Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed

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DRAFT GUIDANCE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

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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.

I. INTRODUCTION

This guidance provides recommendations to applicants seeking licensure under section 351(k) of the Public Health Service (PHS) Act of a proposed biosimilar or proposed interchangeable biosimilar[2] for fewer than all of the reference product's licensed conditions of use. This guidance also provides recommendations on the submission of a supplement to a licensed 351(k) biologics license application (BLA) seeking to add a condition of use that previously has been licensed[3] for the reference product to the labeling[4] of a licensed biosimilar or interchangeable product, including considerations related to the timing of such submissions.

This guidance includes recommendations regarding the following specific issues:

- Submission of an application seeking licensure of a proposed biosimilar or proposed interchangeable biosimilar for fewer than all of the reference product's licensed conditions of use.

[1] This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug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

[2] In this draft guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) *biosimilar* or *biosimilar product* refers to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*, *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). Biosimilarity, interchangeability, and related issues are discussed in more detail in section II of this draft guidance.

[3] 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.

[4] Unless otherwise specified, the terms *biosimilar product labeling* and *labeling* as used in this guidance address only the prescribing information as described in 21 CFR 201.56 and 201.57.

- Development of proposed labeling when the applicant seeks licensure of a proposed biosimilar or proposed interchangeable product for fewer than all of the reference product's licensed conditions of use.
- Submission of a supplement to an application for a biosimilar or interchangeable biosimilar to seek licensure for a condition of use previously licensed for the reference product. This may occur, for example, when (1) the biosimilar or interchangeable product was initially licensed for fewer than all of the reference product's licensed conditions of use, or (2) the reference product is licensed for a new condition of use after licensure of the biosimilar or interchangeable product.
- Timing for the submission of a 351(k) BLA or supplement to a licensed 351(k) BLA described above with the goal of obtaining licensure of a condition of use for a biosimilar or interchangeable product as soon as possible after the expiration of any relevant exclusivity or patents.

This guidance is one in a series of guidances that FDA is developing to implement the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) and includes references to information from other FDA guidances, where appropriate.

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.

II. BACKGROUND

A. The Biosimilar Pathway

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for the licensure of a biosimilar or interchangeable biosimilar. 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" (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,[5] and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) BLA (see section 351(k)(2) of the PHS Act).

[5] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

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 biosimilars may be substituted for the reference product without the intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

B. Licensure of a Biosimilar or Interchangeable Biosimilar for Fewer Than All of the Reference Product's Licensed Conditions of Use

A biosimilar or interchangeable biosimilar may be licensed only for conditions of use that have been previously licensed for the reference product.[6] An applicant generally may obtain licensure of a biosimilar or interchangeable for *fewer* than all of the conditions of use for which the reference product is licensed.[7] However, FDA recommends that an applicant seeking licensure for a proposed interchangeable product seek licensure for all of the reference product's licensed conditions of use when possible.[8]

A variety of circumstances may lead an applicant to seek licensure of a proposed biosimilar or proposed interchangeable product for fewer than all of the conditions of use for which the reference product is licensed. Examples of these circumstances are described below.

Orphan-drug Exclusivity

The reference product may be licensed for one or more indications that are protected by orphan-drug exclusivity. In such cases, until the applicable exclusivity expires, FDA will not be able to license a biosimilar or interchangeable product for the protected indications. However, assuming that the requirements for licensure are met, FDA may be able to license a biosimilar or interchangeable product for one or more indications of the reference product that are not protected by orphan-drug exclusivity. In such circumstances, an applicant may choose to seek licensure of a biosimilar or interchangeable product for such indications.

After the applicable orphan-drug exclusivity expires, the applicant may, in a supplement to the licensed 351(k) BLA, seek licensure of the biosimilar or interchangeable biosimilar for a

[6] Section 351(k)(2)(A)(i)(III) of the PHS Act.

[7] Notably, section 351(k)(4)(A) of the PHS Act provides, among other things, that an application for an interchangeable product must include information sufficient to show that the proposed interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient." 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. Guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019).

[8] Guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019).

previously protected indication, and FDA may license the biosimilar or interchangeable biosimilar for this indication if the requirements for licensure are met.[9]

Circumstances Other Than Exclusivity

- *Patent(s) covering a licensed condition of use of the reference product:* An applicant may conclude that a licensed condition of use of the reference product is protected by one or more patent(s). As a result, the applicant may decide not to seek licensure of a proposed biosimilar or proposed interchangeable product for conditions of use that are protected by patent, according to the applicant's own assessment.

