Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act

Guidance for Industry

DRAFT GUIDANCE

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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)

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Biosimilars

Revision 1

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Guidance for Industry

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Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

INTRODUCTION

This draft guidance provides answers to common questions from prospective applicants and other interested parties regarding the Biologics Price Competition and Innovation Act of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 biologics license applications (BLAs) for biosimilar and interchangeable products. FDA may provide additional Q&As through draft guidances as appropriate.

[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). You may submit comments on a guidance at any time. Submit comments on this guidance 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 on this guidance.

[2] In this draft guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) *biosimilar* or *biosimilar product* refers to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 draft guidance.

This draft guidance revises the draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020) by withdrawing Q.I.27 and Q.I.28 and retaining Q.I.25 and Q.I.26. This draft guidance does not include new Q&As or make changes to currently issued draft Q&As. Additional information about the Q&A format for this draft guidance is provided in the Background section.

After FDA has considered any comments on a draft Q&A, the Q&As in this guidance will be finalized by adding the Q&A, as a revision, to the final guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)* (September 2021),[3] as appropriate. The final guidance is part of a series of guidances that FDA developed to facilitate development of biosimilar and interchangeable products.

The final guidances 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)
- *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 guidances related to the BPCI Act; when finalized, these guidances will represent the FDA's current thinking. These draft guidances include:

- *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* (August 2023)
- *Labeling for Biosimilar and Interchangeable Biosimilar Products* (September 2023)
- *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)* (September 2021)
- *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* (August 2014)

[3] 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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

BACKGROUND

The BPCI Act

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

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") of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, 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 Q&A guidance format to describe the Agency's thinking on and update certain information and recommendations relevant to the development of biosimilar and interchangeable products. This draft guidance includes only Q&As that are in draft form. The guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act*

contains all Q&As that are final. As FDA issues individual Q&As, they will first be incorporated into a Q&A draft guidance. 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&A, individual Q&As will be finalized and moved to the final guidance.

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

FDA will provide the publication date of the current version of each Q&A and information about whether the Q&A has been added to or modified in the relevant draft guidance. FDA has maintained the original numbering of the Q&As used in the September 2021 final guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)*, the September 2021 draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)*, and the November 2020 draft guidance for industry *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 to the final guidance and, where appropriate, when a Q&A is withdrawn from the final guidance and moved to a draft guidance.

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q.I.25 How may the applicant seek FDA review for licensure for an interchangeable biosimilar, and how does FDA intend to review an application submitted under section 351(k) that seeks licensure as an interchangeable biosimilar and includes data and information sufficient to support licensure of the product as a biosimilar product, but does not contain data and information sufficient to support licensure of the product as an interchangeable biosimilar?
[Draft November 2020]

A.I.25 To support licensure of an interchangeable biosimilar under section 351(k) of the PHS Act, an applicant must show that the product meets the standards described in section 351(k)(4).[4] Among the specified criteria that must be met to be licensed as an interchangeable biosimilar under section 351(k)(4), the applicant must show that the

[4] In addition to the requirement under section 351(k)(4) that FDA determine that the information submitted in the application or the supplement is sufficient to show that the biological product "is biosimilar to the reference product," FDA must also find that the proposed product "can be expected to produce the same clinical result as the reference product in any given patient," 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" in order to license the proposed product as an interchangeable biosimilar.

biological product is "biosimilar to the reference product." Thus, there may be situations in which the data and information provided in a BLA seeking licensure as an interchangeable biosimilar can support licensure of the product as a biosimilar product but not as an interchangeable biosimilar.

As an initial matter, if a BLA submitted under section 351(k) of the PHS Act is intended to support licensure as an interchangeable biosimilar, the BLA submission should contain an affirmative statement to that effect. If a BLA submission does not contain such a statement, the Agency plans to evaluate the BLA for licensure only as a biosimilar product. In other words, the Agency intends to evaluate whether the proposed product meets the requirements for licensure as an interchangeable biosimilar only if the 351(k) BLA indicates at the time of submission that it contains information intended to demonstrate that the product meets the standards described in section 351(k)(4) for licensure as an interchangeable biosimilar. This approach provides for a more efficient and predictable review of BLAs.

If an applicant indicates in its cover letter that a BLA submitted under section 351(k) contains information intended to demonstrate interchangeability, the Agency generally plans to evaluate the BLA as both an application for licensure of a biosimilar product and an application for licensure of an interchangeable biosimilar. In such cases, if a BLA submitted under section 351(k) contains data and information sufficient to support licensure of the product as a biosimilar product but does not contain data and information sufficient to support licensure of the product as an interchangeable biosimilar as a scientific matter, FDA intends to split the application for administrative purposes. This will enable the Agency to take separate actions on such a BLA as appropriate. For example, FDA could license the product as a biosimilar product[5] and convey deficiencies in the application for licensure as an interchangeable biosimilar to the applicant in a complete response letter, and FDA could make a determination of interchangeability for the product upon submission of a supplement that contains all data and information necessary to support licensure of the product as an interchangeable biosimilar.[6]

