Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies

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DRAFT GUIDANCE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)

October 2025
Biosimilars

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Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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This draft guidance describes considerations regarding a comparative clinical study or studies with efficacy endpoints (a "comparative efficacy study" or "CES") to support a demonstration of biosimilarity in a biologics license application (BLA) submitted under section 351(k) of the Public Health Service (PHS) Act. Section 351(k) of the PHS Act (42 U.S.C. 262(k)) provides an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product and sets forth the requirements for a BLA submitted under section 351(k) (a "351(k) BLA"). The sponsor of a proposed biosimilar product must, among other things, demonstrate that the proposed product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the proposed product and the reference product in terms of safety, purity, and potency.[2] A 351(k) BLA must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, an assessment of toxicity, and a clinical study or studies,[3] unless the Agency determines, in its discretion, that an element described in section 351(k)(2)(A)(i)(I) of the PHS Act is unnecessary in a 351(k) BLA.[4] Although the 351(k) pathway generally applies to all biological products, this guidance focuses on therapeutic protein

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

[3] See section 351(k)(2)(A)(i)(I) of the PHS Act.

[4] See section 351(k)(2)(A)(ii) of the PHS Act.

products, providing an overview of important scientific considerations for determining when a CES may inform a demonstration of biosimilarity.[5,6]

In April 2015, the agency published the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015) (Scientific Considerations Guidance) which described, among other things, general considerations for comparative clinical studies intended to support a demonstration that a proposed therapeutic protein product (for the purposes of this guidance, these will be referred to as *proposed product, proposed biosimilar,* or *proposed biosimilar product*) is biosimilar to a reference product for the purpose of submitting a marketing application under section 351(k) of the PHS Act (42 U.S.C. 262(k)).[7] The guidance recommended that, as a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there is residual uncertainty about whether there are clinically meaningful differences between the proposed product and the reference product based on comparative analytical studies, an assessment of toxicity, comparative human PK and PD studies (if there is a relevant PD measure(s)), and a clinical immunogenicity assessment. The guidance also stated that a sponsor should provide a scientific justification if it believes that a comparative clinical study is not necessary. Comparative clinical studies typically have been designed to analyze and compare a clinical efficacy outcome or other relevant therapeutic effect between the proposed product and the reference product.

Since the publication of the Scientific Considerations Guidance, the scientific approach to determine the need for CES has evolved, and FDA has gained significant experience in evaluating data from comparative analytical and clinical studies used to support a demonstration of biosimilarity. Accordingly, FDA is issuing this draft guidance to describe an updated framework for determining when a CES may not be necessary to support a demonstration of biosimilarity.

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

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[5] 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 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.

[6] For recommendations regarding a switching study or studies intended to support a demonstration that a biological product is interchangeable with a reference product, see the draft guidance for industry *Considerations in Demonstrating Interchangeability with a Reference Product: Update* (June 2024) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] 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).

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DISCUSSION

Section 351 of the PHS Act sets forth the requirements for an applicant to demonstrate that a biological product is *biosimilar* to a reference product.

An application submitted under section 351(k) of the PHS Act seeking licensure of a biological product as biosimilar or interchangeable must contain, among other things, data from "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in [one] or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product[.]"[8]

FDA has gained significant experience in evaluating analytical differences between proposed biosimilar products and their reference products and understanding the impact of those analytical differences on clinical performance.[,9,10,11] 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. A comparative analytical assessment (CAA) is generally more sensitive than a CES to detect differences between two products, should any exist, that may preclude a demonstration of biosimilarity.[12,13,14] The lack of sensitivity of a CES is potentially due to a number of factors, such as therapeutic dose range selection that is commonly chosen to reach pharmacologic target saturation and the therapeutic plateau, as well as characteristics of the clinical study population

[8] Section 351(k)(2)(A)(i)(I)(cc) of the PHS Act.

[9] Biosimilar Product Information available at https://www.fda.gov/drugs/biosimilars/biosimilar-product-information

[10] Biosimilars | Science and Research available at https://www.fda.gov/drugs/biosimilars/biosimilars-science-and-research

[11] FDA and International Pharmaceutical Regulators Program Biosimilar Working Group workshop, Increasing the Efficiency of Biosimilar Development Programs–Reevaluating the Need for Comparative Clinical Efficacy Studies (September 2023) available at https://www.fda.gov/drugs/news-events-human-drugs/increasing-efficiency-biosimilar-development-programs-reevaluating-need-comparative-clinical.

[12] Cavazzoni, P S Yim, 2024, The Science of Biosimilars–Updating Interchangeability, JAMA, 332;(15):1235–1236.

[13] Kirsch-Stefan, N, E Guillen, N Ekman, S Barry, V Knippel, S Killalea, M Weise, and E Wolff-Holz, 2023, Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars?, BioDrugs, 37(6):855–871.

[14] See also, Guidance for Industry, *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (September 2025) available at https://www.fda.gov/media/159261/download

chosen and primary endpoint selected (e.g., floor and ceiling effects). Accordingly, FDA's scientific approach is evolving as to when a CES may inform a demonstration of biosimilarity.

FDA recommends that sponsors carefully consider what clinical study(ies) would be necessary to support a demonstration of biosimilarity when designing their development programs.

Generally, if the CAA supports a demonstration that the proposed biosimilar is highly similar to its reference product, notwithstanding minor differences in clinically inactive components, an appropriately designed human pharmacokinetic similarity study and an assessment of immunogenicity may be sufficient to evaluate whether there are clinically meaningful differences between the proposed biosimilar and the reference product in terms of safety, purity, and potency.[15] In such an instance, FDA recommends that sponsors consider a streamlined approach where a CES may not be necessary to support a demonstration of biosimilarity. The adequacy of the data from a CAA, pharmacokinetic similarity data, and immunogenicity assessment to support a demonstration of biosimilarity, would be evaluated based on the totality of the evidence submitted in the biologics license application.

A streamlined approach should be considered when:

- The reference product and proposed biosimilar product are manufactured from clonal cell lines, are highly purified, and can be well-characterized analytically;

- The relationship between quality attributes and clinical efficacy is generally understood for the reference product, and these attributes can be evaluated by assays included in the CAA; and

- A human pharmacokinetic similarity study is feasible and clinically relevant.

We note there remain circumstances when a CES may inform a demonstration of biosimilarity, e.g., for locally acting products such as intravitreally administered products where comparative pharmacokinetics is not feasible or clinically relevant. Also, there may be circumstances where a comparative clinical study with a clinically relevant endpoint other than an efficacy endpoint may be useful to support a demonstration of biosimilarity. In both situations, sponsors are encouraged to discuss their proposed approaches with the Agency early in product development and prior to initiating clinical studies.

[15] See sections 351(i)(2) and 351(k)(2)(A)(i)(I)(cc) of the PHS Act.