New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4)

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Division of Drug Information at (855) 543-3784 or (301) 796-3400, or (CBER) Outreach and Development at 800-835-4709 or 240-402-8010.

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)

March 2026
Biosimilars

Revision 4

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New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4) 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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.

INTRODUCTION

This draft guidance provides answers to common questions from prospective applicants and other interested parties regarding the abbreviated licensure pathway in section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)), which was added by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The question and answer (Q&A) format is intended to inform prospective applicants and facilitate the development of *proposed biosimilar products* and *proposed interchangeable products*,[2] as well as describe FDA's interpretation of certain statutory requirements.

Section 351(k) of the PHS Act provides 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) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA's interpretation of section 351(k) of the PHS Act will enhance transparency and facilitate the development and approval of biosimilar and interchangeable products. In addition, these Q&As respond to questions the Agency has received from prospective applicants regarding the submission of biologics license applications (BLAs) for proposed biosimilar and interchangeable products. FDA may provide additional Q&As through draft guidance as appropriate.

[1] This draft guidance has been prepared by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] In this draft 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 section 351(i)(2) and (k)(2) of the PHS Act); and (2) *interchangeable biosimilar* or *interchangeable product* refers to a biosimilar product that FDA has also determined to be interchangeable with the reference product (see section 351(i)(3) and (k)(4) of the PHS Act). The terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe a product that is under development or is the subject of a pending 351(k) biologics license application. Biosimilarity, interchangeability, and related issues are discussed in more detail in the Background section of this guidance.

This draft guidance revises and replaces the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)* (September 2021). The specific changes include:

- Q&A I.8 — revised for public comment with updated content.
- Q&A I.10 and Q&A I.19 — updated with conforming and clarifying revisions and moved from the final guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021) (Revision 2) to this draft guidance.
- Q&A I.12 — retained from the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)* (September 2021) without change.

Additional information about the Q&A format for this draft guidance is provided in the Background section.

After FDA has considered any comments on the revised draft Q&As, the draft Q&As in this guidance will be finalized by adding the Q&As, as a revision, to the final guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (Revision 3) as appropriate. That final guidance is part of a series of guidances that FDA has developed to facilitate development of biosimilar and interchangeable biosimilar products.[3]

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.

BACKGROUND

The BPCI Act

The BPCI Act was enacted as part of the ACA on March 23, 2010. The 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 ACA). Section 351(k) of the PHS Act, added by the BPCI Act, sets forth the requirements for the licensure of a proposed biosimilar or proposed interchangeable product.

[3] To search for specific guidances on biosimilar and interchangeable biosimilar products on the FDA guidance web page (https://www.fda.gov/regulatory-information/search-fda-guidance-documents), select "Biosimilars" in the topic field. Additional guidances that are applicable to biological products, including biosimilar and interchangeable biosimilar products, can be found in other topic areas, such as "Chemistry, Manufacturing, and Controls (CMC)" and "Administrative/Procedural."

Section 351(i) of the PHS Act defines *biosimilarity* to mean "that the biological 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 biological product and the reference product in terms of the safety, purity, and potency of the product" (see section 351(i)(2) of the PHS Act).

A BLA submitted under section 351(k) (known as a *351(k) BLA*) of the PHS Act 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 (see section 351(k)(2)(A)(i)(I) of the PHS Act), unless FDA has determined that an element described in section 351(k)(2)(A)(i)(I) is unnecessary (see section 351(k)(2)(A)(ii) of the PHS Act). To meet the standard for *interchangeability*, an applicant must provide sufficient information to demonstrate biosimilarity to the reference product and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient, and if the biological product is 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 alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

"Question-and-Answer" Guidance Format

FDA has been using the Q&A guidance format to describe the Agency's thinking on and update certain information and recommendations relevant to the development of biosimilar and interchangeable products. This draft guidance includes only Q&As that are in draft form. The guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* contains all Q&As that are final. As FDA issues individual Q&As, they will first be incorporated into a draft Q&A guidance. After FDA has considered any comments on draft Q&As received during the relevant comment period and, if warranted, incorporated suggested changes to the Q&As, individual Q&As will be finalized and moved to the final guidance, as appropriate.

A Q&A that was previously in the final guidance may be withdrawn and moved to a draft guidance if FDA determines that the Q&A should be revised in some respect and reissued in a revised draft Q&A for comment. A Q&A also may be withdrawn and removed from the Q&A guidance if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance.

