Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

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 3

Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

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Contains Nonbinding Recommendations

Questions and Answers on Biosimilar Development and the BPCI Act Guidance for Industry[1]

This guidance represents 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 office responsible for this guidance as listed on the title page.

INTRODUCTION

This guidance provides answers to common questions from prospective applicants and other interested parties regarding 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 biosimilar 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

[1] This 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. You may submit comments on this guidance any time. Submit comments to Docket No. FDA-2011-D-0611 (available at https://www.regulations.gov/docket?D=FDA-2011-D-0611). See the instructions in that docket for submitting comments on this and other Level 2 guidance updates.

[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 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) BLA. Biosimilarity, interchangeability, and related issues are discussed in more detail in the Background section of this guidance.

biosimilar and interchangeable products. FDA intends to update this final guidance to include additional Q&As as appropriate.

This final guidance is part of a series of guidance documents that FDA developed to facilitate development of biosimilar and interchangeable biosimilar products. It revises and replaces the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021) (Revision 2).

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 biosimilar product.

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) (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 (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 healthcare 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 guidance includes all Q&As that are in final form. The draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act)* (September 2023) (Revision 1) (Additional Draft Q&A guidance) and the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4)* (March 2026)[3] contain Q&As that are draft. After FDA has considered any comments on the Q&As contained in the draft guidances received during the relevant comment period and, if warranted, incorporated suggested changes to the Q&A, individual Q&As will be 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 this final guidance document. FDA has maintained the original numbering of the guidance Q&As used in the 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)* (September 2021)[4] (New and Revised Draft Q&A guidance), and the Additional Draft Q&A guidance. 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 Q&As from the Additional Draft Q&A guidance and New and Revised Draft Q&A guidance are finalized and moved to the final guidance, the final guidance will clearly identify the draft guidance in which the Q&As were issued.

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.

[3] 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.

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

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q.I.1. ***Whom should a sponsor contact with questions about its proposed development program for a proposed biosimilar product or a proposed interchangeable product?***
[Final December 2018]

A.I.1. FDA provides current contact information on its website, "Biosimilars," available at https://www.fda.gov/biosimilars (click on the link, "Industry Information and Guidance" listed in the left column).

Q.I.2. ***When should a sponsor request a meeting with FDA to discuss its development program for a proposed biosimilar product or a proposed interchangeable product, and what data and information should a sponsor provide to FDA as background for this meeting?***
[Final December 2018]

A.I.2. See FDA's draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*,[5] for a description of the different meeting types intended to facilitate biosimilar development programs in accordance with the Biosimilar User Fee Act of 2012 (BsUFA), as reauthorized by the Biosimilar User Fee Amendments of 2017 (BsUFA II) and the criteria/data needed to support the request. The type of meeting granted will depend on the stage of product development and whether the information submitted in the meeting package meets the criteria for the type of meeting.

Q.I.3. ***Can a proposed biosimilar product have a formulation that is different from the reference product?***
[Updated/Retained in Final September 2021]

A.I.3. Differences between the formulation of a proposed biosimilar product and the reference product may be acceptable. A 351(k) application must contain information demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. In addition, an applicant would need to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. It may be possible, for example, for a proposed biosimilar product formulated without human serum albumin to demonstrate biosimilarity to a reference product formulated with human serum albumin. For more information about FDA's current thinking on the interpretation of the statutory standard for biosimilarity, see FDA's guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a*

[5] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Reference Product, and draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations.*[6]

Q.I.4. Can a proposed biosimilar product have a delivery device or container closure system that is different from its reference product? [Updated/Retained in Final September 2021]

A.I.4. Some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable, as long as the proposed product meets the standards for biosimilarity, including that such differences would not result in a condition of use that has not been previously approved for the reference product or a dosage form, strength, or route of administration that differs from that of the reference product. It may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a prefilled syringe or in an auto-injector device (which are considered the same dosage form), even if the reference product is licensed in a vial presentation, provided that the proposed biosimilar product meets the statutory standard for biosimilarity and adequate performance data for the delivery device or container closure system are provided. For a proposed biosimilar product in a different delivery device or container closure system, as a scientific matter, the delivery device or container closure system must be shown to be compatible for use with the final formulation of the biological product through appropriate studies, including, for example, extractable/leachable studies and stability studies. Also, for design differences in the delivery device or container closure system, performance testing and a human factors study may be needed.

