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

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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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
A.	Section 351 of the PHS Act.....	2
B.	Q&A Guidance Format.....	3
III.	QUESTIONS AND ANSWERS.....	3
A.	Recommendations for Reporting Categories	3
B.	Recommendations for Product Quality Data	6

Postapproval Manufacturing Changes to Biosimilar and Interchangeable Biosimilar Products Questions and Answers Guidance for Industry¹

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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. The recommendations in this guidance are intended to be consistent with the principles outlined in the International Council for Harmonisation (ICH) guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005) (ICH Q5E).³

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

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 sections 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 sections 351(i)(3) and (k)(4) of the PHS Act).

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>.

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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 quality*) as these factors may relate to the safety or effectiveness of the product.^{4,5} In addition, applicants are required to inform FDA about each change in the labeling established in the approved BLA.⁶

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*.⁷

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

⁴ 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.

⁵ 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 (FD&C 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.

⁶ See § 601.12(a) and (f).

⁷ *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).

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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.”⁸ Interchangeable products may be substituted for the reference product at the pharmacy level without the intervention of the prescribing health care provider, subject to State law.⁹

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.¹⁰

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).¹¹ 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.¹²

1 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 products 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 product or an

⁸ See section 351(k)(4) of the PHS Act.

⁹ See section 351(i)(3) of the PHS Act.

¹⁰ The finalization of this guidance reflects FDA’s current thinking on the topic of postapproval manufacturing changes to biosimilar and interchangeable biosimilar products and supersedes the recommendations provided in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021) at Q&A I.20, which also discusses the topic. FDA intends to withdraw Q&A I.20 from that guidance.

¹¹ The Biosimilar User Fee Act of 2012 (BsUFA I) added sections 744G and 744H to the FD&C 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 117-180) for fiscal years 2023 through 2027.

¹² See the BsUFA III commitment letter titled “Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027” at section II.D.2.d., available at <https://www.fda.gov/media/152279/download>.

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interchangeable biosimilar product 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 product or a licensed interchangeable biosimilar product and report manufacturing changes to FDA using the appropriate reporting category, as described in § 601.12.¹³

For recommendations regarding postapproval reporting categories for commonly reported manufacturing changes for specified biological products (a category that includes currently licensed biosimilar or interchangeable biosimilar products),¹⁴ 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 ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) for a framework to facilitate the management of postapproval manufacturing changes for drug and biological products, including drug substances and drug products.¹⁵ 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).¹⁶

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).¹⁷ 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

¹³ See § 601.12(a)(1), (2), and (b) through (e).

¹⁴ Specified biological products are biological products, as defined in § 600.3(h) (21 CFR 600.3(h)), that fall under one of the categories specified in § 601.2(a) (21 CFR 601.2(a)).

¹⁵ See also the ICH draft guidance for industry *Q12: Implementation Considerations for FDA-Regulated Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic.

¹⁶ 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*. 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.

¹⁷ See § 601.12(b).

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use of the protocol for that type of change reduces the potential risk of an adverse effect.¹⁸

- **Changes Being Effectuated in 30 Days (CBE-30)/Changes Being Effectuated (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.¹⁹ 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 that any of the information required under § 601.12(c)(3) is missing in the supplement, the applicant must not distribute the product made using the change until FDA determines that compliance with § 601.12 is achieved.²⁰ 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.^{21,22}
- **Annual Report:** An applicant must document minor changes in an annual report.²³ A minor change is one that has a minimal potential to have an adverse effect on the identity,

¹⁸ See § 601.12(e). Applicants can also submit a comparability protocol in an original 351(k) BLA. In this guidance, *comparability protocol* is synonymous with the postapproval change management protocol in the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*. 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).

¹⁹ See § 601.12(c).

²⁰ See § 601.12(c)(4).

²¹ 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* and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products*, as applicable.

²² 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.

²³ See § 601.12(d).

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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 product or a licensed interchangeable biosimilar product 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.²⁴ For manufacturing changes that impact labeling, the applicant should include the corresponding labeling changes with the CMC supplement.²⁵

B. Recommendations for Product Quality Data

An applicant who intends to make a manufacturing change to a licensed biosimilar product or a licensed interchangeable biosimilar product should follow the principles outlined in ICH Q5E. 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*²⁶ 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 before and after the manufacturing 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.²⁷

Data and information submitted in support of manufacturing changes should demonstrate that quality attributes remain comparable among the 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 comparisons at multiple stages of manufacture. For instance, if the change occurred

²⁴ See § 601.12(a)(5).

²⁵ 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.

²⁶ ICH Q5E 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 ICH Q5E at 13).

²⁷ 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).

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in the manufacture of the drug substance and the change could impact the drug product quality attributes, it may be appropriate to evaluate intermediates, the drug substance, and the drug product to support the determination of comparability.