FDA will provide the publication date of the current version of each Q&A and information about whether the Q&A has been added to or modified in the relevant draft guidance. FDA has maintained the original numbering of the guidance Q&As used in the final guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (Revision 2), the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)*, and the draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (September 2023)

(Revision 1).[4] For ease of reference, a Q&A retains the same number when it moves from a draft guidance to the final guidance and, where appropriate, when a Q&A is withdrawn from the final guidance and moved to a draft guidance.

When FDA withdraws a Q&A or moves it from draft guidance to final guidance or from final guidance to draft guidance for public comment, it marks the change in the first guidance with several asterisks between nonconsecutive Q&As and provides explanatory text when appropriate.

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q.I.8. Can a sponsor use comparative clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?
[Revised in Draft March 2026]

A.I.8.a Yes, under certain circumstances. If a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product ("non-U.S.-licensed comparator product") to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify why such comparative data are relevant to the assessment of biosimilarity to the U.S.-licensed reference product.

A scientific justification may be acceptable in circumstances that include:

- The proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product are highly purified therapeutic proteins that can be structurally and functionally characterized with a high degree of specificity and sensitivity using currently available analytical technologies; and

- The applicant submits information that the non-U.S.-licensed comparator product has the same or only minor differences in quantitative and/or qualitative composition of inactive ingredients as the U.S.-licensed reference product that would not be expected to affect clinical performance between the U.S.-licensed reference product and the non-U.S.-licensed comparator product; and

- There is an adequate scientific rationale for why analytical differences (if any) identified in product quality attributes between the non-U.S.-licensed comparator product used in the clinical study and the U.S.-licensed

[4] When final, this guidance will represent FDA's current thinking on this topic.

reference product included in the applicant's comparative analytical assessment (described further in part (b) of this response) would not preclude a conclusion that data from a clinical study comparing the proposed biosimilar product to the non-U.S.-licensed comparator product are relevant to a demonstration of biosimilarity to the U.S.-licensed reference product.

Publicly available information describing the relationship between the U.S.-licensed reference product and the non-U.S.-licensed comparator product would not obviate the need for comparative analytical data to scientifically justify use of a non-U.S.-licensed comparator in a clinical study intended to support a demonstration of biosimilarity to the U.S.-licensed reference product.

If the above circumstances apply and an adequate scientific justification is provided, a clinical study (such as an assessment of pharmacokinetics) comparing the proposed biosimilar with the non-U.S.-licensed comparator product could address, in part, the requirements under section 351(k)(2)(A) of the PHS Act and support a demonstration of biosimilarity to the U.S.-licensed reference product.[5,6]

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include the following:

- Whether the non-U.S.-licensed comparator product was manufactured in a facility(ies) licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries); and

- Whether the non-U.S.-licensed comparator product was licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., ICH countries) and the duration and extent to which the product has been marketed.

Sponsors are encouraged to discuss with FDA any plans (including, but not limited to, the circumstances above) to submit and scientifically justify clinical data derived from non-U.S.-licensed comparator products in support of a 351(k) application as early as feasible during product development. A final decision about the adequacy of the data and information intended to scientifically justify

[5] The draft guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies* (October 2025) is available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. When final, this guidance will represent the FDA's current thinking on this topic.

[6] Differences in strength or dosage form between the U.S.-licensed reference product and non-U.S.-licensed comparator product do not necessarily preclude use of the non-U.S.-licensed comparator product in a clinical study intended to support a demonstration of biosimilarity.

the relevance of a non-U.S.-licensed comparator product to the assessment of biosimilarity will be made during review of the 351(k) application.

A.I.8.b Reference Product and Non-U.S.-Licensed Comparator Products[7]

For purposes of the comparative analytical assessment and comparison between the non-U.S.-licensed comparator product and the U.S.-licensed reference product, any lots used in a clinical study supporting a demonstration of biosimilarity should be included in the comparative analytical assessment intended to justify the relevance of comparative data with the non-U.S.-licensed comparator product to a demonstration of biosimilarity.[8] Specifically, if a clinical study compares the proposed biosimilar to a non-U.S.-licensed comparator product, sponsors should ensure that data generated in that clinical study are relevant and applicable to the demonstration of biosimilarity by providing sufficient comparative analytical data based on: (1) the lots of the non-U.S.-licensed comparator product used in the clinical study; and (2) the lots of the U.S.-licensed reference product used in the comparative analytical assessment to support a demonstration that the proposed biosimilar is highly similar to the U.S.-licensed reference product. If analytical differences are observed between the clinical lots of the non-U.S.-licensed comparator product and the U.S.-licensed reference product lots used in the comparative analytical assessment with the proposed biosimilar, the sponsor may provide information (e.g., a risk assessment and relevant analytical data) to scientifically justify why these differences do not preclude a conclusion that the data from the clinical study comparing the proposed biosimilar to the non-U.S.-licensed comparator product are relevant to the demonstration of biosimilarity.