However, an applicant will not be able to obtain licensure of a proposed biosimilar product when a design difference in the delivery device or container closure system results in any of the following:

- A clinically meaningful difference between the proposed biosimilar product and the reference product in terms of safety, purity, and potency;
- A different route of administration;
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved; or
- A proposed biosimilar product that otherwise does not meet the standard for biosimilarity.

[6] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

A proposed biosimilar product in a delivery device will be considered a combination product and may, in some instances, require a separate application for the device.

Q.I.5. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?
[Final April 2015]

A.I.5. Yes. An applicant may obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed. An applicant must demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of safety, purity, and potency. In a limited number of circumstances, this may include providing information from one or more studies using a route of administration for which licensure is not requested (e.g., a study using subcutaneous administration may provide a more sensitive comparative assessment of immunogenicity of the reference product and a proposed biosimilar product, even though licensure of the proposed biosimilar product is requested only for the intravenous route of administration).

Q.I.6. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?
[Final December 2018]

A.I.6. An applicant is not required to obtain licensure of a proposed biosimilar product for all presentations for which the reference product is licensed. However, if an applicant seeks licensure for a particular indication or other condition of use for which the reference product is licensed and that indication or condition of use corresponds to a certain presentation of the reference product, the applicant may need to seek licensure for that particular presentation (see also Q&As I.4 and I.5).

Q.I.7. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?
[Final December 2018]

A.I.7. An applicant generally may obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed. The 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling submitted for the proposed biosimilar product have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act).

For information about the licensure of a proposed interchangeable product, see FDA's guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product*.[7]

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Q.I.8. ***This question and its answer have been revised and retained in FDA's draft guidance for industry* New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4).**

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Q.I.9. ***Is a clinical study to assess the potential of the biological product to delay cardiac repolarization (a QT/QTc study) or a drug-drug interaction study generally needed for licensure of a proposed biosimilar product? [Final December 2018]***

A.I.9. In general, a 351(k) application for a proposed biosimilar product may rely upon the Agency's previous determination of safety, purity, and potency for the reference product, including any clinical QT/QTc interval prolongation and proarrhythmic potential and drug-drug interactions. If such studies were not required for the reference product, then these data generally would not be needed for licensure of a proposed biosimilar product under section 351(k) of the PHS Act. However, if the BLA holder for the reference product has been required to conduct postmarket studies or clinical trials under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to assess or identify a certain risk related to a QT/QTc study or a drug-drug interaction study and those studies have not yet been completed, then FDA may impose similar postmarket requirements on the 351(k) applicant in appropriate circumstances.

* * * * *

Q.I.10. ***This question and its answer have been revised and retained in FDA's draft guidance for industry* New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4).**

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[7] As explained in that guidance, FDA generally expects that applicants seeking to demonstrate interchangeability 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.

Q.I.11. ***This question and its answer have been withdrawn. For information on extrapolation, see FDA's guidance for industry*** **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.**

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Q.I.12. ***This question and its answer have been retained in FDA's draft guidance for industry*** **New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4).**[8]

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Q.I.13. ***What constitutes "publicly-available information" regarding FDA's previous determination that the reference product is safe, pure, and potent to include in a 351(k) application?***
[Final December 2018]

A.I.13. "Publicly-available information" in this context generally includes the current FDA-approved labeling for the reference product and the types of information found in the "action package" for a BLA (see section 505(l)(2)(C) of the FD&C Act). However, FDA notes that submission of publicly available information composed of less than the current FDA-approved labeling for the reference product and the action package for the reference product BLA will generally not be considered a bar to submission or approval of an acceptable 351(k) application.

FDA intends to post on the Agency's website publicly available information regarding FDA's previous determination of safety, purity, and potency for certain biological products to facilitate biosimilar development programs and submission of 351(k) applications. We note, however, that the publicly available information posted by FDA in this context does not necessarily include all information that would otherwise be disclosable in response to a Freedom of Information Act request.

