January 27, 2017

FDA Issues Draft Guidance on Biosimilar Interchangeability

Introduction

On January 17, 2017, the Food and Drug Administration (FDA) issued draft guidance on "Considerations in Demonstrating Interchangeability With a Reference Product." The draft guidance sheds light on the agency's expectations for demonstrating interchangeability of biosimilar therapeutic protein products under the Public Health Service Act (PHS Act).[1] In 2009, the Patient Protection and Affordable Care Act amended the PHS Act to establish an abbreviated licensure pathway for biological products shown to be biosimilar or interchangeable with an FDA-licensed biological reference product. Although FDA has issued a number of guidance documents on approval requirements for biosimilars, the draft guidance marks the first time that FDA has addressed the standards for demonstrating interchangeability.

General Principles

An interchangeable biological product is one that may be substituted by a pharmacist for a reference product without the intervention of the prescribing health care provider.[2] Under the PHS Act, an application for an interchangeable product must demonstrate that: (i) the product candidate is biosimilar to the reference product, (ii) the product candidate can be expected to produce the same clinical results as the reference product in any given patient, and (iii) for a biological product that is administered more than once to an individual, the risk in terms of safety and diminished efficacy of alternating or switching between the product candidate and the reference product is not greater than the risk of using the reference product without alternation or switching.

In the draft guidance, FDA explains that it will consider the totality of evidence when assessing a sponsor's application for interchangeability. Although the 351(k) pathway is generally applicable to all products that meet the definition of a "biological product" under the PHS Act,[3] the draft guidance is confined in scope to therapeutic protein products.

Data Necessary to Support an Interchangeability Determination

In general, FDA believes that the following factors will be relevant in assessing interchangeability:

- Identification and analysis of the critical quality attributes;
- Identification of analytical differences between the reference product and the proposed product, as well as the potential clinical impact of the differences;
- Analysis of the mechanism(s) of action in each condition of use for which the reference product is licensed;
- Pharmacokinetics and biodistribution of the product in different patient populations;
- Immunogenicity risk of the product in different patient populations;

[1] 42 U.S.C. § 262(k).
[2] Id. at 262(i)(3).
[3] Id. at 262(i)(1).

- Differences in expected toxicities in each condition of use and patient population; and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which the reference product is licensed.

For any differences that exist between the reference product and the proposed interchangeable product, FDA recommends that the sponsor provide data and information justifying why those variances still allow for the two products to generate the same clinical result in any given patient. A sponsor may seek licensure for a proposed product with fewer conditions of use than the reference product, but FDA recommends that, when possible, the proposed interchangeable product align with the reference product's license for conditions of use.

In addition to the data and information necessary to demonstrate biosimilarity, as described in previous FDA guidance on biosimilarity, a determination of interchangeability depends on, among other factors, the proposed product's:

- *Complexity and the extent of comparative and functional characterization*. As part of the biosimilarity analysis, FDA must determine that the proposed product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components."[4] The comparative analytical data appropriate to satisfy the biosimilar standard may not, however, be sufficient to meet the standard for interchangeability. FDA recommends the use of highly sensitive analytics and/or sequential analytical methods that can identify molecules with different combinations of attributes as well as a comprehensive assessment of the relationships between attributes, along with identification of steps to address residual uncertainty.
- *Immunogenicity risk*. The clinical experience with the reference product, as well as complete risk assessments of the proposed and referenced product, may inform the type and amount of data appropriate for an interchangeability determination. For example, if a product has an extensive clinical history demonstrating that immunogenicity does not affect clinical outcomes, less data may be needed to support a demonstration of interchangeability, as compared to a product with a documented history of inducing adverse immune responses.

FDA believes that postmarket data collected from products licensed as biosimilars, without corresponding data from prospective and adequately designed studies, would not be sufficient to support a demonstration of interchangeability. However, in certain circumstances, FDA may consider postmarket data on a licensed biosimilar product to determine what additional data are necessary to support an interchangeability determination.

