IQ ANALYSIS: FDA Updates Guidance on Considerations in Demonstrating Interchangeability with a Reference Product

By Michele Dougherty, Ph.D.
Head of Regulatory Affairs Practice
ELIQUENT Life Sciences

Michele brings more than 15 years of regulatory experience to her role as head of ELIQUENT's Regulatory Affairs Practice. A 10-year veteran of the FDA, Michele's career includes regulatory experience across the product quality lifecycle, including multiple leadership roles within FDA's Office of Biotechnology Products.

The Biologics Price Competition Act of 2009 amended the PHS Act to establish the biosimilar pathway in the United States. This created an abbreviated pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product. To achieve a designation of interchangeable a product must meet the following statutory requirements:

- The biologic product must meet the requirements for biosimilarity
- the biological product can be expected to produce the same clinical result as the reference product in any given patient
- for a biological product administered more than once to an individual the risk, in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alteration or switch

The last point is also termed the "switching standard." Once a biologic product has achieved the interchangeability designation it can be substituted for the reference product at the pharmacy level.

The 2019 Guidance for Industry: Considerations in Demonstrating Interchangeability with a Reference Product[1] included the recommendation for a switching study as an important data element for the designation of interchangeability.The information gleaned from the switching study, together with other scientific data, was intended to provide an additional assurance of safety, particularly as it related to the risk of immunogenicity, when a patient's treatment would be switched from the reference product to the interchangeable without the intervention of the healthcare provider.
As more experience with biosimilar and interchangeable products has been gained, FDA's evaluation of that experience has led to an evolution in the scientific approach to establishing interchangeability. As noted in this latest update to the 2019 draft guidance, FDA has observed that the risk in terms of safety or diminished efficacy is insignificant following a single or multiple switches between a reference product and interchangeable[2].

Advancements in analytical methods and technology allow for a more detailed characterization of protein therapeutics and identification of any analytical or functional differences that may exist between the reference product and biosimilar[3],[4]. Experience from evaluating biosimilar products has enhanced FDA's understanding of how analytical differences observed between a reference product and a proposed biosimilar or interchangeable product may impact clinical performance.Consequently, FDA has released an update to the draft guidance with additional recommendations on the approach to establishing interchangeability.

Applicants seeking a designation of interchangeability may now consider providing an assessment of how comparative analytical and clinical data provided in an application or supplement show that the switching standard, as defined above, has been met. Other information or data the applicant considers relevant to support that the risk, in terms of safety and diminished efficacy from switching between the reference product and proposed interchangeable product, should also be provided. The recommendation extends to sponsors with a biosimilar application currently under review via submitting an amendment with the information and data described above.

The recommendations regarding interchangeability reflect a further refinement of the regulatory pathway for biosimilars and interchangeables in the US. This allows developers additional flexibility to meet statutory requirements of the 351(k) pathway when seeking an interchangeability designation. The updates to the guidance align with the goal of the BPCIA act to create an abbreviated pathway for licensure of biosimilar and interchangeable product, resulting in better access for patients to necessary therapeutic products.

[1] See the FDA Guidance for Industry: Considerations in Demonstrating Interchangeability withReference Product

[2] Herndon, T.M., et.al., https://doi.org/10.1371/journal.pone.0292231

[3] Milan-Martin S., et.al., https://doi.org/10.1016/j.jpba.2023.115543

[4] Roger, R.S., et.al., https://doi.org/10.1208/s12248-017-0168-3