The acceptance criteria used to support a demonstration that a proposed biosimilar product is highly similar to the U.S.-licensed reference product should be derived from data generated from a sponsor's analysis of the U.S.-licensed reference product. The comparative analytical assessment should be based on a direct comparison of the proposed biosimilar product to the U.S.-licensed reference product. As a scientific matter, combining data from the U.S.-licensed reference product and non-U.S.-licensed comparator product to determine the acceptance criteria or to perform the comparative analytical assessment for the proposed product would not be acceptable to support a demonstration that the proposed product is biosimilar to the U.S.-licensed reference product.

[7] This draft guidance is not intended to be finalized in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (Revision 3). Instead, the recommendations in this draft guidance, after considering any comments received in the docket, are intended to inform future revisions to the guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (September 2025) such as changes to recommendations in section VI.A.3 related to the subject addressed in this guidance.

[8] For additional information on the comparative analytical assessment, see section VI of the guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (September 2025).

Sponsors are encouraged to discuss with FDA any plans to submit clinical data derived from a study using a non-U.S.-licensed comparator product in support of a 351(k) application as early as feasible during product development. A final decision about the adequacy of the data and information intended to scientifically justify the relevance of a non-U.S.-licensed comparator product to the assessment of biosimilarity will be made during review of the 351(k) application.

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Q.I.10. How long and in what manner should sponsors retain reserve samples of the biological products used in comparative clinical PK and/or PD studies intended to support a 351(k) application?
[Revised in Draft March 2026]

A.I.10. Reserve samples establish the identity of the products tested in the actual study, allow for confirmation of the validity and reliability of the results of the study, and facilitate investigation of further follow-up questions that arise after the studies are completed. FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples for at least 5 years following the date on which the 351(k) application is licensed, or, if such application is not licensed, at least 5 years following the date of completion of a comparative clinical pharmacokinetic (PK) and/or pharmacodynamic (PD) study of the reference product and the proposed biosimilar product (or other clinical study in which PK or PD samples are collected with the primary objective of assessing PK or PD similarity) that is intended to support a submission under section 351(k) of the PHS Act. Contact FDA for specific advice if an alternative approach is being considered. For a PK similarity study, FDA recommends that samples of the proposed biosimilar and the reference product or, if applicable, non-U.S.-licensed comparator product be retained.

For most protein therapeutics, FDA recommends that a sponsor retain the following quantities of product and dosage units, which are expected to be sufficient for evaluation by state-of-the-art analytical methods:

- A minimum of 10 dosage units each of the proposed biosimilar product, reference product and, if applicable, non-U.S.-licensed comparator product, depending on the amount of product within each unit; in general, this should provide for a total product mass of equal to or greater than 200 milligrams (mg) in a volume equal to or greater than 10 milliliters (mL).

FDA recommends that the sponsor contact the review division to discuss the appropriate quantities of reserve samples in the following situations:

- A product mass of equal to or greater than 200 mg in a volume equal to or greater than 10 mL requires a large number of dosage units

- Biological products other than protein therapeutics

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Q.I.12. How can an applicant demonstrate that its proposed injectable biosimilar product or proposed injectable interchangeable product has the same "strength" as the reference product?
[Draft December 2018]

A.I.12. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the "strength" of the proposed biosimilar product or proposed interchangeable product is the same as that of the reference product. Data and information generated as part of the analytical similarity assessment may inform the determination that a proposed biosimilar product or proposed interchangeable product has the same strength as its reference product. As a scientific matter, there may be a need to take into account different factors and approaches in determining the strength of different biological products. Sponsors should discuss their proposed approach with FDA and provide an adequate scientific basis for their approach to demonstrating same strength.

In general, a sponsor of a proposed biosimilar product or proposed interchangeable product with an injection dosage form (e.g., a solution) can demonstrate that its product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity) and the same concentration of drug substance (in mass or units of activity per unit volume). In general, for a proposed biosimilar product or proposed interchangeable product that is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, a sponsor can demonstrate that the product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity).

Although not a part of demonstrating same strength, if the proposed biosimilar product or proposed interchangeable product is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, the 351(k) application generally should contain information that the concentration of the proposed biosimilar product or proposed interchangeable product, when constituted or reconstituted, is the same as that of the reference product, when constituted or reconstituted.