Further, if the proposed product is determined to be interchangeable with respect to a particular condition of use of the reference product, the sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each additional condition of use for which the sponsor seeks licensure of the proposed product.

Switching Studies

To support a determination that the risks of alternating or switching between the proposed product and the reference product are not greater than the risk of using the reference product without switching, FDA recommends that sponsors conduct "switching studies." The design of a switching study may be informed by how the proposed product will be used in clinical practice and should consider, among other things, when alternating or switching might cause the most clinical concern. The draft guidance outlines a flexible approach with respect to the design of a switching study that FDA determines is necessary to support interchangeability. FDA strongly recommends that

[4] Id. at 262(i)(2)(A).

sponsors of proposed products rely on a U.S.-licensed reference product in a switching study. The key design issues addressed in the draft guidance are:

- *Study endpoints*. FDA recommends that the primary endpoint of a switching study assess the effects of switching on clinical pharmacokinetics (PK) and pharmacodynamics (PD), because these metrics are most likely to be sensitive to changes in immunogenicity and/or exposure resulting from switching;

- *Study design*. FDA recommends a study with a lead-in period of treatment with the reference product, followed by a randomized two-arm period (one arm incorporating switching and the other arm receiving only the reference product). The draft guidance also makes recommendations on calculating sample size, determining the number and duration of switches, and other aspects of the study design.

The draft guidance also includes detailed recommendations on proposed integrated study designs that can be used to support both a biosimilarity and interchangeability determination. FDA recommends that an integrated study should be adequately powered to (i) evaluate the appropriate endpoint(s) to support a biosimilarity demonstration of no clinically meaningful differences for biosimilarity and (ii) evaluate PK and PD following the last switch to support a demonstration of interchangeability.

Presentations for Interchangeable Products

FDA recognizes that the data and information necessary to support a demonstration of interchangeability also may be influenced by the proposed product's "presentation," which means the container closure system or delivery device. FDA recommends that a sponsor not seek licensure for a presentation for which the reference product is not licensed. For example, if the reference product is only marketed in a pre-filled syringe, the sponsor generally should not seek licensure for an auto-injector. FDA states that the presentation should be shown to be compatible for use with the final formulation of the proposed product through sufficient testing, such as extractable and leachable studies, performance testing, and stability studies. In conducting the analysis of the presentations for the purpose of identifying the differences, FDA recommends that sponsors examine the external critical design attributes of the proposed product against those of the reference product. Differences in the design of the presentation may be acceptable if they do not negatively impact the ability of patients and caregivers to use the product appropriately without requiring additional user training or the intervention of the prescriber.

Additional Topics for Comment

The Federal Register notice announcing the availability of the draft guidance also identifies two topics for public comment:[5]

1. Since the mid-1990s, FDA has approved manufacturing changes for biological products based on data comparing the pre-change and post-change product using comparative analytical, and, when necessary, animal or clinical (*e.g.*, pharmacokinetic, immunogenicity) studies. With respect to interchangeable products, FDA asks whether there are considerations in addition to such comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products.

2. As explained in the draft guidance, FDA expects that sponsors seeking an interchangeability determination will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use. FDA asks how, if at all, it should consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed.

[5] 82 Fed. Reg. 5579, 5580 (January 18, 2017).

Next Steps

With the authorization of four biosimilars within the last two years, the biologics industry is paying increased attention to the regulatory and financial inducements for pursuing this route to market. Biosimilar products determined to be interchangeable are further incentivized by being substitutable at the point of sale for the reference biologic. As a result, manufacturers of reference biological products as well as companies seeking to demonstrate interchangeability should understand the proposed recommendations in the draft guidance and consider whether to submit comments to the docket. The public comment period closes on March 20, 2017.

Ropes & Gray will continue to monitor developments in this area. If you have any questions, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray Advisor.