Labeling for Biosimilar and Interchangeable Biosimilar Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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)

September 2023
Labeling
Revision 1

Labeling for Biosimilar and Interchangeable Biosimilar Products

Guidance for Industry

Additional copies are available from:

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
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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)

September 2023
Labeling
Revision 1

TABLE OF CONTENTS

Labeling for Biosimilar and Interchangeable Biosimilar Products 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 is intended to help applicants develop draft labeling for proposed biosimilar and interchangeable biosimilar products[2] for submission in an application under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)) (351(k) application). The recommendations for biosimilar and interchangeable biosimilar product labeling[3] in this guidance pertain only to the Prescribing Information, except for certain recommendations in section V, FDA-Approved Patient Labeling of Biosimilar and Interchangeable Biosimilar Products, pertaining to FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).[4]

When finalized, this guidance will revise and replace the guidance for industry *Labeling for Biosimilar Products* (July 2018). Significant changes from the July 2018 guidance include recommendations on the following topics:

- Labeling for interchangeable biosimilar products
- Product identification when the reference product labeling describes a clinical study conducted with a non-U.S.-approved biological product

[1] This guidance has been prepared by the Office of New Drugs, Office of Therapeutic Biologics and Biosimilars, in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] In this guidance, *interchangeable biosimilar 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 Public Health Service Act).

[3] For clarity, the recommendations in this guidance generally apply to all biosimilar and interchangeable biosimilar products that are subject to the requirements in 21 CFR 201.56(d) and 201.57.

[4] Unless otherwise specified, the term *labeling* as used in this guidance addresses only the Prescribing Information as described in 21 CFR 201.56 and 201.57.

- Pediatric use statements

- Incorporating relevant immunogenicity data and information from the reference product labeling in the biosimilar or interchangeable biosimilar product labeling

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

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.[5] Section 351(k) of the PHS Act sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable biosimilar product.

Section 351(i) of the PHS Act defines *biosimilarity* to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

To meet the standard for *interchangeability*, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[6] Interchangeable biosimilar products may be substituted for the reference product without the intervention of the prescribing health care provider.[7]

An application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from the following:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;

[5] *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).

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

[7] See section 351(i)(3) of the PHS Act. Information about whether a biosimilar product is licensed as an interchangeable biosimilar product can be found at https://purplebooksearch.fda.gov.

- An assessment of toxicity (which may rely on, or consist of, a study or studies described in section 351(k)(2)(A)(i)(I)(aa) or (cc)); and

- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

Under the PHS Act, FDA has the discretion to determine that an element described above is unnecessary in a 351(k) application.

Under FDA regulations, prescription drug and biological product labeling must provide adequate information to enable health care providers to "use the drug safely and for the purposes for which it is intended;"[8] to this end, approved Prescribing Information summarizes the essential scientific information needed by health care providers for the safe and effective use of a drug or biological product.[9] Prescription drug and biological product labeling reflects FDA's finding of safety and effectiveness[10,11] for the drug or biological product under the labeled conditions of use and facilitates prescribing decisions, thereby enabling the safe and effective use of drugs and biological products and reducing the likelihood of medication errors.[12]

[8] See 21 CFR 201.100.

[9] See 21 CFR 201.56(a)(1).

[10] The standard for licensure of a biological product as potent under section 351(a) of the PHS Act has long been interpreted to include effectiveness. See 21 CFR 600.3(s) and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). See also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), which, when final, will represent the FDA's current thinking on this topic. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] In this guidance, the terms *safety and effectiveness* and *safety, purity, and potency* are used synonymously in the discussions pertaining to biosimilar and interchangeable biosimilar products.

[12] Section 351(k)(2)(A)(iii) of the PHS Act requires that a biosimilar or interchangeable biosimilar product application include "publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent." FDA has stated that *publicly-available information* in this context generally includes the current FDA-approved labeling for the reference product and the types of information found in the *action package* for a biologics license application (BLA) (see section 505(l)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)). See Q.I.13 in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021) (Final QA Biosimilar guidance).

III. GENERAL PRINCIPLES FOR DRAFT LABELING OF PROPOSED BIOSIMILAR AND INTERCHANGEABLE BIOSIMILAR PRODUCTS

The goal of a biosimilar product development program is to demonstrate biosimilarity (or, for a proposed interchangeable biosimilar product, to demonstrate interchangeability) between the proposed product and the reference product — not to independently establish safety and effectiveness of the proposed product. A demonstration of biosimilarity or interchangeability means, among other things, that FDA has determined that there are no clinically meaningful differences between the proposed product and the reference product in terms of safety, purity, and potency.[13] Thus, FDA's finding of safety and effectiveness for the reference product, as reflected in its FDA-approved Prescribing Information, may be relied upon to provide health care providers with the essential scientific information needed to facilitate prescribing decisions for the proposed biosimilar or interchangeable biosimilar product's labeled conditions of use (e.g., indication(s), dosing regimen(s)). Accordingly, FDA recommends that biosimilar and interchangeable biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate modifications, such as those described in sections IV, Specific Recommendations on Content of Biosimilar and Interchangeable Biosimilar Product Labeling, V, FDA-Approved Patient Labeling of Biosimilar and Interchangeable Biosimilar Products, and VI, Revising Biosimilar and Interchangeable Biosimilar Product Labeling.[14]