- *Other reasons:* Reasons other than patents or exclusivity may lead an applicant to choose to seek licensure for fewer than all conditions of use for which the reference product is licensed.

III. RECOMMENDATIONS FOR APPLICANTS SEEKING LICENSURE OF A BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR FOR FEWER THAN ALL OF THE REFERENCE PRODUCT'S LICENSED CONDITIONS OF USE

A. Submission of Original 351(k) BLA or Supplement to a 351(k) BLA

1. Submission of an Original 351(k) BLA for Licensure for Fewer Than All of the Reference Product's Licensed Conditions of Use

As part of an original 351(k) BLA, an applicant is expected to submit draft labeling that includes the conditions of use for which the applicant is seeking licensure of the proposed biosimilar or proposed interchangeable product.[10, 11] Additional considerations regarding draft labeling are described in section III.B in this guidance. Applicants may contact the appropriate review division in FDA for more information about submitting a 351(k) BLA for licensure of a proposed biosimilar or proposed interchangeable biosimilar for fewer than all of the reference product's licensed conditions of use.

[9] Similarly, as provided by section 351(m) of the PHS Act, an additional six-month period of exclusivity will attach to certain applicable periods of exclusivity if the sponsor conducts pediatric studies that meet the requirements for pediatric exclusivity pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). As with orphan-drug exclusivity, during the applicable period of pediatric exclusivity FDA may be able to license a biosimilar or interchangeable product for one or more indications of the reference product that are not protected by such exclusivity, and FDA may license the biosimilar or interchangeable biosimilar for a previously protected indication after the applicable pediatric exclusivity expires.

[10] FDA has issued draft guidance regarding the submission of data and information to support approval of a proposed biosimilar or interchangeable product for an indication for which the reference product has unexpired exclusivity. See Q.I.24 in the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (December 2018). When finalized, this guidance will represent FDA's current thinking on this topic.

[11] See section 351(k)(2)(A)(i)(III) of the PHS Act, which requires that a 351(k) application include 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.

2. Submission of a Supplement to a 351(k) BLA Seeking Licensure of a Biosimilar or Interchangeable Biosimilar for an Additional Condition of Use Previously Licensed for the Reference Product

The holder of a licensed 351(k) BLA may, in a supplement to the 351(k) BLA, seek licensure of its biosimilar or interchangeable biosimilar for an additional condition of use that has been previously licensed for the reference product and for which the applicant did not originally seek licensure. A 351(k) BLA holder seeking licensure for an additional condition of use must submit a supplement in accordance with 21 CFR 601.12 seeking licensure of the proposed change. See section III.C.

A supplement to a 351(k) BLA seeking licensure of a biosimilar or interchangeable biosimilar for an additional condition of use should contain all the data and information needed to support licensure of the biosimilar or interchangeable biosimilar for the proposed condition of use, which may include reference to data and information previously submitted to the 351(k) BLA with appropriate scientific justification. Applicants may contact the appropriate clinical review division at FDA for more information about licensure of a biosimilar or interchangeable biosimilar in such circumstances.

B. Development of Draft Labeling for a Proposed Biosimilar or Interchangeable Product for Fewer Than All of the Reference Product's Licensed Conditions of Use

FDA's guidance for industry *Labeling for Biosimilar Products* ("Biosimilar Labeling Guidance"), provides general recommendations on the development of draft labeling for proposed biosimilar products for submission in a 351(k) BLA.[12] In the Biosimilar Labeling Guidance, FDA recommends that labeling for a biosimilar product incorporate relevant data and information from the reference product labeling, with appropriate modifications. The Biosimilar Labeling Guidance also explains that determining which data and information from the reference product labeling should be incorporated into the proposed labeling for a biosimilar will depend on whether the applicant is seeking licensure for all—or fewer than all—of the conditions of use licensed for the reference product.

