Postapproval Manufacturing Changes to Biosimilar and Interchangeable Biosimilar Products Questions and Answers Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Nidhi Pamidimukkala 301-796-3397 or Nidhi.Pamidimukkala@fda.hhs.gov, 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)

July 2024
Biosimilars

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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
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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.

I. INTRODUCTION

This guidance provides answers to commonly asked questions from applicants and other interested parties (collectively referred to as applicants throughout this guidance) regarding postapproval manufacturing changes (referred to as manufacturing changes throughout this guidance) made to licensed *biosimilars* and licensed *interchangeable biosimilars*.[2] This question-and-answer (Q&A) guidance is intended to inform prospective and current applicants of the nature and type of information that applicants should provide in support of manufacturing changes to licensed biosimilars and licensed interchangeable biosimilars in different reporting categories.

Under § 601.12 (21 CFR 601.12), applicants must inform FDA about each change in the product, production process, quality controls, equipment, facilities, or responsible personnel, established in the approved biologics license application (BLA). Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product (i.e., *product*

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in consultation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] In this guidance, the following terms are used to describe biological products licensed under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)): (1) *biosimilar* or *biosimilar product* refers to a product that FDA has determined to be biosimilar to an FDA-licensed biological reference product (see section 351(i)(2) (42 U.S.C. 262(i)(2)) and (k)(2) of the PHS Act); and (2) *interchangeable biosimilar*, *interchangeable biosimilar product*, 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).

quality) as these factors may relate to the safety or effectiveness of the product.[3,4] In addition, applicants are required to inform FDA about each change in the labeling established in the approved BLA.[5]

This guidance applies to manufacturing changes made to products licensed under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)) determined to be biosimilar to or interchangeable with an FDA-licensed biological reference product.[6]

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. Section 351 of the PHS Act

Section 351 of the PHS Act provides an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product. Section 351(k) of the PHS Act sets forth the requirements for licensure of such biosimilar products and interchangeable biosimilar products.

Section 351(i)(2) 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." To meet the standard for interchangeability, the applicant must: (1) demonstrate biosimilarity to the reference product; (2) demonstrate that the biological product "can be expected to produce the same clinical result as the reference product in any given patient"; and (3) 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."[7] Interchangeable products may be substituted for the reference product at

[3] See § 601.12(a) through (d). In this guidance, *product quality* refers to the identity, strength, quality, purity, and potency of a product as these factors may relate to the safety or effectiveness of the product.

[4] Manufacturers of biosimilars and interchangeable biosimilars must also comply with other statutory and regulatory requirements, including the current good manufacturing practice requirements described in section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and regulations in 21 CFR parts 4, 210, 211, 600 through 680, and 820, as applicable to the specific product.

[5] See § 601.12(a) and (f).

[6] 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 section 351(k)(4) of the PHS Act.

the pharmacy level without the intervention of the prescribing health care provider, subject to State law.[8]

B. Q&A Guidance Format

FDA has been using the Q&A guidance format to describe FDA's thinking and to update certain information and recommendations relevant to the development of biosimilar and interchangeable biosimilar products. This guidance discusses recommendations regarding manufacturing changes to licensed biosimilar and licensed interchangeable biosimilar products.[9]

FDA is publishing this guidance to fulfill the commitment made as part of the negotiations relating to reauthorization of the Biosimilar User Fee Act (BsUFA).[10] FDA is committed to a focused effort to further advance the development of safe and effective biosimilar and interchangeable biosimilar products through the development of foundational guidances for these products.[11]

III. QUESTIONS AND ANSWERS

Q1. What is the nature and type of information, for different reporting categories, that FDA recommends to support postapproval manufacturing changes to licensed biosimilar and licensed interchangeable biosimilar products?

A. Recommendations for Reporting Categories

Similar to manufacturing changes to biological products licensed under section 351(a) of the PHS Act, applicants must report manufacturing changes to a biosimilar or an interchangeable biosimilar licensed under section 351(k) of the PHS Act according to the requirements in § 601.12. Applicants must evaluate the potential impact of the proposed changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety and effectiveness of a licensed biosimilar or a licensed interchangeable biosimilar and report

[8] See section 351(i)(3) of the PHS Act.

[9] Postapproval manufacturing changes to biosimilars is the subject of Q&A I.20 in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021). FDA intends to withdraw Q&A I.20 from that guidance when this guidance becomes final. 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.

