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FDA Biosimilar Policy: More Questions, More Answers

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On May 13, 2015, the U.S. Food and Drug Administration released yet another biosimilar Q&A guidance document — Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. This draft guidance arrives on the heels of the April 28 release of three final biosimilar guidance documents, which also included a Q&A regarding implementation of the BPCI Act of 2009.

As in the other Q&A guidances, there are three categories of questions and answers: (1) part I biosimilarity or interchangeability; (2) part II provisions related to requirement to submit a biologics license application ("BLA") for a "biological product"; and (3) part III exclusivity.

The newly released draft Q&A guidance contains questions and answers from the original 2012 draft guidance document that were excluded from the April 28 final guidance. The draft guidance also contains new questions and answers not previously provided by the FDA. Additionally, some of the questions and answers that originated from the 2012 draft guidance have been revised in the new guidance.

Biosimilarity or Interchangeability Q&A

One question and answer that was revised is Q.I.10. This question discusses the length of time sponsors should retain reserve samples of the biological products used in comparative clinical pharmacokinetic ("PK") and/or pharmacodynamic ("PD") studies. As in the 2012 draft guidance, the FDA recommends retaining reserve samples for at least five years, but it now also provides recommendations as to the quantity of product and dosage units expected to be reserved. These recommendations include retaining a minimum of 10 dosage units each of the proposed biosimilar, reference product and, if applicable, comparator product. The FDA also recommends that the applicant contact the review division in order to discuss the appropriate quantities of reserve samples in certain situations. These situations include, among others, biologics other than protein therapeutics and a product intended for multidose administration.

Additionally, although some of the 2012 draft guidance questions and answers have been revised, the FDA has maintained other questions and answers in the same form as in the 2012 Q&A guidance document. Notably, the FDA has not updated its answer regarding the determination of interchangeability between a proposed product and reference product in an original 351(k) application

(Q.I.14). The FDA still takes a negative position regarding a biosimilar applicant's ability to establish interchangeability in an original application stating, "At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment." (May 2015 Draft Q&A at 7). Further, the FDA has maintained its position that the FDA "is continuing to consider the type of information sufficient to enable the FDA to determine that a biological product is interchangeable with the reference product." (Id.). Thus, despite the FDA's efforts to issue either revised or new guidance documents, it has still failed to provide any direction about critical elements of the biosimilar application evaluation process.

The FDA's new questions and answers regarding biosimilarity or interchangeability address topics such as the requirement for assessment under the Pediatric Research Equity Act ("PREA") (Q.I.16); the timing for submission of an initial pediatric study plan ("PSP") (Q.I.17); whether a separate IND is required for a non-U.S. licensed comparator product used in bridging clinical PK and/or PD studies (Q.I.19); and a question regarding injectable biological products (Q I.18).

The FDA addresses injectable biological products and how to demonstrate that a proposed biosimilar product has the same "dosage form" as the reference product (Q.I.18). Here, the FDA applies a strict interpretation of the term "dosage form" in the Section 351(k)(2)(A)(i)(IV) same dosage form requirement. The FDA "considers the dosage form to be the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product." (May, 2015 Draft Q&A at p. 10). Therefore, if the reference product is an "injection" (e.g., a solution), an applicant could not obtain licensure of a proposed biosimilar "for injection" (e.g., a lyophilized powder) even if the applicant could show that the proposed biosimilar product, when constituted or reconstituted, could meet other requirements for an application for a proposed biosimilar product.

Provisions Related to Requirement to Submit a BLA for a Biological Product

Another new question and answer presented in this guidance addresses the marketing applications necessary for a proposed antibody-drug conjugate (Q.II.3). The FDA states that a BLA should be submitted for a proposed monoclonal antibody that is linked to a drug (antibody-drug conjugate), and that it considers an antibody-drug conjugate to be a combination product composed of a biological product constituent part and a drug constituent part.

Exclusivity

Finally, the FDA has provided one question and answer on exclusivity regarding whether or not an applicant can include a request for reference product exclusivity in its 351(a) BLA submission. The FDA does not provide a definitive answer and instead references another draft guidance document. The agency states, "The FDA is continuing to review the reference product exclusivity provisions of Section 351(k)(7) of the PHS Act and has published a draft guidance addressing certain exclusivity issues ..." (May 2015 Draft Q&A at 13). The draft guidance the FDA refers to describes the types of information that reference product sponsors should provide to facilitate the FDA's determination of the date of first licensure for their products.

Conclusion

As it did when the original 2012 draft guidance was released, the FDA has provided a two-month period for the public to submit comments on the draft questions and answers. The FDA has not provided any

indication of how quickly after the two-month comment period ends it intends to release final versions of these questions and answers. However, after recent urging by the Senate Health, Education, Labor and Pensions Committee for the "FDA to act expeditiously to publish and finalize additional guidance on which the public can rely,"[1] it will be interesting to see how quickly the agency turns around the final guidance documents.

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[1] April 30, 2015 Senate Health Committee Letter to the FDA, available at: http://www.help.senate.gov/newsroom/press/release/?id=bd255c6b-2436-4738-bcb3-a2234b5412c8&groups=Chair.