Classification Categories for Certain Supplements Under BsUFA III

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Sandra Benton at 301-796-1042 or (CBER) Office of Communication, Outreach and Development, at 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)

August 2023
Biosimilars

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Classification Categories for Certain Supplements Under BsUFA III 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 for applicants and FDA review staff on classification categories A, B, C, D, E, and F for original and resubmitted prior approval supplements (hereafter referred to as *PAS* or *supplements*) submitted to approved applications under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)).[2] The commitment letter associated with the Biosimilar User Fee Amendments of 2022 (BsUFA III) sets forth these supplement classification categories and their associated review performance goals (refer to Section I.A. of the BsUFA III commitment letter).[3] This guidance is intended to help applicants identify the appropriate classification category and review goal date of the supplement being submitted.

The classification categories pertain to supplements for biosimilar and interchangeable biosimilar[4] products for applicants seeking the following:

[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).

[2] In this guidance, *supplement* refers to a request to FDA to approve a change in a biosimilar biological product application which has been approved, including a supplement requesting that FDA determine that the biosimilar biological product meets the standards for interchangeability. See section 744G(14) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The term *biosimilar biological product application* is defined in section 744G(4) of the FD&C Act, and applications under section 351(k) of the PHS Act discussed in this guidance are limited to those applications that meet the definition of biosimilar biological product application in section 744G(4).

[3] See the BsUFA III commitment letter titled "Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027" available on the FDA website at https://www.fda.gov/media/152279/download

[4] 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 biological product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and (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 (k)(4) of the PHS Act).

- To update Prescribing Information and, if applicable, FDA-approved patient labeling (e.g., Patient Package Insert, Medication Guide, Instructions for Use)[5] with safety information that has been updated in the reference product[6] labeling and is applicable to one or more indications for which the biosimilar or interchangeable biosimilar product is licensed

- To receive licensure for an additional indication

- To remove an approved indication

- To receive an initial determination of interchangeability

Supplements to approved 351(k) biologics license applications (BLAs) that do not meet the criteria under Categories A through F are outside the scope of this guidance and will not be addressed here.

When submitting supplements seeking to update labeling information, applicants should note that biosimilar and interchangeable biosimilar product labeling must meet the content and format requirements of the physician labeling rule[7] as described in 21 CFR 201.56(d) and 201.57.[8] Additionally, applicants should consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change. If, after consulting the relevant guidances, an applicant has additional questions, such as whether the supplement classification categories described in this guidance apply to a supplement, or what information should be submitted in a supplement to support a particular labeling change, the applicant can consult the appropriate FDA review staff for advice.

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.

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[5] Unless otherwise specified, the term *labeling* as used in this guidance refers only to the Prescribing Information as described in 21 CFR 201.56 and 201.57 and FDA-approved patient labeling (e.g., Patient Information, Medication Guide, and Instructions for Use).

[6] The term *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).

[7] See the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006). This rule is commonly referred to as the physician labeling rule because it addresses prescription drug labeling that is used by prescribing physicians and other health care providers.

[8] 21 CFR 201.56(c)(1). See the guidance for industry *Labeling for Biosimilar Products* (July 2018). 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.

II. BACKGROUND

Section 351(k) of the PHS Act provides an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference product (hereafter referred to as *351(k) BLA*). Several circumstances may lead the applicant of an approved 351(k) BLA to seek to amend its labeling. One circumstance could be when the holder of a licensed 351(k) BLA seeks to include safety labeling updates following revisions to the approved labeling of the reference product, where the revisions are applicable to one or more conditions of use for which the biosimilar or interchangeable biosimilar product is licensed. Another circumstance could be that following approval, an applicant may choose to remove from the Prescribing Information an indication for which the applicant sought and received licensure. Additionally, an applicant of an approved biosimilar or interchangeable biosimilar product may submit a supplement to seek licensure for an additional indication previously licensed for the reference product. This may occur, for example, when (1) the biosimilar or interchangeable biosimilar product was initially licensed for fewer than all of the reference product's licensed conditions of use[9] or (2) the reference product is licensed for a new condition of use after licensure of the biosimilar or interchangeable biosimilar product. Furthermore, after receiving licensure initially as only a biosimilar product, an applicant may submit a supplement to seek licensure as an interchangeable biosimilar.