1. Content of Draft Labeling

The applicant should develop draft labeling for the proposed biosimilar or proposed interchangeable biosimilar that includes information from the reference product labeling that is relevant to the proposed conditions of use for the proposed biosimilar or interchangeable, with appropriate modifications. In preparing such draft labeling, the applicant should carefully scrutinize the content of all sections of the labeling to ensure that relevant information is

[12] See guidance for industry *Labeling for Biosimilar Products* (July 2018), which states that it does not provide specific labeling recommendations for interchangeable products and that any specific recommendations for interchangeable products will be provided in future guidance.

included, based on the proposed conditions of use for the proposed biosimilar or interchangeable product.[13]

FDA will evaluate the labeling to determine whether it complies with applicable requirements.[14] For example, the labeling must summarize the essential scientific information needed for the safe and effective use of the product.[15] FDA regulations also require that prescription drug labeling contain:

> "adequate information … including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely *and for the purposes for which it is intended* …"[16]

2. Information to Support Draft Labeling for a Biosimilar or Interchangeable Product for Fewer Than All of the Reference Product's Licensed Conditions of Use

In general, FDA does not expect an applicant to submit a justification for the applicant's decision not to seek licensure of a biosimilar for all of the reference product's licensed conditions of use. FDA does not consider the applicability of patents to a proposed biosimilar product (e.g., the validity or enforceability of patents or potential infringement) in its review of a 351(k) BLA or supplement to a 351(k) BLA.[17] An applicant seeking licensure of a biosimilar or interchangeable biosimilar for fewer than all of the reference product's licensed conditions of use may, in a 351(k) BLA or a supplement to a 351(k) BLA, submit information that is intended to inform FDA's review of the draft labeling. For example, an applicant may submit a justification as to why, in the applicant's view, the draft labeling meets the requirements for approval, considering the conditions of use for which the applicant is seeking licensure.

C. Timing Considerations for Submission of a 351(k) BLA or Supplement to a 351(k) BLA

The recommendations in this section are intended to facilitate submission of a 351(k) BLA or supplement to a licensed 351(k) BLA with the goal of obtaining licensure of a biosimilar or interchangeable biosimilar soon after expiration of any relevant exclusivity or expiration of a

[13] For example, as noted in the guidance for industry *Labeling for Biosimilar Products* (July 2018), "in certain circumstances it may be necessary to include information in the biosimilar product labeling relating to an indication(s) for which the biosimilar product is not licensed, in order to help ensure safe use …" Additionally, 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).

[14] See, e.g., 21 CFR 201.56 and 21 CFR 201.57.

[15] See 21 CFR 201.100 and 201.56(a)(1).

[16] See 21 CFR 201.100(d)(1) (emphasis added).

[17] For more information about the exchange of confidential information for purposes of determining whether a claim of patent infringement could reasonably be asserted against a 351(k) applicant, refer to section 351(l) of the PHS Act (42 U.S.C. 262(l)).

patent that, in the 351(k) applicant's assessment, protects a licensed condition of use of the reference product. These recommendations also are applicable to a supplement to a licensed 351(k) BLA that seeks licensure of a biosimilar or interchangeable biosimilar for an additional condition of use for which the applicant did not originally seek licensure but that has since been licensed for the reference product.

1. Targeted Timelines for Review

Original 351(k) BLA

As described in the Biosimilar User Fee Act (BsUFA) II Goals Letter, FDA is committed to reviewing and acting on original 351(k) BLAs within 10 months of the 60-day filing date.[18]

Supplements to a Licensed 351(k) BLA

In the BsUFA II Goals Letter, FDA also committed to reviewing and acting on original 351(k) BLA supplements with clinical data within 10 months of receipt.[19] In light of the anticipated FDA review burden (among other considerations), FDA anticipates that it will review and act on many supplements seeking licensure for additional conditions of use for a licensed biosimilar or interchangeable product before the BsUFA goal date. To the extent practicable, FDA intends that a supplement to a licensed 351(k) BLA seeking licensure of the biosimilar or interchangeable product for an additional condition of use that has been previously licensed for the reference product will be reviewed and acted upon in a 6-month timeframe, without regard to whether the biosimilar or interchangeable product was initially licensed for fewer than all of the reference product's licensed conditions of use or the reference product is licensed for a new condition of use after licensure of the biosimilar or interchangeable product.

