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FDA Finalizes Guidance Documents on Biosimilarity

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On Tuesday, and over three years after the initial guidance documents were released, the US Food and Drug Administration released final versions of three guidance documents discussing how FDA will evaluate applications for regulatory approval of biosimilar products:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Link)
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein (Link)
- Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Link)

Draft versions of the guidance documents were originally released by FDA for public comment in February 2012. In general, the final versions released Tuesday track the draft versions fairly closely, with a few noteworthy differences.

The guidance documents reiterate that the FDA will use a *totality of the evidence approach* to review applications for biosimilar products, and encourages a *stepwise approach to demonstrating biosimilarity* which with rare exceptions will include a comparison of the proposed biosimilar product with the reference product in terms of structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness. This stepwise approach is intended to better address residual uncertainty about biosimilarity that might remain at each step of the approval process.

The final guidance documents contain a few changes from the draft versions that are noteworthy:

- Most of the discussion of issues related to demonstrating the heightened standard for interchangeability was removed from the guidances with a note that it will be the subject of a separate guidance document that is forthcoming.
- The final guidances reiterate that, in most instances, a sponsor will need to provide information to demonstrate biosimilarity based on data directly comparing the proposed biosimilar product to FDA-approved reference product. However, they elaborate on the type of bridging data needed when a biosimilar applicant seeks to use a non-US licensed comparator product to support a demonstration of biosimilarity.
- Specific comments have been provided for biosimilar developers considering manufacturing/process changes after completing the initial analytical similarity assessment including a requirement to demonstrate comparability between the pre- and post-change proposed product.
- More detailed comments regarding animal toxicity studies were added.
- Previous Q and As relating to what constitutes the "publicly-available information" that should be included in a 351(k) application and whether an applicant can include a request for reference product exclusivity in its 351(a) application were deleted – an indication that the FDA is still considering its position on these points.

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