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THE SEARCH IS OVER

INNsight article by Vicki G. Norton, Ph.D., and Siegfried J.W. Ruppert, Ph.D., February 2012

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FDA's Draft Guidance on "Biosimilar" Pathway Leaves Key Questions on Specific Clinical Data Requirements and Interchangeability Unanswered

On February 9, 2012, the U.S. Food and Drug Administration ("FDA" or "The Agency") issued long-awaited draft guidance documents proposing a framework for developing biosimilar products under the Biologics Price Competition and Innovation Act ("BPCIA") of 2009. BPCIA amended the Public Health Service Act ("PHSA") by creating an abbreviated licensure pathway for biological products shown to be biosimilar[1] to, or interchangeable[2] with, a previously FDA-approved biological reference product. Under section 351(k) of the PHSA, a proposed biological product demonstrated to be biosimilar to, or interchangeable with, a reference product can rely on safety, purity and potency data of the reference product to support its licensure.

FDA issued the biosimilars draft "Guidance for Industry" in three installment documents, to which the Agency invited comments within 60 days of the FDA notice[3] :

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product;
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; and
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (collectively "Biosimilar Draft Guidances").

Although industry players eagerly awaited the FDA's guidance in view of the projected billion-dollar market for biosimilar

products in the United States, the Biosimilar Draft Guidances leave some key questions unanswered.

Scientific and Quality Considerations for Demonstrating Biosimilarity

FDA (1) proposed a risk-based, *totality-of-the-evidence* approach to evaluate all data and information provided by a sponsor to support a demonstration of biosimilarity; (2) recommended that sponsors use a stepwise approach in their development of biosimilar products; (3) indicated that it will determine the type and amount of analyses and testing required to demonstrate biosimilarity on a product-specific basis; and (4) outlined general scientific principles in conducting comparative analyses.

The stepwise approach in demonstrating biosimilarity may include analyzing the proposed biosimilar product and the respective FDA-licensed biologic product ("reference product") side-by-side for structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness. FDA recommended that at each stage, sponsors evaluate the extent to which there is residual uncertainty about the biosimilarity and identify and design studies to address those uncertainties. The Agency has discretion to determine that one or more elements—such as certain analytical studies, animal testing, an immunogenicity study or a clinical trial—may not be required in a particular application, and it encourages sponsors to approach the Agency and discuss their product development plan and data to determine what additional information must be provided to satisfy FDA's determination of biosimilarity. Under section 351(k)(6) of the PHSA, a first-approved interchangeable biological product would enjoy a one-year market exclusivity during which FDA would be barred from approving a subsequent interchangeable product, thereby providing a significant market share for the sponsor of a first interchangeable biological product. However, to the disappointment of those seeking clarity on the threshold for interchangeability, FDA indicated that it is still considering what data will be sufficient to support a finding that a biologic product is interchangeable with a reference product.

FDA also proposed that under certain circumstances, instead of comparing the proposed biological product to an FDA-licensed reference product, a sponsor may seek to use animal testing and clinical study data that compare the proposed product with a non-U.S.-licensed product, as long as the sponsor can "establish an acceptable bridge to the U.S.-licensed reference product." FDA's willingness to consider that data will likely benefit sponsors who have already obtained marketing approval of biosimilar products in other markets, *e.g.*, Europe, where a biosimilar approval process was implemented years earlier. However, FDA noted that, at this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be adequate to meet the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.

Additionally, FDA confirmed that a sponsor may be able to demonstrate biosimilarity even though there are formulation or minor structural differences (*e.g.*, post-translational modifications, different excipients), as long as the sponsor provides sufficient evidence demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity.

FDA also provided guidance on analytical studies for expression systems, manufacturing processes, assessing physiochemical properties, functional activities, receptor binding and immunochemical properties, impurities, and stability in the context of the sponsored and reference products.

Biosimilars Q-&-A

FDA responded to questions from sponsors interested in developing biosimilar products, biologics license application ("BLA") holders and other interested parties with respect to (1) biosimilarity or interchangeability, (2) provisions related to requirement to submit a BLA for a "biological product" and (3) exclusivity.

FDA confirmed that a proposed biosimilar product may have a different formulation than the reference product. The products may also differ with respect to the delivery device or container closure system. Further, an applicant for a proposed biosimilar product may obtain a licensure for (1) fewer than all routes of administration for which an injectable reference product is licensed; (2) fewer than all presentations (*e.g.*, strengths or delivery device or closure systems) for which a reference product is licensed; and (3) fewer than all conditions of use for which the reference product is licensed. FDA also confirmed that an applicant can extrapolate clinical data to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed.

Further, FDA provided guidance on determining whether a "biological product" is subject to a BLA or a new drug application ("NDA"). The Agency defined a "protein" as a biological product and subject to a BLA submission as "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size." In contrast to that, chemically synthesized polypeptides (defined as "any alpha amino acid polymer that (1) is made entirely by chemical synthesis and (2) is less than 100 amino acid in size") and peptides (defined as having 40 or fewer amino acids) would not meet the statutory definition of a biological product and will be regulated under the U.S. Food Drug, and Cosmetic Act, requiring NDA submission.

FDA additionally proposed that a BLA applicant may include in its section 351(a) submission a request for reference product exclusivity by specifically describing and evidencing how the proposed product meets the statutory requirements for exclusivity.

Conclusion

Overall, FDA's proposed stepwise totality-of-the evidence approach provides enough leeway in its requirements for a biosimilarity determination that the Biosimilar Draft Guidances appear friendly to the biosimilar industry. Nevertheless, key questions regarding the requirements for clinical data and the additional criteria for meeting the interchangeability threshold necessary to secure potentially lucrative one-year exclusivity remain unanswered.

Notes

[1] A biosimilar product must be "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and there must be "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

[2] "Interchangeable" or "interchangeability" means that the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

[3] Stakeholders have until April 16, 2012, to provide comments to FDA on the draft guidances issued on February 9, 2012. *See* 77 Fed. Reg. 8885 (February 15, 2012).

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