not one but three new draft guidance documents intended to facilitate the submission of marketing applications for biosimilars. The three draft guidances can be accessed through the following links:

- “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009” (Biosimilars Q&A) is available online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>.
- “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product” (Biosimilars Scientific Guidance) is available online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.
- “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product” (Biosimilars Quality Guidance) is available online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>.

FDA is encouraging the submission of comments on all three of these draft guidances **within the next 60 days**. Note, however, that each draft guidance document is assigned a unique docket number for the submission of comments.

This LawFlash provides a brief overview of the draft guidances released today. We are preparing a more detailed analysis, which will include potential implications for stakeholders interested in submitting applications under the developing biosimilars pathway.

The first draft guidance, Biosimilars Q&A, provides an overview of FDA’s current interpretation of some of the statutory requirements created by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The Biosimilars Q&A is also intended to respond generally to comments submitted to the public docket and raised during meetings with stakeholders on the biosimilar pathway. The Biosimilars Q&A is structured in a Q&A format to address specific issues, some of which have been

received from potential applicants, and which FDA apparently intends to expand upon in light of additional comments and questions it may receive concerning the draft document. Currently, the Biosimilars Q&A:

- Summarizes statutory requirements for biosimilarity and interchangeability
- Provides general guidance on content to be included in the 351(k) application
- Recommends that sponsors of biosimilar products that are to be submitted under 351(k) meet early with FDA to discuss the proposed plan for biosimilar development programs and anticipated study requirements
- Responds to some preliminary questions concerning exclusivity

Notably, the Biosimilars Q&A, as well as the other draft guidances, reveals FDA's current view that comparative animal or clinical data developed using a non-U.S.-licensed product can provide evidence that the proposed product is biosimilar to a U.S.-licensed reference product.

In addition, the Biosimilars Q&A provides a potentially controversial definition of "chemically synthesized polypeptide" as meaning any alpha amino acid polymer that is made entirely by chemical synthesis and is fewer than 100 amino acids in size. The Biosimilars Q&A seems to go beyond just revealing FDA's current thinking by asserting a jurisdictional argument that a chemically synthesized polypeptide, as defined, is not a "biological product" but instead a product that should be regulated as a drug under the Federal Food, Drug, and Cosmetic Act unless the polypeptide otherwise meets the definition of a biological product under the Public Health Services Act (e.g., if it is a peptide vaccine).

The second draft guidance, Biosimilars Scientific Guidance, sets out three approaches as central to FDA's current thinking on demonstrating biosimilarity:

1. A stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.
2. The totality-of-the-evidence approach that FDA will use to review applications for biosimilar products.
3. General scientific principles in conducting comparative structural and functional analysis, animal testing, human PK and PD studies, clinical immunogenicity assessment, and clinical safety and effectiveness studies (including clinical study design issues).

The third draft guidance, Biosimilars Quality Guidance, provides direction on analytical studies that may be relevant to assessing whether the proposed biosimilar protein product and a reference product are "highly similar" as defined in the BPCI Act. Interestingly, this document does not address FDA's current thinking on an appropriate approach to determining interchangeability, instead indicating that FDA is continuing to consider the type of information sufficient to enable it to determine that a biological product is interchangeable with the reference product.

Importantly, the Biosimilars Quality Guidance suggests that there may be an opportunity for innovators to argue that current technology does not permit for the demonstration of "biosimilarity" of a potentially competitive biosimilar product in a manner adequate to gain approval under 351(k), thus necessitating the filing of a full biologics license application (BLA). According to the Biosimilars Quality Guidance, "if the reference product and the proposed protein product cannot be adequately characterized with state

of the art technology as recommended by this guidance, FDA recommends that the sponsor consult FDA for guidance on whether an application for the proposed protein product is appropriate for submission under section 351(k)” of the Public Health Services Act.

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