However, if an applicant specifically requests that the Agency approve an application for licensure submitted under 351(k) only if FDA determines the product to be interchangeable with the reference product, the Agency plans to evaluate only whether the application for the biological product meets the standards described in section 351(k)(4) for licensure as an interchangeable biosimilar (an "interchangeable-only" review). The Agency recommends that an applicant requesting this type of review clearly note the request for "INTERCHANGEABLE-ONLY REVIEW" in the cover letter accompanying the BLA. If upon an "interchangeable-only" review the Agency determines that a BLA is not approvable for licensure as an interchangeable biosimilar, the Agency intends to send a complete response letter addressing the

[5] Section 351(k)(3) of the PHS Act. 21 CFR 601.4.

[6] 21 CFR 601.3.

request for licensure as an interchangeable biosimilar.[7] The complete response letter would also include deficiencies pertaining to a demonstration of biosimilarity, if any, because biosimilarity is a condition necessary for approval of a 351(k) BLA as an interchangeable product. Consistent with the applicant's request, however, the complete response letter would not address whether the application was sufficient to support a demonstration of licensure as a biosimilar product alone. Upon receipt of an "interchangeable-only" complete response letter, the applicant may then choose to amend and resubmit their application to address the deficiencies and support a demonstration of interchangeability or to amend and resubmit their BLA seeking licensure as a biosimilar product.[8]

Q.I.26 How should a 351(a) BLA holder proceed if it seeks licensure of its biological product under section 351(k) as biosimilar to or interchangeable with another biological product licensed under section 351(a) (a "reference product")? [Draft November 2020]

A.I.26 FDA reviews data and information intended to support licensure of a proposed biological product as a biosimilar product in an original application submitted under section 351(k) of the PHS Act.[9] Similarly, FDA reviews data and information intended to support licensure of a proposed biological product as an interchangeable biosimilar in an original application submitted under section 351(k) of the PHS Act or a supplement to an approved application submitted under section 351(k) of the PHS Act.[10] Therefore, if a holder of a BLA for a biological product licensed or deemed licensed[11] under section 351(a) wishes to submit an application for licensure of that biological product as a biosimilar to or interchangeable with another biological product, i.e. the reference product, it should do so by submitting an original application for licensure under section 351(k).

As with any application under section 351(k), such an application should specify the single biological product licensed or deemed licensed under section 351(a) of the PHS Act as the reference product, as that term is defined in section 351(i), against which the proposed biosimilar or proposed interchangeable product will be evaluated. The application for licensure under section 351(k) also should include data and

[7] See 21 CFR 601.3.

[8] See 21 CFR 601.3.

[9] See sections 351(k)(2) and (3) of the PHS Act. See also guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[10] See sections 351(k)(3) and (4) of the PHS Act. See also guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019) (Interchangeability Guidance).

[11] See guidance for industry *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (December 2018).

information sufficient to demonstrate biosimilarity,[12] and, if interchangeability is sought, interchangeability with the specified reference product.[13]

An applicant may support a demonstration of biosimilarity or interchangeability under section 351(k) using relevant data and information from the applicant's own 351(a) BLA. It is not necessary for the holder of a 351(a) BLA for a biological product licensed or deemed licensed under section 351(a) to seek revocation of its 351(a) license in order to submit a 351(k) application. The 351(a) BLA holder may continue to market the biological product licensed or deemed licensed under section 351(a) while the 351(k) BLA is pending and after licensure of the biological product under section 351(k).[14]

FDA believes that this approach balances the opportunity for continued innovation with respect to the biological product licensed or deemed licensed under section 351(a) of the PHS Act while facilitating robust market competition through the approval of biosimilar and interchangeable products under the 351(k) pathway.

***Q.I.27 This question and its answer have been withdrawn. For information on labeling for interchangeable biosimilar products, see FDA's draft guidance for industry* Labeling for Biosimilar and Interchangeable Biosimilar Products.[15]**

***Q.I.28 This question and its answer have been withdrawn. For information on labeling for interchangeable biosimilar products, see FDA's draft guidance for industry* Labeling for Biosimilar and Interchangeable Biosimilar Products.[16]**

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

There are no draft Q&As for this section.

[12] For more information on demonstrating biosimilarity, see draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019) (this draft guidance, when finalized, will represent FDA's current thinking on this topic) and guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[13] For more information on interchangeability, see the Interchangeability Guidance. A biosimilar product or interchangeable biosimilar may be licensed only for conditions of use that have been previously approved for the reference product. Section 351(k)(2)(A)(i)(III) of the PHS Act. See also draft guidance for industry *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed* (February 2020), which, when finalized, will represent FDA's current thinking on the topic.

[14] 21 CFR 601.5. Each product would need to be marketed in accordance with its respective approved conditions of use, as reflected in each product's FDA-approved product labeling.

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

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

III. EXCLUSIVITY

There are no draft Q&As for this section.