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)

December 2018
Biosimilars

Revision 1

Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)

December 2018
Biosimilars

Revision 1

Contains Nonbinding Recommendations

TABLE OF CONTENTS

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 staff responsible for this guidance as listed on the title page.

INTRODUCTION

This guidance document provides answers to common questions from prospective applicants and other interested parties regarding 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 *biosimilars* and *interchangeable biosimilars*,[2] as well as to describe FDA's interpretation of certain statutory requirements added by the BPCI Act.

The BPCI Act amended the Public Health Service Act (PHS Act) and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act 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 (Pub. L. 111–148) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA's interpretation of the BPCI 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 appropriate statutory authority under which certain products will be regulated. FDA intends to update this guidance document to include additional Q&As as appropriate.

---

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency).

We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

This guidance document revises the final guidance document entitled *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,* to clarify and update certain Q&As and to add new Q&As. For certain Q&As, FDA has updated the Q&A by abbreviating the answer and, where appropriate, referring the reader to a separate guidance document that provides additional information on the topic. Alternatively, FDA may have withdrawn a Q&A if the topic is addressed in a separate guidance document or if FDA determined that the Q&A should be revised in some respect and reissued. Additional information about the Q&A format for this guidance document is provided in the Background section.

FDA is also issuing a draft guidance document entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).* When finalized, this draft guidance document will be part of a series of guidance documents that FDA has developed to facilitate development of biosimilar and interchangeable products. The final guidance documents issued to date address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (December 2016)
- Labeling for Biosimilar Products (July 2018)

In addition, FDA has published draft guidance documents related to the BPCI Act, which, when finalized, will represent FDA's current thinking. These draft guidance documents include:

- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018)
- Considerations in Demonstrating Interchangeability With a Reference Product (January 2017)
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018)
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (August 2014)

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 (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar or interchangeable product.

Section 351(i) defines the term *biosimilar* or *biosimilarity* "in reference to a biological product that is the subject of an application under [section 351(k)]" to mean "that the biological product is highly similar to the reference product[3] 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).

Section 351(k)(4) of the PHS Act provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or a supplement to such application) is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient"[4] and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[5]

Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

---

[3] *Reference product* means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act).
[4] Section 351(k)(4)(A) of the PHS Act.
[5] Section 351(k)(4)(B) of the PHS Act.

In this guidance document, the terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe products that are under development or are the subject of a pending 351(k) biologics license application (BLA).

Certain other provisions of the BPCI Act are discussed in the context of the relevant Q&A.

"Question and Answer" Guidance Format

This final guidance document is a companion to the draft guidance document entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).* In this pair of guidance documents, FDA issues each Q&A in draft form in the draft guidance document, receives comments on the draft Q&A, and, as appropriate, moves the Q&A to this final guidance document after reviewing comments and incorporating suggested changes to the Q&A, when appropriate. A Q&A that was previously in the final guidance document may be withdrawn and moved to the draft guidance document if FDA determines that the Q&A should be revised in some respect and reissued in the draft Q&A guidance document. A Q&A also may be withdrawn and removed from the Q&A guidance documents if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance document.

A reference will follow each question in this final guidance document describing the publication date of the current version of the Q&A, and whether the Q&A has been added to or modified in this final guidance document. FDA has maintained the original numbering of the Q&As used in the April 2015 final guidance document (*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*) and May 2015 draft guidance document (*Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*). For ease of reference, a Q&A retains the same number when it moves from the draft guidance document to the final guidance document and, where appropriate, when a Q&A is withdrawn from the final guidance document and moved to the draft guidance document.

Where a Q&A has been withdrawn from the final guidance document, this is marked in the final guidance document by several asterisks between nonconsecutively numbered Q&As and, where appropriate, explanatory text.

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?
[Updated/Retained in Final December 2018]

A. I.1. FDA provides current contact information on its website. See FDA's website, "Biosimilars," available at https://www.fda.gov/biosimilars and 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?
[Updated/Retained in 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*[6] 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 December 2018]

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

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

the interpretation of the statutory standard for biosimilarity, see FDA's guidances for industry on *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* and *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*

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 December 2018]

A. I.4. Some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable. It may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a pre-filled 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, 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 or dosage form; or
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved;

or otherwise does not meet the standard for biosimilarity.

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.

For information about a delivery device or container closure system for a proposed interchangeable product, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product*.[7]

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

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?
[Issued 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?
[Updated/Retained in 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 questions and answers 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?
[Updated/Retained in 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 draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product*.[8]

Q. I.8. Can a sponsor use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?
[Updated/Retained in Final December 2018]

A. I.8. A sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is *biosimilar* to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed.

If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed 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 the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity. The acceptability of such an approach will be evaluated on a case-by-case basis, and should be discussed in advance with the Agency. For certain complex biological products, a modified approach may be needed. A final determination about the adequacy of the scientific justification and bridge will be made during the review of the application.

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include, but are not limited to, the following:

- The relevance of the design of the clinical program to support a demonstration of biosimilarity to the U.S.-licensed reference product for the condition(s) of use and patient population(s) for which licensure is sought;

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

- The relationship between the license holder for the non-U.S.-licensed comparator product and BLA holder for the U.S.-licensed reference product;

- 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);

- 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; and

- The scientific bridge between the non-U.S.-licensed comparator product and the U.S.-licensed reference product, including comparative physicochemical characterization, biological assays/functional assays, degradation profiles under stressed conditions, and comparative clinical PK and, when appropriate, PD data, to address the impact of any differences in formulation or primary packaging on product performance.