In previous authorizations of BsUFA, FDA's review performance goals did not include commitments specifically related to various types of labeling changes. For BsUFA III, the commitment letter sets forth specific categories (categories A, B, C, D, E, and F) for supplements seeking to update biosimilar and interchangeable biosimilar product labeling, and FDA committed to specific review performance goals associated with those categories. FDA is committed to continuing to ensure effective scientific coordination and review consistency, as well as efficient governance and operations across the biosimilar product review program. These supplement categories will help to ensure consistent processes for reviewing these supplements across review divisions.

III. DISCUSSION

A. General Considerations

Generally, only one 351(k) BLA supplement classification category will be assigned to a submission. Applicants should submit separate supplements using the appropriate classification categories if multiple types of labeling changes are being requested that fall within different classification categories.

[9] 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).

FDA will confirm the appropriateness of the classification proposed by the applicant after receipt of the submission and will also assign the appropriate review timeline. If FDA disagrees with the applicant's proposed classification, additional information may be requested by FDA, and FDA intends to notify the applicant of the appropriate classification category.

FDA's goal is to issue a letter to the applicant for original Category A through D supplements within 60 calendar days of receipt. The letter will acknowledge receipt of the submission and provide the date for FDA to take action on the supplement. FDA's goal is to issue a filing letter to the applicant for original Category E and F supplements within 74 calendar days of receipt. Consistent with the underlying principles articulated in the Good Review Management Principles and Practices (GRMP) guidance, the letter will acknowledge receipt of the submission and inform the applicant of the planned review timeline and whether substantive review issues were identified. If no substantive review issues were identified during the filing review, FDA will so notify the applicant.

Applicants may refer to the Section I.A. of the BsUFA III commitment letter, which provides more information about these goals and sets forth the associated review performance goals for these supplement classification categories.[10]

If an applicant would like to propose further updates to its biosimilar or interchangeable biosimilar product labeling during the intervening period between the submission of a PAS and before action is taken by FDA, FDA generally recommends that the 351(k) applicant submit a new PAS proposing such additional changes instead of adding such changes to the pending PAS and note the appropriate classification category.

1. How to Submit

a. FDA form

When applicants submit a supplement for one of the categories described in this guidance, FDA recommends that applicants select *other* when completing Form FDA 356h, Application to Market a New or Abbreviated New Drug or Biologic for Human Use, and fill in *biosimilar supplement category [X]* in line 21 of the application information block. This will allow rapid identification and processing of the submitted supplements.

b. Cover letter considerations

Applicants should prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

[10] See the BsUFA III commitment letter titled "Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027" available on the FDA website at https://www.fda.gov/media/152279/download

NEW SUPPLEMENT FOR BLA ######
PRIOR APPROVAL SUPPLEMENT – BIOSIMILAR CATEGORY [X] or
RESUBMITTED SUPPLEMENT FOR BLA ######/S-XXX -
PRIOR APPROVAL SUPPLEMENT – BIOSIMILAR CATEGORY [X]

Applicants should clearly and briefly state the basis for the proposed supplement category in the supplement submission.

Applicants should be aware that FDA may review and act on (i.e., license or issue a complete response letter to) a supplement to a 351(k) BLA before any applicable BsUFA goal date. If an applicant does not want FDA to take action on a supplement to a 351(k) BLA before a specified date, the applicant should request that FDA refrain from acting on the supplement before the specified date, as long as that date falls on or before the applicable BsUFA goal date.[11] To request that FDA not take action on a supplement to a 351(k) BLA before a specified date, the applicant should include the following language prominently on the cover page of the supplement above the body of the cover letter using the bold typeface as shown below:

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

c. Labeling submission

The applicant is required to describe the proposed change(s) in the labeling and include the information necessary to support the proposed change(s).[12] , For recommendations regarding how to submit initial and revised labeling, please refer to the guidance for industry *Labeling for Biosimilar Products* (July 2018).[13]

2. Performance Goals

The following table summarizes the BsUFA III performance goals for review of 351(k) BLA supplement Categories A through F.[14]

[11] See also the timing considerations for submission of a 351(k) BLA or supplement to a 351(k) BLA in the draft guidance for industry *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed* (February 2020). When final, this guidance will represent the FDA's current thinking on this topic.

[12] 21 CFR 601.12(f)(1).

[13] See the guidance for industry *Labeling for Biosimilar Products* (July 2018). See also Q.I.27 in the draft guidance for industry, *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020); when final, this guidance will represent the FDA's current thinking on this topic.