Q.I.14. ***Can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) application?***
[Updated/Retained in Final September 2021]

A.I.14. Yes. For more information, see FDA's guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product*, and Q&A I.26 in FDA's draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020).[9]

[8] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

[9] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Q.I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?
[Updated/Retained in Final September 2021]

A.I.15. Under PREA (codified at section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing and administration, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.[10]

Under section 505B(l) of the FD&C Act,[11] a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a new active ingredient for purposes of PREA. However, if an applicant first seeks licensure of its proposed product as a biosimilar product, the applicant must address applicable PREA requirements for its noninterchangeable biosimilar product even if it ultimately intends to seek licensure of the product as an interchangeable product.

See Q&A I.16 of this guidance for information on how a proposed biosimilar product applicant may fulfill the requirement for pediatric assessments under PREA.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies as early as practicable during product development. If there is no active investigational new drug (IND) application for the proposed biosimilar product and the sponsor intends to conduct a comparative clinical study as part of its development program, the initial pediatric study plan (PSP) should be submitted as a pre-IND submission. In this scenario, FDA encourages the sponsor to meet with FDA before submission of the initial PSP to discuss the details of the planned development program. A sponsor should submit the initial PSP before initiating any comparative clinical study in its biosimilar development program. For more information, see Q&A I.17 of this guidance. See also the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

[10] Section 505B(a)(1) was amended in 2017 by section 504 of the FDA Reauthorization Act of 2017 (Public Law 115-52) (August 18, 2017) to include requirements for the submission of molecularly targeted pediatric cancer investigations for certain applications submitted on or after August 18, 2020, under section 505 of the FD&C Act or section 351 of the PHS Act. These requirements are not specifically addressed in this Q&A.

[11] The statutory provision that appears in section 505B(l) of the FD&C Act was originally enacted as section 505B(n) of the FD&C Act (as amended by the BPCI Act on March 23, 2010). The provision was subsequently redesignated as 505B(m) of the FD&C Act. See section 501(b) of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144) (July 9, 2012). The provision was redesignated again as section 505B(l). See section 3102(3) of the 21st Century Cures Act (Public Law 114-255) (December 13, 2016).

Q.I.16. How can a proposed biosimilar product applicant fulfill the requirement for pediatric assessments or investigations under PREA? [Moved to Final from Draft September 2021]

A.I.16. Applicants for proposed biosimilar products should address PREA requirements based upon the nature and extent of pediatric information in the reference product labeling. As detailed below, PREA requirements are applicable to proposed biosimilar products that have not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in (1) a condition of use that has not been previously approved for the reference product; or (2) a dosage form, strength, or route of administration that differs from that of the reference product.

As a preliminary matter, there are differences in the use of the term *extrapolation* in the context of a proposed biosimilar product under the PHS Act and in the context of PREA:

- An applicant may provide scientific justification for extrapolation to support approval of a biosimilar product under section 351(k) of the PHS Act for one or more conditions of use. For more information on extrapolation in this context, see FDA's guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

- "Pediatric extrapolation" refers to an approach to providing evidence to establish the effectiveness of a drug in a pediatric population "when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population."[12]

In the discussion that follows, the term *extrapolation* generally is used to refer to extrapolation to support approval of a biosimilar product under section 351(k) of the PHS Act for one or more conditions of use, and not to pediatric extrapolation:

- Adequate pediatric information in reference product labeling. If the labeling for the reference product contains adequate pediatric information (e.g., information reflecting an adequate pediatric assessment):

  - If the biosimilar applicant seeks licensure in adults for an indication for which the reference product is approved for pediatric use, a biosimilar applicant may fulfill its PREA requirements for that indication by satisfying the statutory requirements for demonstrating biosimilarity and providing adequate scientific justification under the BPCI Act to support extrapolation of data and information to support licensure. If the

[12] Guidance for industry *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018). See also sections 505B(a)(2)(B) and 505B(a)(3)(B) of the FD&C Act.

submitted scientific justification for extrapolation is inadequate, a biosimilar applicant must submit appropriate data to fulfill applicable PREA requirements.