A sponsor should determine the content of drug substance for both the reference product and the proposed biosimilar product or proposed interchangeable product using the same method. The strength of the proposed product generally should be expressed using the same units of measure as the reference product.

* * * * *

Q.I.19. If a non-U.S.-licensed comparator product is proposed for importation and use in the United States in a clinical investigation intended to support licensure of a proposed product under section 351(k), is a separate IND required for the non-U.S.-licensed product?
***[Revised in Draft March 2026*]**

A.I.19. A sponsor may submit a single investigational new drug application (IND) for a development program that is intended to support licensure of a proposed product under section 351(k) of the PHS Act and includes use of a non-U.S.-licensed comparator product. The sponsor should submit information supporting the proposed clinical investigation with the non-U.S.-licensed comparator product under the IND. This scenario may occur if a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed comparator product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. For example, a sponsor may propose to conduct a clinical PK study in the United States with the proposed biosimilar product and a non-U.S.-licensed comparator product.

A non-U.S.-licensed comparator product is considered an investigational new drug in the United States, and thus would require an IND for importation and use in the United States (see 21 CFR 312.110(a)). If a sponsor intends to conduct a clinical investigation in the United States using a non-U.S.-licensed comparator product, the IND requirements in 21 CFR part 312 also would apply to this product (see, e.g., 21 CFR 312.2).

With respect to chemistry, manufacturing, and controls (CMC) information, a sponsor should submit to the IND as much of the CMC information required by 21 CFR 312.23(a)(7) as is available. However, FDA recognizes that a sponsor may not be able to obtain all the CMC information required by 21 CFR 312.23(a)(7) for a non-U.S.-licensed comparator product for which it is not the manufacturer. In these circumstances, the sponsor can request in an IND submission that FDA waive the regulatory requirements related to CMC information on the non-U.S.-licensed comparator product (21 CFR 312.10). The waiver request must include at least one of the following:

- An explanation why compliance with the requirements of 21 CFR 312.23(a)(7) is unnecessary or cannot be achieved

- Information that will satisfy the purpose of the requirement by helping to ensure that the investigational new drug will have the proper identity, strength, quality, and purity

- Other information justifying a waiver[9]

Information that is relevant to whether the investigational new drug will have the proper identity, strength, quality, and purity may include, for example, information indicating whether the investigational new drug has been licensed by a regulatory authority that has similar scientific and regulatory standards as FDA, and whether the manufacturing facilities have been inspected by a regulatory authority that has similar scientific and regulatory standards as FDA, (e.g., ICH countries). This should include, to the greatest extent possible, summary approval information and current product labeling made public by the foreign regulatory authority. In addition, a sponsor should also provide information on the conditions and containers that will be used to transport the drug product to the U.S. clinical site(s) and information on the relabeling and repackaging operations that will be used to relabel the drug product for investigational use. This should include information on how exposure of the product to light and temperature conditions outside of the recommended storage conditions will be prevented. A risk assessment on the impact the relabeling operations may have on drug product stability should also be included.

The sponsor should consult with the appropriate FDA review division regarding the CMC information necessary to support the proposed clinical study.

As would be applicable to all investigational new drugs, FDA reminds sponsors that the investigator brochure (IB) for studies to be conducted under the IND should be carefully prepared to ensure that it is not misleading, erroneous, or materially incomplete, which can be a basis for a clinical hold (see 21 CFR 312.42(b)(1)(iii) and (b)(2)(i)). For example, the term *reference product* should be used in the IB only to refer to the single biological product licensed under section 351(a) of the PHS Act against which the proposed product is evaluated for purposes of submitting a 351(k) application.

The IB and study protocol(s) should use consistent nomenclature that clearly differentiates the proposed product from the reference product. Additionally, the IB and study protocol(s) should both clearly describe whether the comparator used in each study is the U.S.-licensed reference product or a non-U.S.-licensed comparator product and use consistent nomenclature that clearly differentiates these products. If a non-U.S.-licensed comparator product is being used in a study conducted in the United States, the IB and study protocol(s) should clearly convey that the product is not FDA-approved and is considered an investigational new drug in the United States. The IB and study protocol(s) also should avoid conclusory statements regarding regulatory determinations (e.g., "comparable," "biosimilar," "interchangeable," "highly similar") that have not been made.

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[9] See 21 CFR 312.10(a).

II. PROVISIONS RELATED TO REQUIREMENTS TO SUBMIT A BLA FOR A *BIOLOGICAL PRODUCT*

There are no draft Q&As for this section.

III. EXCLUSIVITY

There are no draft Q&As for this section.