Considerations in Demonstrating Interchangeability With a Reference Product: Update

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2024
Biosimilars

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Considerations in Demonstrating Interchangeability With a Reference Product: Update Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance describes considerations regarding a switching study or studies intended to support a demonstration that a proposed therapeutic protein product is interchangeable with a reference product (*proposed interchangeable biosimilar*[2] or *proposed interchangeable product*) for the purposes of submitting a marketing application or supplement under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)). Although the 351(k) pathway applies generally to all biological products, this guidance focuses on therapeutic protein products.[3]

FDA issued the guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019)[4] (Interchangeability Guidance) before receiving and reviewing any biologics license applications (BLAs) submitted under section 351(k) of the PHS Act for a proposed interchangeable biosimilar. Since publication of the Interchangeability Guidance, experience has shown that for the products approved as biosimilars to date, the risk in terms of safety or diminished efficacy is insignificant following single or multiple switches between a

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] In this guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) *biosimilar* or *biosimilar product* refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) *interchangeable biosimilar* or *interchangeable product* refers to a biosimilar product that FDA has determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act).

[3] For recommendations regarding comparative clinical immunogenicity studies (including switching studies) to support licensure of proposed biosimilar and interchangeable insulin products, see the draft guidance for industry *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products* (November 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

reference product and a biosimilar product.[5,6,7] Accordingly, FDA's scientific approach to when a switching study or studies may be needed to support a demonstration of interchangeability has evolved.

This draft guidance is not intended to be finalized as a standalone guidance. Instead, the recommendations in this draft guidance, when finalized, are intended to revise the Interchangeability Guidance and to replace certain sections in that document, such as sections VI.A and VII, to reflect FDA's current thinking regarding the subject addressed in this guidance. FDA is issuing this draft guidance to seek public comment through the accompanying docket.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DISCUSSION

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Public Law 111–148). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for the licensure of a proposed biosimilar or proposed interchangeable biosimilar product.

A biosimilar product must, among other things, be demonstrated to be highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and have no clinically meaningful differences from the reference product in terms of the safety, purity, and potency of the product.[8] Additionally, the proposed biosimilar product must be shown to have the same mechanism(s) of action as the reference product (but only to the extent known for the reference product), same route of administration, same dosage form, and same strength as the reference product, and may be licensed only for conditions of use that have been previously licensed for the reference product.[9] Typically, the data and information supporting a

[5] Herndon, TM, Ausin C, Brahme NN, Schrieber SJ, Luo M, Andrada FC, Kim C, Sun W, Zhou L, Grosser S, Yim S, and Ricci MS, 2023, Safety Outcomes When Switching Between Biosimilars and Reference Biologics: A Systematic Review and Meta-Analysis, PLoS ONE, 18(10):e0292231. https://doi.org/10.1371/journal.pone.0292231

[6] Kurki, P, Barry S, Bourges I, Tsantili P, and Wolff-Holz E,2021, Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective, Drugs, 81(16):1881–1896.

[7] Kurki, P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M, 2017, Interchangeability of Biosimilars: A European Perspective, BioDrugs, 31(2):83-91.

[8] Section 351(i)(2) of the PHS Act.

[9] Section 351(k)(2) of the PHS Act.

determination of biosimilarity includes a rigorous and comprehensive comparison of physicochemical and biological functional attributes of a proposed biosimilar to its reference product, along with one or more clinical studies that includes an assessment of immunogenicity. FDA generally expects that applications for proposed biosimilar biological products will include an assessment of immunogenicity. This assessment may include information to address the possibility that treatment with one biological product (e.g., the proposed biosimilar) following treatment with another biological product (e.g., the reference product) may affect a patient's immune response to the treatment. Once a biosimilar is licensed, healthcare providers can prescribe the biosimilar product to patients who have not previously received the reference product (i.e., treatment-naïve patients) or who have previously received the reference product (or another biosimilar product) (i.e., treatment-experienced patients).

The BPCI Act distinguishes between biosimilar products and biosimilar products that are interchangeable with the corresponding reference product with respect to the standards that must be met for approval and the effect of such approvals. For an interchangeable biosimilar, in addition to meeting the requirements for biosimilarity, FDA must determine that the information submitted in the application or supplement is sufficient to show 1) that the biological product can be expected to produce the same clinical result as the reference product in any given patient,[10] and 2) that for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (*the switching standard*).[11] If FDA makes such a determination and approves the interchangeable biosimilar, the statute provides that the interchangeable biosimilar may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.[12] Therefore, the switching standard is intended to provide added assurances regarding safety and efficacy in cases where the decision to switch a patient's treatment from the reference product to the interchangeable biosimilar is not made by the prescribing healthcare provider.

In the Interchangeability Guidance, the Agency recommended that applications or supplements seeking a determination of interchangeability include data from a switching study or studies to help provide the added assurance with respect to any immunogenicity risk associated with switching or alternating between the reference product and the proposed interchangeable biosimilar. However, since publication of the Interchangeability Guidance, the Agency has gained further experience in evaluating the potential analytical differences between proposed biosimilar products and their reference products and understanding their impact on clinical performance. Moreover, currently available analytical technologies can structurally characterize highly purified therapeutic proteins and model in vivo functional effects with a high degree of specificity and sensitivity using in vitro biological and biochemical assays.

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[10] Section 351(k)(4)(A)(ii) of the PHS Act.

[11] Section 351(k)(4)(B) of the PHS Act.

[12] Section 351(i)(3) of the PHS Act.

Therefore, FDA intends to revise the Interchangeability Guidance consistent with the scientific approach discussed above and has the following recommendations to applicants for proposed interchangeable biosimilar products:

- Applicants may choose to provide an assessment of why the comparative analytical and clinical data provided in the application or supplement support a showing that the switching standard set forth in section 351(k)(4)(B) of the PHS Act has been met. Any such assessment should include any other information the applicant considers relevant to support a showing that the risk, in terms of safety and diminished efficacy, from alternating or switching between the reference product and the proposed interchangeable product is not greater than the risk of using the reference product without such alternation or switch.

- Applicants with a pending 351(k) BLA for a proposed biosimilar product may choose to submit an amendment to their pending BLA with the above-described assessment along with any additional data and/or information that they consider relevant to address the requirements in section 351(k)(4) of the PHS Act and request that their BLA be reviewed as a proposed interchangeable biosimilar.[13,14]

[13] See section IV of the draft guidance for industry and review staff *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[14] See Q&A I.25 in the draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.