New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)

Guidance for Industry

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted as electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2011-D-0611.

For questions regarding this draft document, contact (CDER) Sandra Benton, 301-796-1042, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

September 2021
Biosimilars

Revision 3

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

INTRODUCTION

This 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 biosimilar products* and *proposed interchangeable products*,[2] as well as describe FDA's interpretation of certain statutory requirements added by the BPCI Act.

The BPCI Act created an abbreviated licensure pathway in section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)) 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 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 submission of

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

[2] In this draft guidance, the following terms are used to describe biological products licensed under section 351(k) of the Public Health Service Act (PHS Act): (1) *biosimilar* or *biosimilar product* refers to a product that FDA has determined to be biosimilar to the reference product (see section 351(i)(2) and (k)(2) of the PHS Act) and (2) *interchangeable biosimilar* or *interchangeable product* refers to a biosimilar product that FDA has also determined to be interchangeable with the reference product (see section 351(i)(3) and (k)(4) of the PHS Act). The terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe a product that is under development or is the subject of a pending 351(k) biologics license application. Biosimilarity, interchangeability, and related issues are discussed in more detail in the BACKGROUND section of this guidance.

biologics license applications (BLAs) for biosimilar and interchangeable products. FDA may provide additional Q&As through draft guidance as appropriate.

This draft guidance document revises the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (December 2018) and retains Q.I.12. This draft guidance does not include new Q&As or make changes to currently issued draft or final Q&As. Additional information about the Q&A format for this draft guidance document is provided in the Background section.

After FDA has considered any comments on a draft Q&A, the Q&A will be finalized by adding the Q&A, as a revision, to the final guidance document *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021), as appropriate. This final guidance document is 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:

- *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016)
- *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019)
- *Labeling for Biosimilar Products* (July 2018)
- *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)* (September 2021)
- *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015)

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:

- *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020)
- *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019)
- *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)

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations,

unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

BACKGROUND

The BPCI Act

The BPCI Act was enacted as part of the ACA on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the ACA). Section 351(k) of the PHS Act, added by the BPCI Act, sets forth the requirements for the licensure of a proposed biosimilar or proposed interchangeable product.

Section 351(i) 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, animal studies, and a clinical study or studies (see section 351(k)(2)(A)(i)(I) of the PHS Act), unless FDA has determined that an element described in section 351(k)(2)(A)(i)(I) is unnecessary (see section 351(k)(2)(A)(ii) of the PHS Act). To meet the standard for "interchangeability," an applicant must provide sufficient information to demonstrate biosimilarity to the reference product and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient, and if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

"Question-and-Answer" Guidance Format

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

during the relevant comment period and, as appropriate, incorporated suggested changes to the Q&As, individual Q&As will be finalized and moved to the final guidance document.

A Q&A that was previously in the final guidance document may be withdrawn and moved to a draft guidance document 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 documents if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance document.

FDA will provide the publication date of the current version of each Q&A, and information about whether the Q&A has been added to or modified in the relevant draft guidance document. FDA has maintained the original numbering of the guidance Q&As used in the December 2018 final guidance document (*Questions and Answers on Biosimilar Development and the BPCI Act*), December 2018 draft guidance document (*New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2))*, and the November 2020 draft guidance document (*Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act*). For ease of reference, a Q&A retains the same number when it moves from a 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 a draft guidance document.

In this draft guidance document, several asterisks appear where Q&As have already been withdrawn or moved to the final guidance document.

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

* * * * *

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

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

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

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

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

* * * * *

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

There are no draft Q&As for this section.

III. EXCLUSIVITY

There are no draft Q&As for this section.