[10] The Biosimilar User Fee Act of 2012 (BsUFA I) added sections 744G and 744H to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379j–51 and 379j–52), authorizing FDA to collect user fees for a 5-year period from persons who develop biosimilar and interchangeable biosimilar products. BsUFA was reauthorized for a 5-year period for a third time on September 30, 2022 (Biosimilar User Fee Amendments of 2022 (BsUFA III)), Title IV–Fees Relating to Biosimilar Biological Products, Public Law 112-144) for fiscal years 2023 through 2027.

[11] See Section II.D.2.d. of Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027 (BsUFA III commitment letter) available at https://www.fda.gov/media/152279/download.

manufacturing changes to FDA using the appropriate reporting category, as described in § 601.12.[12]

For recommendations regarding postapproval reporting categories for commonly reported manufacturing changes for specified biological products[13] (a category that includes currently licensed biosimilar or interchangeable biosimilar products), applicants should refer to the guidances for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997) and *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (December 2021). Applicants can also refer to the International Council for Harmonisation (ICH) guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021)[14] for a framework to facilitate the management of postapproval manufacturing changes for drug substances and drug products, including biological products. Additionally, as applicable, applicants can consider the recommendations in the guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021).[15]

As described in § 601.12, the reporting categories for manufacturing changes to an approved application are provided below:

- **Prior Approval Supplement (PAS):** An applicant must submit a PAS for major changes and must obtain approval of the PAS from FDA before distribution of the product manufactured using the change(s).[16] A major change is one that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Applicants can submit a comparability protocol in a PAS to propose specified types of postapproval chemistry, manufacturing, and controls (CMC) change(s), which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.[17]

[12] See § 601.12(a)(1), (2), and (b) through (e).

[13] Specified biological products are biological products, as defined in 21 CFR 600.3(h), that fall under one of the categories specified in § 601.2(a) (21 CFR 601.2(a)).

[14] See also the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[15] Products licensed under a 351(k) application (i.e., licensed biosimilars and licensed interchangeable biosimilars) are outside the scope of the guidance for industry *Chemistry, Manufacturing and Controls Changes to an Approved Application: Certain Biological Products* (June 2021). However, the scientific principles regarding reporting categories and recommendations described in that guidance might also help inform which reporting categories are appropriate for manufacturing changes to licensed biosimilars and licensed interchangeable biosimilars.

[16] See § 601.12(b).

[17] See § 601.12(e). In this guidance, *comparability protocol* is synonymous with postapproval change management protocol in the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021). For recommendations pertaining to the submission of comparability protocols for postapproval CMC changes, see the guidance for industry *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA* (October 2022).

- **Changes Being Effected in 30 Days (CBE-30)/Changes Being Effected (CBE-0) Supplements:** An applicant must request approval for moderate changes that require a CBE-30 supplement to FDA, and the supplement must be received by FDA at least 30 days before distribution of the product made using the change.[18] A moderate change is one that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. If FDA informs the applicant within 30 days after receipt of the supplement that the change requires approval prior to distribution or any of the information required to be included in the supplement is missing, the applicant must not distribute the product made using the change until FDA determines that compliance with § 601.12 is achieved.[19] In certain circumstances, FDA may determine that, based on FDA's experience with a particular type of change, the supplement for such a change is usually complete and provides the proper information, and there are particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved comparability protocol. In these circumstances, FDA may determine that the product made using the change may be distributed at the time of receipt of the supplement (CBE-0 supplement) by FDA.[20,21]

- **Annual Report:** An applicant must document minor changes in an annual report.[22] A minor change is one that has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

When reporting a manufacturing change to a licensed biosimilar or a licensed interchangeable biosimilar to FDA, the applicant should clearly identify the reporting category under which the change is being reported. If the manufacturing change requires a supplement submission (i.e., PAS, CBE-30, or CBE-0), the applicant should specify the supplement as a CMC supplement and identify the reporting category in the submission. Additionally, the cover letter must include a complete list of all the changes contained in the supplement.[23] For manufacturing changes that

[18] See § 601.12(c).

[19] See § 601.12(c)(4).