[14] See the BsUFA III commitment letter titled "Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027" available on the FDA website at: https://www.fda.gov/media/152279/download.

Table 1: BsUFA III Performance Goals

Category	Category Description	Acknowledgement or Filing Letter Timeline	Action Timelines: Original Submission / Resubmission
A	Safety Information	Acknowledgement within 60 calendar days of receipt	3 months / 3 months
B	Additional Indication(s) Without New Data Sets		4 months / 4 months
C	Removal of Indication(s)		
D	Additional Indication(s) With New Data Sets or Without New Data Sets But Subject To Section 505B(a) of the FD&C Act and Does Not Contain An Up-To-Date Agreed iPSP		6 months / 6 months
E	Additional Indication(s) With Efficacy Data Sets	Filing letter within 74 calendar days of receipt	10 months / 6 months
F	Initial Determination of Interchangeability		

B. Classification Categories

1. Category A – Safety Information

Category A is for a 351(k) BLA supplement seeking to update the labeling for a licensed biosimilar or interchangeable biosimilar product with safety information that has been updated in the reference product labeling and is applicable to one or more indications for which the biosimilar or interchangeable biosimilar product is licensed. For purposes of this classification category, FDA considers safety information to have been updated in the reference product labeling after FDA has approved a supplement for the reference product's labeling change. Biosimilar and interchangeable biosimilar product labeling should incorporate relevant data and information from the reference product labeling, with appropriate modifications.[15] When new information becomes available that causes information in labeling to be inaccurate, false, or misleading, the application holder must take steps to change the content of its product labeling,

[15] See the guidance for industry *Labeling for Biosimilar Products* (July 2018). See also Q.I.27 in the draft guidance for industry, *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020); when final, this guidance will represent the FDA's current thinking on this topic.

in accordance with 21 CFR 601.12. [16] All holders of marketing applications for biological products have an ongoing obligation to ensure their labeling is accurate and up-to-date.[17]

FDA anticipates Category A supplements to be straightforward changes incorporating safety labeling updates approved for the reference product labeling that also apply to the biosimilar or interchangeable biosimilar product labeling. If additional changes beyond safety information are proposed to the biosimilar or interchangeable biosimilar product labeling, then Category A would not be considered the appropriate supplement category.

In the occasional circumstance where safety information (approved in the reference product labeling)[18] being updated in the biosimilar or interchangeable biosimilar product labeling includes related changes to container label(s) and carton labeling, FDA generally intends to review the revised container label(s) and carton labeling in the same Category A supplement.

2. Category B – Additional Indication(s) Without New Data Sets

Category B is for a 351(k) BLA supplement seeking licensure for an additional indication for a licensed biosimilar or interchangeable biosimilar product when the submission does not include new data sets (other than analytical in vitro data obtained by use of physical, chemical and/or biological function assays, if needed to support the scientific justification for extrapolation), provided that:

- The supplement does not seek a new route of administration, dosage form, dosage strength, formulation, or presentation; and

- The supplement contains an up-to-date agreed initial pediatric study plan (iPSP) if the supplement is subject to section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). For purposes of this commitment, FDA considers an up-to-date agreed iPSP to be an agreed iPSP that addresses Pediatric Research Equity Act (PREA) requirements for the additional indication proposed for licensure.[19]

For example, an applicant may have previously submitted data and information to support approval of a proposed biosimilar or interchangeable biosimilar product for one or more indications for which the reference product had unexpired orphan or pediatric exclusivity or was

[16] See e.g., 21 CFR 201.56(a)(2): "In accordance with . . . [21 CFR 601.12], the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."

[17] Id.

[18] For more information about safety information on container labels and carton labeling see the guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).

[19] FDA has issued final guidance about how a proposed biosimilar applicant can fulfill the requirement for pediatric assessments or investigations under PREA. See Q.I.16 in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021).

protected by a patent at the time of the submission. If the applicant subsequently submits a supplement seeking licensure for the previously protected indications after the applicable exclusivities or patent protections expire,[20] such supplement would be appropriately categorized as a Category B, subject to the limitations described in the two bullets above.

The inclusion in a 351(k) BLA supplement of scientific justifications to support the extrapolation of data and information in the application to support licensure for the indication(s) being added in the supplement, or where applicable, the inclusion of a cross-reference to a prior submission to the BLA where such scientific justification was previously included, would be consistent with classification of the supplement as Category B.