A sponsor should also address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed comparator product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed comparator product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. The complexity of the products, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation), and the degree of heterogeneity associated with the product may affect the considerations for the scientific justification regarding the extent of bridging data. Additional factors that FDA may consider regarding the extent of bridging data include, but are not limited to, the following:

- Whether the formulation, dosage form, and strength of the U.S.-licensed reference product and non-U.S.-licensed comparator products are the same;

- The route of administration of the U.S.-licensed reference product and non-U.S.-licensed comparator products;

- The design of the physicochemical and biological/functional assessments and the use of multiple orthogonal methods with adequate sensitivity to detect differences among the products;

- The scientific justification for the selection of the non-U.S.-licensed comparator lots used to establish the scientific bridge and how the selected lots relate to the material used in the nonclinical and clinical studies. The scientific bridge should include a sufficient number of lots of non-U.S.-licensed comparator product to adequately capture the variability in product quality attributes. When possible, the non-U.S.-licensed comparator lots used in the nonclinical or clinical studies should be included in the assessment performed to establish the analytical bridge.

Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by FDA during review of the 351(k) application.

For more information about whether a non-U.S.-licensed comparator can be used in studies intended to support the additional criteria required for a determination of interchangeability with the reference product, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product*.[9]

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? [Moved to Final from Draft 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.

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

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?
[Moved to Final from Draft December 2018]

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 PK and/or 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 the FDA for specific advice if an alternative approach is being considered. For a 3-way PK similarity study, FDA recommends that samples of both comparator products be retained, in addition to samples of the proposed biosimilar product.

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 mg in a volume equal to or greater than 10 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.

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

* * * * *

Q.I.12. This question and answer have been withdrawn and moved to FDA's draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).*

* * * * *

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?
[Moved to Final from Draft 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 Web site 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?
[Moved to Final from Draft December 2018]

A. I.14. Yes. For more information, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product.*[10]

Q. I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?
[Updated/Retained in Final December 2018]

A. I.15. Under the Pediatric Research Equity Act (PREA) (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, safety, and effectiveness of the

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

product for the claimed indication unless this requirement is waived, deferred, or inapplicable. [11]

Section 505B(l) of the FD&C Act[12] provides that 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 non-interchangeable biosimilar product even if it ultimately intends to subsequently seek licensure of the product as an interchangeable product.

See question and answer I.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2),* 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 application (IND) 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. It is expected that the sponsor will submit the initial PSP before initiating any comparative clinical study in its biosimilar development program. For more information see question and answer I.17 of this guidance. See also the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (March 2016).*[13]

* * * * *

[11] Section 505B(a)(1) was amended in 2017 by section 504 of the Food and Drug Administration Reauthorization Act (FDARA) (**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 guidance.

[12] The statutory provision that appears in section 505(l) of the FD&C Act was originally enacted as section 505(n) of the FD&C Act (as amended by the BPCI Act on March 23, 2010). The provision was subsequently redesignated as 505(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 505(l). See section 3102(3) of the 21st Century Cures Act (**Public Law 114-255**) (December 13, 2016).

[13] This guidance, when finalized, will provide FDA's current thinking on issues related to pediatric study plans.

Q. I.17. When should a proposed biosimilar product applicant submit an initial pediatric study plan (PSP)?
[Moved to Final from Draft December 2018]

A. I.17. Section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires applicants subject to the Pediatric Research Equity Act (PREA) to submit an initial pediatric study plan (PSP) no later than 60 calendar days after the date of an end-of-Phase 2 (EOP2) meeting, or at another time agreed upon by FDA and the applicant. FDA has issued draft guidance on the PSP process, including the timing of PSP submission.[14]

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 Public Health Service (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 guidance 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, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

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?
[Moved to Final from Draft 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

[14] See the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (March 2016)*. This draft guidance, when finalized, will provide FDA's current thinking on this topic.

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.

Q. I.19. If a non-U.S.-licensed product is proposed for importation and use in the U.S. in a clinical investigation intended to support licensure of a proposed product under section 351(k) (e.g., a bridging clinical PK and/or PD study), is a separate IND required for the non-U.S.-licensed product?
[Moved to Final from Draft December 2018]

A. I.19. A sponsor may submit a single 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 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, for example, if a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, and proposes to conduct a clinical PK and/or PD study in the U.S. with all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed product) to support establishment of a bridge between all three products and scientific justification for the relevance of these comparative data to an assessment of biosimilarity to the U.S.-licensed reference 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 of 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 drug will have the proper identity, strength, quality, and purity; or
- Other information justifying a waiver.[15]

Information that is relevant to whether the investigational drug will have the proper identity, strength, quality, and purity may include, for example, information indicating whether the investigational drug has been licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries). This should include, to the 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 US clinical site(s) and information on the relabeling and repackaging operations that will be used to relabel the drug product vials 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.

[15] See 21 CFR 312.10(a).

As would be applicable to all investigational 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. The IB and study protocol(s) also should clearly describe whether the comparator used in each study is the US-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.

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

Q.II.1. [This question and answer have been withdrawn and moved to FDA's draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).*]

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?
[Issued April 2015]

A. II.2. For purposes of section 7002(e)(2) of the Affordable Care Act, 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 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 pharmacokinetics.

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 Affordable Care Act.

Q. II.3. What type of marketing application should be submitted for a proposed antibody-drug conjugate?
[Moved to Final from Draft 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 pharmacokinetics).

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?
[Moved to Final from Draft 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 on *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act.*[16] 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?
[Issued April 2015]

A. III.2. A searchable database for Orphan Designated and/or Approved Products and indications is available on FDA's Web site, and is updated on a monthly basis (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.

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