May 23, 2019

FDA Issues Final Guidance on "Considerations in Demonstrating Interchangeability With a Reference Product"

Introduction

On May 10, 2019, the Food and Drug Administration (FDA) issued final guidance on "Considerations in Demonstrating Interchangeability With a Reference Product," which describes the agency's current thinking related to demonstrating interchangeability of biosimilar therapeutic protein products under the Public Health Service Act (PHS Act).[1] In his announcement on the final guidance, Acting Commissioner Ned Sharpless described it as "a significant action that will help promote competition in the biologic market" and indicated that such competition would increase access to lower cost biosimilar and interchangeable products. The guidance is the final version of the draft guidance document issued on January 17, 2017, as previously reported by Ropes & Gray.

Although the recommendations in the final guidance for demonstrating interchangeability are largely in line with those provided in the draft guidance, the final guidance contains a few notable changes as described below. Overall, the guidance includes recommendations to provide clarity to developers of proposed interchangeable products and explains that development plans and data requirements will ultimately be decided on a case-by-case basis. Sponsors are encouraged to meet with FDA early on in the development program to discuss what information will be required in an interchangeability submission.

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 guidance, FDA explains that it will consider the totality of evidence when assessing a sponsor's application for interchangeability. Although the biosimilar pathway is generally applicable to all products that meet the definition of a "biological product" under the PHS Act,[3] the 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;

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

- Analysis of any differences in the expected pharmacokinetics and biodistribution of the product in different patient populations for which the reference product is licensed;
- Analysis of any differences in the expected immunogenicity risk of the product in different patient populations for which the reference product is licensed;
- Analysis of any differences in the expected differences in expected toxicities in each condition of use and patient population for which the reference product is licensed; and
- Information on 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.

These factors are largely unchanged from those described in the draft guidance. To the extent that data required to support an interchangeability determination has been previously submitted by the applicant to support a demonstration of biosimilarity, the applicant should consult with FDA about how to reference or re-submit these data when seeking licensure for the proposed interchangeable product. 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 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] FDA acknowledges that there is a range of comparative analytical data that may be submitted to support licensure as a biosimilar or interchangeable product, and that the product's degree of structural and functional complexity may influence the extent of clinical data needed to support a demonstration of interchangeability.
- *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, generally would not be sufficient to support a demonstration of interchangeability. However, 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 sufficient to support an interchangeability for each additional condition of use covered by the application.

Switching Studies

FDA generally recommends that sponsors conduct "switching studies" to assess risks associated with switching from the reference product to the proposed interchangeable product. The design of a switching study may be informed by how the

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

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 final guidance outlines a flexible approach with respect to the design of a switching study that FDA determines is necessary to support interchangeability. Additionally, the guidance now more clearly states that a switching study may not be necessary, even for a biological product that is administered more than once to an individual, if the sponsor provides a justification for not needing such data.

The key design issues addressed in the final 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) between the switching arm and non-switching arm following the final switch. These metrics, as distinguished from clinical efficacy endpoints, are more likely to be sensitive to changes in immunogenicity and/or exposure resulting from switching. Where PK and/or PD are not adequately sensitive endpoints, FDA expects sponsors to propose and justify other selected endpoints.
- *Study design.* FDA recommends a switching 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 final guidance provides a new illustrative example of a switching study design, and makes recommendations on calculating sample size, determining the number and duration of switches, and other aspects of the study design. The final guidance also includes detailed recommendations on proposed integrated study designs that can be used to support both a biosimilarity and interchangeability determination. FDA explains that an integrated study has to 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.
- *Study population.* FDA recommends that the study population for switching studies be adequately sensitive for detection of differences that are a result of switching between the reference product and the proposed product. FDA notes, however, that healthy subjects or a patient population that is different from that used to support licensure of the reference product may be used so long as adequate scientific justification is provided.

Use of a Non-U.S.-licensed Comparator in Switching Studies

The final guidance contemplates use of a non-U.S.-licensed comparator in switching studies, at least in some circumstances, so long as the sponsor establishes an adequate bridge between the non-U.S.-licensed comparator and the U.S. reference product. In the draft version, FDA had said that using a non-U.S.-licensed comparator "generally would not be appropriate in a switching study" and recommended that sponsors of proposed products rely on a U.S.-licensed reference product in a switching study.

The guidance describes considerations for the type and extent of data needed to establish an adequate bridge to justify use of a non-U.S.-licensed comparator. FDA explains that, because in a switching study the comparator product is used in both the switching arm and the control non-switching arm, the bridging data needed to justify use of a non-U.S.-licensed comparator in a switching study may be different or more extensive than is needed in other contexts in which a non-U.S.-licensed comparator is used. For example, subtle differences in levels of specific structural features may not preclude use of a non-U.S.-licensed comparator in studies to support a demonstration of biosimilarity, where the comparator is being used as a control. In contrast, in a switching study, multiple exposures to the reference product and the proposed interchangeable product may potentially prime the immune system to recognize the subtle differences in structural features and the overall immune response could be increased. FDA encourages sponsors to discuss with the agency the design of a switching study early in the product development process.

Presentations for Interchangeable Products

The draft guidance set forth a detailed framework on the types of data and information that sponsors should submit related to the proposed presentation (*i.e.*, container closure system or delivery device). The final guidance omits the

previous framework in favor of high-level recommendations, and FDA has indicated that it intends to provide more detailed recommendations in a separate guidance.[5] FDA makes clear in the final guidance, however, that a sponsor not seek licensure for a presentation for which the reference product is not licensed, and that the presentation should be shown to be compatible for use with the final formulation of the proposed product through sufficient testing. FDA encourages sponsors to contact the agency early during product development to discuss the proposed presentation and specific considerations related to the licensure of the proposed product as an interchangeable product.

Next Steps

Although no interchangeable products have been approved to date, 19 biosimilars have been licensed since the creation of the abbreviated licensure pathways for biologics, with a majority of those being licensed within the past two years. The agency has signaled in its public announcements a priority of enhancing competition in this space by facilitating patient access to biosimilar and interchangeable products. This guidance provides recommendations that manufacturers of reference biological products as well as companies seeking to demonstrate interchangeability should understand as they consider the regulatory and commercial hurdles associated with pursuing this route to market. In particular, stakeholders should note the agency's shift in position on use of a non-U.S.-licensed comparator in switching studies to support a demonstration of interchangeability, which may contribute to an earlier entrance to the market of interchangeable products than had been anticipated before issuance of this final guidance. For example, if a product is first approved as interchangeable in an ex-U.S. jurisdiction, the manufacturer may be able to obtain approval of that product as an interchangeable in the U.S. without conducting a new switching study, so long as the manufacturer provides bridging data to demonstrate that use of the ex-U.S. switching study was appropriate

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.

[5] 84 Fed. Reg. 21342, 21344 (May 14, 2019).