FDA recognizes that targeting a 6-month timeline for such supplements may surpass, in many cases, the performance goal commitment FDA made in the BsUFA II Goals Letter. Supplements seeking licensure for additional conditions of use for a licensed biosimilar or interchangeable product likely will include clinical data or reference clinical data submitted previously to the 351(k) BLA. As noted, the BsUFA II Goals Letter describes a 10-month goal date for original 351(k) BLA supplements with clinical data. However, at this time, FDA believes that a review timeframe of 6 months will generally be appropriate for a supplement to a licensed 351(k) BLA seeking licensure of the biosimilar or interchangeable product for an additional condition of use that has been previously licensed for the reference product, assuming the supplement does not raise novel review issues. Among other considerations, this is based on the anticipated FDA review burden associated with these types of supplements. FDA intends to notify applicants in an acknowledgement letter if it believes that the 10-month review timeline described in the BsUFA II Goals Letter is more appropriate for any such supplement.

[18] See *Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022* ("BsUFA II Goals Letter") at https://www.fda.gov/media/100573/download.
[19] See BsUFA II Goals Letter.

2. Unexpired Exclusivity

The Agency cannot license a biosimilar or interchangeable product for an indication protected by orphan-drug exclusivity or pediatric exclusivity until the expiration of that exclusivity.[20] If an applicant's proposed labeling includes conditions of use that are protected by unexpired orphan-drug exclusivity or unexpired pediatric exclusivity, the Agency may communicate this issue to the applicant in the Day 74 letter.[21] In these circumstances, an applicant may seek to time the submission of a 351(k) BLA or supplement to a 351(k) BLA with the goal of obtaining licensure after a specific date, such as the expiration of orphan-drug or pediatric exclusivity.

3. Circumstances Other Than Exclusivity, Including Patents

As described above, an applicant may choose to seek licensure of a proposed biosimilar or interchangeable biosimilar for fewer than all of the reference product's licensed conditions of use based on an assessment by the applicant that one or more of the reference product's licensed conditions of use is protected by patent. In these circumstances, an applicant may seek to time the submission of a 351(k) BLA or supplement to a 351(k) BLA with the goal of obtaining licensure after a specific date, such as the expiration of a patent. Other nonpatent reasons may also lead an applicant to take this approach.

In contrast to orphan-drug and pediatric exclusivity, the BPCI Act does not limit FDA's ability to license a 351(k) BLA or a supplement to a 351(k) BLA where a biosimilar seeks licensure for a condition of use which may be subject to one or more patents. FDA may therefore license the product for such condition of use if FDA determines that the requirements for licensure have been met.

Applicants should be aware that FDA may review and act on (i.e., license or issue a complete response letter to)[22] a 351(k) BLA or supplement to a 351(k) BLA *before* any applicable BsUFA goal date or 6-month targeted review timeline. If an applicant does not want FDA to take action on a 351(k) BLA or supplement to a 351(k) BLA before a specified date, the applicant should request that the Agency refrain from acting on the BLA or supplement before the specified date, so long as that date falls on or before the applicable BsUFA goal date.

To request that FDA not take action on a 351(k) BLA or supplement to a 351(k) BLA before a specified date, the applicant should include the following language on the cover letter of their BLA or supplement, in bold typeface and prominently placed above the body of the cover letter:

> **351(k) BLA action timing request:** [Applicant Name] requests that FDA not take action on this [application/supplement] before [specified date].

If the applicant requests that FDA refrain from taking action on the 351(k) BLA or a supplement to a 351(k) BLA until a specified date that is on or before any applicable BsUFA goal date, the

[20] See section 527 of the FD&C Act; section 351(m) of the PHS Act; 21 CFR 316.31.
[21] See BsUFA II Goals Letter, p. 10.
[22] See BsUFA II Goals Letter, p. 32 (defining "review and act on" to mean "the issuance of a complete action letter after complete review of a filed complete application").

Agency intends to honor the applicant's request, where appropriate. Applicants should take BsUFA goal dates into consideration before making such requests. If the requested date extends beyond any applicable BsUFA goal date, the Agency does not intend to honor the applicant's request.

Upon receipt of the 351(k) BLA or supplement to a 351(k) BLA containing a request not to act before any applicable BsUFA goal date (or another specified date prior to a BsUFA goal date), FDA intends to acknowledge the applicant's request along with the date of receipt of the 351(k) BLA or supplement to a 351(k) BLA through an acknowledgment letter.

Applicants may contact the appropriate review division in FDA with specific questions about the timing of submission for a 351(k) BLA or supplement to a 351(k) BLA.