- If the reference product is not approved for pediatric use but its labeling includes pediatric information (e.g., where a pediatric study was conducted but failed to meet the requirements for licensure of a pediatric indication but information is included in the reference product labeling), the biosimilar applicant may fulfill PREA requirements for that indication by including the relevant pediatric information in its labeling.

- Lack of adequate pediatric information in reference product labeling:

  - If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and applicable PREA requirements were deferred for the reference product for those pediatric age groups, a biosimilar applicant should request a deferral of PREA requirements for those pediatric age groups. Once the reference product labeling is updated with relevant pediatric information, the biosimilar applicant should amend or supplement its 351(k) BLA, as appropriate, to seek approval for updated labeling, supported by extrapolation or appropriate data.

  - If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and PREA requirements were waived for, or inapplicable to, the reference product for those pediatric age groups, a biosimilar applicant should note this information, if any, in its initial PSP, but it does not need to request a waiver of PREA requirements for those age groups. For proposed biosimilars, obligations under PREA are circumscribed by the BPCI Act to require an assessment only for indications and age groups or other conditions of use in which the reference product has been or will be assessed. In other words, the Agency has determined that PREA requirements are applicable to a proposed biosimilar product that has not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in (1) a condition of use that has not been previously approved for the reference product, or (2) a dosage form, strength, or route of administration that differs from that of the reference product.

FDA's recommendations to biosimilar applicants with respect to the PREA requirements reflect a clarification based on the Agency's interpretation of the interaction between section 505B of the FD&C Act (PREA) and section 351(k) of the PHS Act. Biosimilar applicants previously requested, and the Agency

granted, waivers in instances where PREA requirements were waived for or determined to be inapplicable to the reference product. However, upon further consideration, waivers for biosimilars applicants under those circumstances were not necessary, and the practice is more accurately described in terms of the Agency's interpretation of the BPCI Act and PREA. The BPCI Act added section 351(k) of the PHS Act and amended section 505B of the FD&C Act to specify that PREA is applicable to a biosimilar product that has not been determined to be interchangeable with a reference product (see section 7002(a),(d)(2) of the BPCI Act). FDA reads section 351(k) of the PHS Act and PREA together with respect to conducting assessments of and seeking licensure for certain pediatric uses and pediatric formulations.

An application submitted under section 351(k) of the PHS Act must include, among other things, information demonstrating that "the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product" and "the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product" (section 351(k)(2)(A)(i)(III)-(IV) of the PHS Act). FDA has determined that, when the reference product does not have adequate pediatric use information in its labeling or an age-appropriate formulation for a relevant pediatric population, the obligations for the biosimilar applicant under PREA are circumscribed by section 351(k) of the PHS Act. Specifically, the biosimilar applicant would not be expected to obtain licensure for a pediatric use (or describe that use in product labeling) that has not been licensed for the reference product and would not be expected to obtain licensure of a product that would result in a dosage form, strength, or route of administration that differs from that of the reference product.

By establishing an abbreviated licensure pathway for biosimilar and interchangeable products, the BPCI Act reflects the strong public health interest in the licensure and availability of those products. Such licensure could result in increased competition, as well as greater access to biological products. The Agency's interpretation of section 351(k) and PREA assures that biosimilar applicants are not subject to greater regulatory burdens than those faced by reference product sponsors with respect to the study of pediatric uses.

This approach preserves the intent and availability of an abbreviated licensure pathway for biosimilars while helping to ensure that a biosimilar product is labeled and formulated for relevant pediatric conditions of use that have been approved for the reference product. FDA also recognizes the important interests furthered by PREA and appreciates the need to study pediatric uses of biological products and to include pediatric use information in product labeling. Consequently, in appropriate cases, FDA may take additional steps within its authority to assure that pediatric use information is included in biological product

labeling.[13] Such actions may include invoking the "marketed drugs" provision under PREA, in certain circumstances, to require sponsors to conduct pediatric assessments, or take other appropriate steps, to support pediatric labeling for both the biosimilar product and the reference product.[14]

If a biosimilar applicant believes that none of the situations described above apply to its proposed product, the applicant should contact FDA for further information.