A supplement subject to PREA would be categorized as Category B only if it includes an up-to-date agreed iPSP. For purposes of this commitment, FDA generally considers a supplement to include an agreed iPSP if it cross references a prior submission to the application that includes such agreed iPSP. As noted, an agreed iPSP is considered "up-to-date" for purposes of this commitment if it addresses PREA requirements for the additional indication(s) proposed for licensure in the supplement.

- If the supplement would otherwise fall under Category B, but FDA has not confirmed agreement on the iPSP, the supplement should be submitted as a Category D supplement (see Category D below).

As a general reminder, as noted in the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020), a sponsor should not submit a marketing application or supplement that is subject to PREA until FDA confirms agreement on the iPSP.

3. Category C – Removal of Indication(s)

Category C is for 351(k) BLA supplements seeking to remove an approved indication for a licensed biosimilar or interchangeable biosimilar product.

The applicant seeking removal of a previously licensed indication must submit in a supplement information necessary to support the labeling change.[21]

Applicants are encouraged to include supporting labeling documentation in their supplement describing how removing indication(s) affects other sections of the labeling, and whether these sections need revisions, based on the proposed removal of indication(s), and how revisions to any related data have been approached.

[20] FDA has issued 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 orphan exclusivity. See Q.I.24 in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021).

[21] 21 CFR 601.12(f)(1).

4. Category D – Additional Indication(s) With New Data Sets or Without New Data Sets But Subject To Section 505B(a) of the FD&C Act and Does Not Contain An Up-To-Date Agreed iPSP

Category D is for 351(k) BLA supplements seeking licensure for an additional indication for a licensed biosimilar or interchangeable biosimilar product when the submission either:

- Contains new data sets *other than* 1) efficacy data, 2) data to support a supplement seeking an initial determination of interchangeability, or 3) only analytical in vitro data obtained by use of physical, chemical, and/or biological function assays. Examples of datasets consistent with this supplement type include those from studies supporting a new presentation associated with an added indication, such as a comparative human factors study or comparative PK studies.

Or,

- Does not contain new data sets with the exception of analytical in vitro data obtained by use of physical, chemical, and/or biological function assays but is subject to section 505B(a) of the FD&C Act, and the supplement does not contain an up-to-date agreed iPSP that addresses PREA requirements for the additional indication(s) proposed for licensure.

A supplement to an approved 351(k) BLA that triggers PREA would not be eligible for Category B but may be eligible for Category D if the applicant does not have an up-to-date agreed iPSP addressing the additional indication(s) being sought. One such Category D scenario is as follows: If an applicant submits a supplement before FDA has confirmed agreement on the iPSP, then the supplement would not be eligible for Category B but could be eligible for Category D, regardless of whether the applicant submits a pediatric assessment in the supplement.

5. Category E – Additional Indication(s) With Efficacy Data Sets

Category E is for 351(k) BLA supplements for a licensed biosimilar or interchangeable biosimilar product seeking licensure for an additional indication that has been previously approved for the reference product and where the submission contains efficacy data sets. A Category E supplement may be appropriate in the unlikely scenario where, subsequent to an initial 351(k) BLA approval, an additional indication is being sought which was approved for the reference product after the initial 351(k) BLA approval and uses a novel mechanism of action, for which a comparative clinical study is necessary. Given that, in general, the mechanism(s) of action of a product are known and the discovery of novel mechanism(s) of action unlikely, FDA expects these supplements to be exceedingly rare.

Applicants are strongly encouraged to discuss any planned Category E submissions with FDA in an appropriate Biosimilar Biological Product Development (BPD) meeting before submission of the supplement.[22]

[22] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (Rev 1)* (August 2023). When final, this guidance will represent the FDA's current thinking on this topic.

6. Category F – Interchangeability

Category F is for 351(k) BLA supplements seeking an initial determination of interchangeability.

For a product first licensed as a biosimilar to the reference product, the applicant may later seek licensure of the biosimilar product as an interchangeable biosimilar product in a supplement.[23]

Category F supplements may include, for example, a clinical study report for a switching study or a scientific justification for not needing such data as part of the demonstration of interchangeability in the submission.

[23] See the guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019). See also the draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020), which when final, will represent the FDA's current thinking on this topic.