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 product or the licensed interchangeable biosimilar product. The comparability exercise should include a side-by-side analytical comparison of a sufficient number of lots of prechange and postchange materials,²⁸ including stability data, as appropriate. As described in ICH Q5E, for certain manufacturing process changes, even slight modifications of the production 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.²⁹ 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 generated on the postchange material to the historical analytical data (i.e., data generated on the prechange material) may be sufficient to support a manufacturing change if the quality attributes of the prechange and the postchange materials are comparable. The historical analytical data should include results from biosimilar or interchangeable biosimilar lots used in the comparative analytical assessment (CAA),³⁰ biosimilar or interchangeable biosimilar lots used in the clinical development of the biosimilar or the interchangeable biosimilar product, 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 product, adequate assay bridging data on assay performance should be provided.

²⁸ For the purposes of this guidance, *prechange material(s)* and *postchange material(s)* can refer to intermediates, drug substance, and/or drug product, as applicable.

²⁹ See ICH Q5E at 8. For further information, see the ICH 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).

³⁰ For recommendations on the design and evaluation of comparative analytical studies, see the guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (September 2025).

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

In general, in addition to the prechange and postchange product, an applicant should include a well-qualified, in-house reference material in the comparability exercise to support that the 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.³¹

If applicants submit sufficient data to demonstrate comparability, supporting that the manufacturing change(s) will have no adverse impact on the quality, safety or efficacy, including immunogenicity, of the postchange product, FDA will generally consider the data adequate to support the change without the inclusion of reference materials beyond the in-house reference material in the comparability exercise. When differences in the quality attributes are observed between the prechange and the postchange materials that may preclude a demonstration of comparability based solely on the comparison of the prechange and postchange materials, one approach to assessing the potential impact and acceptability of these differences would be to use the CAA data from the reference product that were submitted to support the original licensure of the biosimilar or interchangeable biosimilar product to inform a justification for the comparability of the postchange product.

Q3. How should proposals to introduce a licensed biosimilar product and/or a 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 facility³² should refer to the guidances for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*; *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports*; and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain*

³¹ 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).

³² As recognized in § 200.10(b) (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).

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Biological Products, 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.³³

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 distinguish the different products. Therefore, in addition to identity tests for each product, current good manufacturing practice requirements must be followed, 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.³⁴ 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., dosage form or strength not previously licensed in the 351(k) BLA),³⁵ applicants must include information demonstrating, among other things, that the dosage form and the strength of the proposed biosimilar product or the proposed interchangeable biosimilar product “are the same as those of the reference product.”³⁶ 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

³³ See § 610.14 (21 CFR 610.14).

³⁴ See, for example, 21 CFR 211.42, 211.80, 211.100, and §§ 601.2(d) and 610.14.

³⁵ This guidance does not cover route of administration changes, as such changes might raise additional considerations.

³⁶ See section 351(k)(2)(A)(i)(IV) of the PHS Act.

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clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”³⁷ 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.³⁸ 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 generally would 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 the licensed biosimilar product or interchangeable biosimilar product (i.e., “prechange product” or “licensed product”) and the proposed biosimilar product or interchangeable biosimilar product with the new dosage form or strength (i.e., “postchange product” or “proposed product”); (2) manufacturing data (e.g., process validation) to support the proposed product; and (3) CAA data. In some cases, additional data (such as pharmacokinetic studies) may be needed to support approval of the supplement for the proposed dosage form or strength.³⁹

The extent of comparability data and CAA data provided in the supplement should be commensurate with the level of risk associated with the proposed change. Applicants should include a risk assessment of the differences between the licensed product and the proposed product with a new dosage form or new strength to support the justification of the comparability and CAA data provided in the supplement. Based on the differences observed between the licensed product and the proposed product, and the associated risk assessment, targeted CAA data may be needed; however, in some cases, it may be reasonable to leverage the CAA data previously submitted in the 351(k) BLA, potentially without additional, risk-based, targeted CAA studies comparing the proposed product to its reference product. For example, if an applicant submits a supplement proposing a new strength or dosage form, and the same drug substance is used to manufacture the licensed product and the proposed product, leveraging the CAA previously submitted in the 351(k) BLA along with a risk-based comparability exercise between the licensed product and the proposed product may be reasonable. If differences in quality attributes are observed between the licensed product and the proposed product, an additional, risk-based, targeted CAA should be submitted in the supplement to support a demonstration that the proposed product is highly similar to its reference product. Applicants should justify how these targeted CAA data address any product quality differences observed between the licensed product and the proposed product.

³⁷ See section 351(k)(3) and (i)(2) of the PHS Act.

³⁸ See section 351(k)(3) and (i)(3) of the PHS Act.

³⁹ 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.

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In addition to the comparability data and 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 supplements requiring CMC data, the extent of product quality data and information that should be submitted is dependent on the nature of the proposed change. FDA recommends that applicants discuss with the appropriate FDA review division the type of analytical and manufacturing data that should be provided to support approval of a supplement for a new dosage form or a new strength before submitting the supplement.⁴⁰

⁴⁰ See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (July 2025).