[20] See § 601.12(c)(5). Changes that, in FDA's experience, have been submitted properly with the appropriate information and could be implemented under § 601.12(c)(5) at the time of receipt of the supplement by FDA without a previously approved comparability protocol are described in the guidances for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997) and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021), as applicable.

[21] Where the applicant has an approved comparability protocol under § 601.12(e) for the use of a CBE-0 supplement and presents evidence in the CBE-0 supplement that the change has been validated in accordance with the approved protocol, the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

[22] See § 601.12(d).

[23] See § 601.12(a)(5).

impact labeling, the applicant should include the corresponding labeling changes with the CMC supplement.[24]

B. Recommendations for Product Quality Data

An applicant who intends to make a manufacturing change to a licensed biosimilar or a licensed interchangeable biosimilar should follow the principles outlined in the ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005). When changes are made to the manufacturing process, the applicant should evaluate the comparability of the biosimilar or interchangeable biosimilar product before and after the manufacturing change (*comparability exercise*). The extent of data and information necessary to establish comparability should be commensurate with the type of manufacturing change and its overall potential to adversely affect the quality, safety, and efficacy of the product. The design of the comparability exercise, including the *quality attributes*[25] to be compared and analytical methods to be used, should address the risks of the manufacturing change(s) and should provide sufficient data and information to demonstrate the comparability of the biosimilar or interchangeable biosimilar product premanufacturing and postmanufacturing change. In addition to comparability data, other product quality data and information, such as process validation data, should be included in the supplement, as applicable.[26]

Data and information submitted in support of manufacturing changes should demonstrate that quality attributes remain comparable among prechange and postchange products and should demonstrate that consistency in the quality, safety, and efficacy of the postchange product is predictable. The postchange biosimilar or interchangeable biosimilar product should be evaluated at the process step most appropriate to detect a change in the quality attributes. This may entail evaluating the product at multiple stages of manufacture. For instance, in some cases, it might be appropriate to compare prechange and postchange data on intermediates most affected by the manufacturing change in addition to the drug substance and the drug product to support the determination of comparability.

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[24] See § 601.12(a) and (f) for the requirements pertaining to reporting labeling changes to FDA. If applicants have questions about the reporting classification recommendations for submissions that include both manufacturing and labeling changes, FDA advises applicants to consult with the appropriate FDA review division. For recommendations on labeling for biosimilars and interchangeable biosimilars, see the draft guidance for industry *Labeling for Biosimilar and Interchangeable Biosimilar Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic. For recommendations on classification categories A through F for certain supplement submissions, as established in BsUFA III, see the draft guidance for industry *Classification Categories for Certain Supplements Under BsUFA III* (August 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[25] The ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005) defines *quality attribute* as "[a] molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency, and stability of the product, and safety with respect to adventitious agents. . . ." (See page 13 of ICH Q5E.)

[26] For general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of drugs, including biological products, see the guidance for industry *Process Validation: General Principles and Practices* (January 2011).

The goal of the comparability exercise is to ensure that manufacturing process changes do not lead to an adverse impact on the quality, safety, and efficacy of the licensed biosimilar or the licensed interchangeable biosimilar. The comparability exercise should include a side-by-side analytical comparison of a sufficient number of lots of prechange and postchange material, including stability data, as appropriate. As described in ICH Q5E, for certain manufacturing process changes, even slight modifications of the production and procedures might cause changes in the stability of the postchange product, and appropriate studies should be considered to confirm that suitable storage conditions and controls are selected. Comparative stability studies conducted under relevant storage conditions (e.g., accelerated testing, stress testing) among prechange and postchange materials can detect subtle differences that may not be readily detectable by characterization studies and may, therefore, provide greater insight into differences between the prechange and the postchange product. These comparative stability studies are especially important when the proposed manufacturing changes can alter protein structure or purity and impurity profiles.[27] The selection of the conditions for the stability studies should be justified based on relevance to the product and risks associated with the manufacturing change. A comparison of analytical data from the postchange material to the historical analytical data (i.e., prechange material) may be sufficient to support a manufacturing change if the quality attributes of the prechange and the postchange material are comparable. The historical analytical data should include results from biosimilar or interchangeable biosimilar lots used in the comparative analytical assessment (CAA),[28] biosimilar or interchangeable biosimilar lots used in the clinical development of the biosimilar or the interchangeable biosimilar, lots used to support process consistency, and commercial materials manufactured after approval, as applicable. When a subset of all available historical data is selected for the comparison, a scientific justification should be provided. If an analytical assay has changed since licensure of the biosimilar or the interchangeable biosimilar, adequate assay bridging data on assay performance should be provided.