Q.I.17. When should a proposed biosimilar product applicant submit an initial pediatric study plan (PSP)?
[Updated/Retained in Final September 2021]

A.I.17. Section 505B(e) of the FD&C Act requires applicants subject to PREA to submit an initial pediatric study plan (PSP) before the date on which the applicant submits the required assessments or investigation, and no later than 60 calendar days after the date of an end-of-phase 2 (EOP2) meeting or at such other time as agreed upon by FDA and the applicant. FDA has issued guidance on the PSP process, including the timing of PSP submission.[15]

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process for reaching agreement between an applicant and FDA on an initial PSP that generally lasts up to 210 days. Given the potential length of this process, and in the absence of an EOP2 meeting for a proposed biosimilar product, FDA recommends that if a sponsor has not already initiated a comparative clinical study intended to address the requirements under section 351(k)(2)(A)(i)(I)(cc) of the PHS Act, the sponsor should submit an initial PSP as soon as feasible, but no later than 210 days before initiating such a study. This is intended to provide adequate time to reach agreement with FDA on the initial PSP before the study is initiated. Depending on the details of the clinical program, it may be appropriate to submit an initial PSP earlier in development. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP.

For additional information on submission of the PSP, including a PSP template, please refer to: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm. After the initial PSP is submitted, FDA and the sponsor work to reach timely agreement on the plan; this process is set forth in section

[13] For instance, if the Agency determines that the basis for the reference product's waiver under PREA no longer applies to a particular age group (e.g., because it is now feasible to study a younger pediatric age group), FDA may, as appropriate, contact the 351(k) biosimilar product sponsor, as well as the reference product sponsor, and require further action by both parties to comply with PREA. See section 505B(a)(5) of the FD&C Act.

[14] See section 505B(b) of the FD&C Act.

[15] See the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

505B(e)(2)-(3) of the FD&C Act. FDA does not formally grant or deny a request for a waiver or deferral in response to the initial PSP.

Q.I.18. For biological products intended to be injected, how can an applicant demonstrate that its proposed biosimilar product has the same dosage form as the reference product?
[Final December 2018]

A.I.18. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the "dosage form" of the proposed biosimilar or interchangeable product is the same as that of the reference product. For purposes of implementing this statutory provision, FDA considers the dosage form to be the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. In the context of proposed biosimilar products intended to be injected, FDA considers, for example, "injection" (e.g., a solution) to be a different dosage form from "for injection" (e.g., a lyophilized powder). Thus, if the dosage form of the reference product is "injection," an applicant could not obtain licensure of a proposed biosimilar product with a dosage form of "for injection" even if the applicant demonstrated that the proposed biosimilar product, when constituted or reconstituted, could meet the other requirements for an application for a proposed biosimilar product.

For purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act, FDA also considers emulsions and suspensions of products intended to be injected to be distinct dosage forms. Liposomes, lipid complexes, and products with extended-release characteristics present special scenarios due to their unique composition, and prospective applicants seeking further information should contact FDA.

It should be noted, however, that this interpretation regarding the same dosage form is for purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act only. For example, this interpretation should not be cited by applicants seeking approval of a new drug application under section 505(c) of the FD&C Act, approval of an abbreviated new drug application under section 505(j) of the FD&C Act, or licensure of a BLA under section 351(a) of the PHS Act for purposes of determining whether separate applications should be submitted and assessed separate fees for different dosage forms.