Q2. What reference materials should applicants include in the comparability exercise?

In general, an applicant should include a well-qualified, in-house reference material in the comparability exercise to evaluate whether a postchange biosimilar or interchangeable biosimilar remains comparable to the prechange product. The in-house reference material serves as an important calibration point for the evaluation(s) conducted in a comparability exercise.[29]

If applicants submit sufficient data to enable an informed prediction that no adverse impact on the quality, safety, or efficacy of the postchange product is expected, FDA may consider the data

[27] See page 8 of ICH Q5E. For further information, see the guidances for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996) and *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

[28] For recommendations on the design and evaluation of comparative analytical studies, see the draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[29] In this guidance, *in-house reference material* refers to the appropriately characterized material prepared in-house by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots. For further information on in-house reference materials, see the ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

adequate to support the change without the inclusion of reference materials beyond the in-house reference material in the comparability exercise. However, demonstration of comparability to support manufacturing change(s) should provide adequate assurance that a postchange product remains biosimilar to or interchangeable with the reference product. When differences in the quality attributes are observed between the prechange and the postchange material, comparison to the data from the reference product submitted to support licensure should be considered to help assess the potential impact and acceptability of these differences.

Q3. How should proposals to introduce a licensed biosimilar and/or licensed interchangeable biosimilar product into a multiproduct manufacturing area or a multiproduct contract manufacturing facility be reported?

An applicant proposing to introduce its licensed biosimilar or licensed interchangeable biosimilar into a multiproduct manufacturing area or a multiproduct contract manufacturing facility[30] should refer to the guidances for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997), *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (December 2021), and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021), as applicable, for recommendations on the appropriate postapproval reporting category to report such changes. The reporting category should be determined based on risks associated with product introduction(s) to the quality attributes of the licensed biosimilar or the licensed interchangeable biosimilar.

Risks associated with introducing a licensed biosimilar or a licensed interchangeable biosimilar into a multiproduct manufacturing area or a multiproduct contract manufacturing facility depend on the type of product being introduced and the potential addition of further control measures to ensure that the product meets its intended quality characteristics, including purity. Identity testing is one tool used to detect and control such risks.[31]

The introduction of a licensed biosimilar or a licensed interchangeable biosimilar into a multiproduct manufacturing area or a multiproduct contract manufacturing facility — where the reference product is manufactured and/or another applicant's biosimilar or interchangeable biosimilar product(s) referencing the same reference product is manufactured — poses risks such as cross-contamination or product mix-ups. In these cases, a respective single identity test for each product might not always be able to distinguish the different products. Therefore, in

[30] As recognized in 21 CFR 200.10(b) and § 211.22(a) (21 CFR 211.22(a)), FDA is aware that some drug manufacturing activities may be performed at contract facilities. When a drug manufacturer uses a contract facility, the drug manufacturer's quality control unit is responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company (§ 211.22(a)). Additionally, FDA's biological product regulations define manufacturer in 21 CFR 600.3(t) to include an applicant for a licensed product where the applicant assumes responsibility for compliance with the applicable product and facility standards. See 21 CFR 210.3(b)(15) for the definition of quality control unit, § 211.22 for the requirements and responsibilities of the quality control unit, and 21 CFR 600.10 through 600.15 for establishment standards for biological product facilities. For further information, see also the guidances for industry *Cooperative Manufacturing Arrangements for Licensed Biologics* (November 2008) and *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016).

[31] See § 610.14 (21 CFR 610.14).

addition to identity tests for each product, current good manufacturing practice requirements, including applicable manufacturing and procedural controls (e.g., separate manufacturing areas, control of personnel, process, and material flow, and control of materials, as applicable) to prevent cross-contamination or mix-ups, must be followed.[32] Such manufacturing and procedural controls should be described in sufficient detail to enable FDA to evaluate whether the proposed controls are adequate to address such risks.

Q4. What is the nature and type of CMC information that FDA recommends to support the approval of a supplement for a dosage form or a strength that has not previously been licensed under the 351(k) BLA?

When submitting a supplement to a BLA submitted under section 351(k) of the PHS Act (a *351(k) BLA*) that proposes a new dosage form or a new strength (i.e., a dosage form or strength not previously licensed in the 351(k) BLA), applicants must include information demonstrating, among other things, that the dosage form and the strength of the proposed biosimilar or the proposed interchangeable biosimilar product "are the same as those of the reference product."[33,34] In addition, to support approval of a supplement to a 351(k) BLA proposing a new dosage form or a new strength, the supplement must include information demonstrating that the proposed biosimilar or the proposed interchangeable biosimilar is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and "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."[35] Further, to support approval of a supplement for a new dosage form or a new strength as an interchangeable biosimilar product, information submitted in the supplement needs to be sufficient to show that the proposed product meets the interchangeability standards described in section 351(k)(4) of the PHS Act.[36] The proposal of a new dosage form or a new strength that has not previously been licensed under the 351(k) BLA is generally considered a major change; therefore, the appropriate reporting category for these changes would generally be a PAS.

A supplement proposing a new dosage form or a new strength generally should include the following CMC-related information: (1) adequate comparability data between a licensed biosimilar or interchangeable biosimilar (i.e., prechange product) and the proposed biosimilar or interchangeable biosimilar with the new dosage form or strength (i.e., postchange product), (2) CAA data, and (3) manufacturing data (e.g., process validation) to support the proposed postchange product. The extent of the comparability data and the CAA data should be justified based on a risk assessment of the differences between the prechange product and the postchange product. In some cases, additional data (such as pharmacokinetic studies) should be submitted to

[32] See, e.g., 21 CFR 211.42, 211.80, 211.100 and §§ 601.2(d) and 610.14.

[33] See section 351(k)(2)(A)(i)(IV) of the PHS Act.

[34] As noted in Q&A I.21 of the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act*, "an applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, for a route of administration, a dosage form, or a strength that is different from that of the reference product."

[35] See section 351(k)(3) and (i)(2) of the PHS Act.

[36] See section 351(k)(3) and (i)(3) of the PHS Act.

support approval of the supplement for the proposed dosage form or strength.[37] It may be considered reasonable for the design of the CAA studies used to support the proposed dosage form or strength to leverage the CAA data previously submitted in the 351(k), without additional CAA studies comparing the proposed new dosage form or strength to its reference product. However, applicants should assess whether additional CAA studies with the new dosage form or the new strength are appropriate to address the potential impact of the differences in the dosage form or strength on product quality. Applicants should also consider how the proposed product would be used (e.g., whether the dosage form or strength is indication- and/or population-specific for the reference product).

Consider the following illustrative examples to help applicants determine when leveraging the CAA data previously submitted in the 351(k) BLA may be appropriate. The provided examples presume that the same drug substance is used to manufacture the prechange and postchange products.

- The applicant submits a supplement proposing a new strength that has the same route of administration, dosage form, and excipients, and the same patient population and indication as a biosimilar or an interchangeable biosimilar product licensed under the 351(k) BLA. In this case, leveraging the CAA previously submitted in the 351(k) BLA along with a risk-based comparability exercise between the prechange strength(s) and the proposed postchange strength may be reasonable.

- The applicant submits a supplement proposing a new dosage form and a new strength intended for a different patient population or indication than the biosimilar or interchangeable biosimilar product(s) licensed under the 351(k) BLA. In this case, although the CAA data previously submitted in the 351(k) BLA may be leveraged, the applicant should also include a risk-based targeted CAA between the proposed product with the new dosage form and strength and its reference product and include a risk-based comparability exercise between the prechange and postchange products.

In both cases, in addition to the comparability exercise and potentially new CAA data, the applicant should include all relevant manufacturing information for the proposed strength or dosage form in the supplement, including process validation data. As with other changes requiring CMC data, the extent of product quality data and information that should be submitted would be dependent on the proposed change.

Various additional scenarios are possible, and the data and information appropriate to support each unique scenario may be different. FDA recommends that applicants discuss[38] with the appropriate FDA review division the adequacy of the analytical and manufacturing data that should be provided to support approval of a supplement for a dosage form or a strength that has not previously been licensed under the 351(k) BLA before submitting the supplement.

[37] This guidance does not address the circumstances under which such additional data should be submitted or provide recommendations on the nature and type of information (other than CMC information) that should be submitted in those circumstances.

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