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***Q.I.19. This question and its answer have been revised and retained in FDA's draft guidance for industry* New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 4).**

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Q.I.20. What is the nature and type of information that a sponsor should provide to support a postapproval manufacturing change for a licensed biosimilar product?
[Moved to Final from Draft September 2021]

A.I.20. In general, similar to manufacturing changes under section 351(a) of the PHS Act, a sponsor that intends to make a manufacturing change to a licensed biosimilar product should follow the principles outlined in the ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process* (June 2005). Accordingly, the sponsor should provide sufficient data and information to demonstrate the comparability of the biosimilar product before and after the manufacturing change. The comparability assessment should include (1) side-by-side analytical comparison of a sufficient number of lots of prechange and postchange material, including stability data, as appropriate; and (2) comparison of analytical data from the postchange material to historical analytical data from biosimilar lots used in the analytical similarity assessment, including data from lots used in clinical studies that supported licensure of the biosimilar product. A well-qualified, in-house reference standard should also be included in the comparability exercise. In certain cases, additional reference materials, such as an international reference standard or a specific impurity reference material, may be included in the comparability study. The extent of data and information necessary to establish comparability would be commensurate with the type of manufacturing change and its potential impact on product quality, safety, and efficacy.

In addition, FDA continues to consider the nature and type of information a sponsor should provide to support a postapproval manufacturing change to a biological product determined by FDA to be interchangeable with the reference product under section 351(k)(4) of the PHS Act. FDA intends to provide specific recommendations for postapproval manufacturing changes to interchangeable biological products in future guidance.

A sponsor may seek approval, in a supplement to an approved 351(k) BLA, of a route of administration, a dosage form, or a strength that is the same as that of the reference product, but that has not previously been licensed under the 351(k) BLA.[16] FDA intends to provide specific recommendations on this topic in future guidance.

[16] As described elsewhere in this guidance (Q&A I.21), a 351(k) applicant may not seek approval of a route of administration, a dosage form, or a strength that is different from the reference product, including in a supplement to an approved 351(k) application. See Q&A I.21 and the draft guidance for industry *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed* (*Licensure for Fewer than All Conditions of Use Guidance*) (February 2020) for additional information. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Q.I.21. May a sponsor seek approval, in a 351(k) application or a supplement to an approved 351(k) BLA, of a route of administration, a dosage form, or a strength that is different from that of the reference product?
[Moved to Final from Draft September 2021]

A.I.21. No. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, a 351(k) application must include information demonstrating that "the route of administration, the dosage form, and the strength" of the proposed biosimilar or interchangeable product "are the same as those of the reference product." An applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, for a route of administration, a dosage form, or a strength that is different from that of the reference product.

Q.I.22. May a sponsor seek approval, in a 351(k) application or a supplement to an approved 351(k) BLA, for a condition of use that has not previously been approved for the reference product?
[Moved to Final from Draft September 2021]

A.I.22. No. Under section 351(k)(2)(A)(i)(III) of the PHS Act, the 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the proposed biosimilar or interchangeable product have been previously approved for the reference product. A 351(k) applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, of a condition of use (e.g., indication, dosing regimen) that has not been previously approved for the reference product.

Whether an applicant is seeking licensure of a proposed biosimilar product for all—or fewer than all—of the conditions of use licensed for the reference product affects which data and information from the reference product labeling should be incorporated into the proposed biosimilar labeling.[17]

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Q.I.23. This question and its answer have been withdrawn.

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[17] For additional information, see FDA's guidance for industry *Labeling for Biosimilar Products.* As also stated in that guidance, FDA recommends that labeling for a biosimilar product incorporate relevant data and information from the reference product labeling, with appropriate modifications. Additionally, FDA's draft guidance for industry *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed*, states that although biosimilar labeling need not be identical to reference product labeling, deviations should be carefully considered to ensure that the condition or conditions of use prescribed, recommended, or suggested in the draft labeling for the proposed biosimilar product have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act). This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Q.I.24. May an applicant submit data and information to support approval of a proposed biosimilar or interchangeable product for an indication for which the reference product has unexpired orphan exclusivity?
[Moved to Final from Draft September 2021]

A.I.24. When an applicant is seeking licensure for an indication for which the reference product has unexpired orphan exclusivity, an applicant should submit data and information to support approval of a proposed biosimilar or interchangeable product for this indication.[18] For example, an applicant may submit data and information intended to provide sufficient scientific justification for extrapolation to support approval of a proposed biosimilar or interchangeable product for one or more indications, including an indication(s) for which the reference product has unexpired orphan exclusivity. In reviewing such information under section 351(k), FDA will not approve the proposed product for the protected indication(s).[19]

II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A "BIOLOGICAL PRODUCT"

Q.II.1. This question and its answer have been withdrawn. For information on the definition of "protein" in section 351(i)(1) of the PHS Act, see Final Rule on* Definition of the Term "Biological Product" *(85 FR 10057, February 21, 2020) and 21 CFR 600.3(h)(6).

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Q.II.2. How is "product class" defined for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period?
[Final April 2015]

A.II.2. For purposes of section 7002(e)(2) of the ACA, a proposed biological product will be considered to be in the same *product class* as a protein product previously approved under section 505 of the FD&C Act on or before March 23, 2010, if both products are homologous to the same gene-coded sequence (e.g., the INS gene for insulin and insulin glargine) with allowance for additional novel flanking

[18] As stated in FDA's guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019), FDA expects that applicants seeking to demonstrate interchangeability 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. We update guidances periodically. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[19] See Licensure for Fewer than All Conditions of Use Guidance for information about timing of submissions for supplements seeking licensure for indications protected by unexpired exclusivity. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

sequences (including sequences from other genes). Products with discrete changes in gene-coded sequence or discrete changes in post-translational modifications may be in the same product class as the previously approved product even if the result may be a change in product PK.

For naturally derived protein products that do not have identified sequences linked to specific genes and that were approved under section 505 of the FD&C Act on or before March 23, 2010, a proposed biological product is in the same product class as the naturally derived protein product if both products share a primary biological activity (e.g., the 4-number Enzyme Commission code for enzyme activity).

However, for any protein product (whether naturally derived or otherwise), if the difference between the proposed product and the protein product previously approved under section 505 of the FD&C Act alters a biological target or effect, the products are not in the same product class for purposes of section 7002(e)(2) of the ACA.

Q.II.3. What type of marketing application should be submitted for a proposed antibody-drug conjugate?
[Final December 2018]

A.II.3. A BLA should be submitted for a proposed monoclonal antibody that is linked to a drug (antibody-drug conjugate). FDA considers an antibody-drug conjugate to be a combination product composed of a biological product constituent part and a drug constituent part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857–49858 (August 25, 2005)).

CDER is the FDA center assigned to regulate antibody-drug conjugates, irrespective of whether the biological product constituent part or the drug constituent part is determined to have the primary mode of action. For more information, see section 503(g) of the FD&C Act; see also, e.g., Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research (June 30, 2003), available at https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm; Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (October 31, 1991), available at https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm.

To enhance regulatory clarity and promote consistency, CDER considered several factors to determine the appropriate marketing application type for antibody-drug conjugates, including the relative significance of the safety and effectiveness questions raised by the constituent parts, particularly the highly specific molecular

targeting by the antibody to a cell type, cellular compartment, or other marker at the site of action (as distinguished from mere alteration of systemic PK).

In light of such factors, CDER considers submission of a BLA under section 351 of the PHS Act to provide the more appropriate application type for antibody-drug conjugates.

Sponsors seeking to submit a BLA for a proposed antibody-drug conjugate may contact CDER's Office of New Drugs at 301-796-0700 for further information.

III. EXCLUSIVITY

Q.III.1. Can an applicant include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act?
[Final December 2018]

A.III.1. Yes. An applicant may include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act, and FDA will consider the applicant's assertions regarding the eligibility of its proposed product for exclusivity. For more information, see FDA's draft guidance for industry *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*.[20] The draft guidance describes the types of information that reference product sponsors should provide to facilitate FDA's determination of the date of first licensure for their products.

Q.III.2. How can a prospective biosimilar applicant determine whether there is unexpired orphan exclusivity for an indication for which the reference product is licensed?
[Updated/Retained in Final September 2021]

A.III.2. The FDA's Orphan Drug Product designation database is available to search for orphan drug designations and/or approvals. The database is updated monthly (see https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm). FDA will not approve a subsequent application for the same drug for the same indication during the 7-year period of orphan exclusivity, except as otherwise provided in the FD&C Act and 21 CFR part 316.

[20] This draft guidance, when finalized, will represent FDA's current thinking on this topic.