Relevant data and information from the reference product labeling that should be incorporated in biosimilar and interchangeable biosimilar product labeling, with appropriate modifications, includes clinical data and other information that supported FDA's finding of safety and effectiveness for the reference product. As a general matter, biosimilar and interchangeable biosimilar product labeling should not include a description of, or data from, clinical studies conducted to support a demonstration of biosimilarity or interchangeability.[15] The proposed biosimilar or interchangeable biosimilar product labeling should describe information and data from a clinical study of the proposed product in the proposed product's labeling only when necessary to inform safe and effective use by a health care provider.

As part of the demonstration of biosimilarity, a 351(k) application generally will contain data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and for which the biosimilar or interchangeable biosimilar product applicant is seeking licensure.[16]

---

[13] See sections 351(i)(2) and 351(k)(4) of the PHS Act.

[14] Sections V and VI of this guidance describe examples of areas in which the reference product labeling and biosimilar or interchangeable biosimilar product labeling might differ.

[15] FDA posts on its website certain documents generated by FDA related to its review of a 351(k) application, as appropriate. For products regulated by CDER, see the web page Drugs@FDA: FDA-Approved Drugs available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. For products regulated by CBER, see the CBER Freedom of Information Office Biologics Electronic Reading Room (eFOI) web page at https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/biologics-electronic-reading-room-efoi. You can refer to those documents if interested in FDA's review of data and information submitted in a 351(k) application.

[16] See section 351(k)(2)(A)(i)(I)(cc) of the PHS Act.

Generally, however, clinical studies conducted to support a demonstration of biosimilarity or interchangeability are not designed to support an independent demonstration of safety or effectiveness of the proposed biosimilar or interchangeable biosimilar product. Thus, in general, inclusion of data from such studies in labeling would not be expected to facilitate an understanding of the proposed biosimilar or interchangeable biosimilar product's safety and effectiveness. For example, the endpoints used in a clinical study conducted to support a demonstration of no clinically meaningful differences may not be the same endpoints evaluated to support licensure of the reference product and thus may not inform prescribing decisions.

Similarly, the patient population in a study or studies conducted to support a demonstration of biosimilarity or interchangeability may differ from the patient population studied in the clinical trials that supported the determination of safety and effectiveness of the reference product. For example, in a study conducted to support a demonstration of no clinically meaningful differences between the biosimilar or interchangeable biosimilar product and the reference product, subjects could have been healthy volunteers, or the study could have been conducted in a condition of use for which the reference product has not been previously licensed,[17] but for which sufficient data indicate that the population or condition of use is adequately sensitive to detect clinically meaningful differences between the products, should they exist.[18]

As required under 21 CFR 201.56(c)(1), biosimilar and interchangeable biosimilar product labeling must meet the content and format requirements of the physician labeling rule (PLR) as described in 21 CFR 201.56(d) and 201.57 regardless of the format of the reference product labeling.[19] In addition, biosimilar and interchangeable biosimilar product labeling must meet the content and format requirements of the pregnancy and lactation labeling final rule (PLLR) as described in 21 CFR 201.57(c)(9)(i) through (iii), regardless of whether the reference product must meet these requirements.[20]

[17] A BLA submitted under section 351(k) of the PHS Act cannot be licensed for a condition of use for which the reference product has not been previously approved, even if the biosimilar or interchangeable biosimilar product applicant conducts a clinical study in such a condition of use. See section 351(k)(2)(A)(i)(III) of the PHS Act.

[18] See the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[19] See the final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," published January 24, 2006 (71 FR 3922). This rule is commonly referred to as the *physician labeling rule* because it addresses prescription drug and biological product labeling that is used by prescribing physicians and other health care providers. Also, see additional labeling guidances on the FDA Prescription Drug Labeling Resources web page at https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

[20] See the final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" published December 4, 2014 (79 FR 72064). The final rule describes the implementation schedule for applications submitted on or after the effective date of the rule, applications pending at the time the rule became effective, and applications approved before the rule became effective (79 FR 72064 at 72095–96).

IV. SPECIFIC RECOMMENDATIONS ON CONTENT OF BIOSIMILAR AND INTERCHANGEABLE BIOSIMILAR PRODUCT LABELING

FDA recommends that biosimilar and interchangeable biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate modifications, as explained in this section and in sections V, FDA-Approved Patient Labeling of Biosimilar and Interchangeable Biosimilar Products, and VI, Revising Biosimilar and Interchangeable Biosimilar Product Labeling. The relevant data and information from the reference product labeling that should be incorporated into the biosimilar and interchangeable biosimilar product labeling will depend on whether the applicant is seeking licensure for all conditions of use (e.g., indication(s), dosing regimen(s)) or fewer than all conditions of use for which the reference product has been previously licensed.[21]

In sections of the biosimilar and interchangeable biosimilar product labeling that are based on the reference product labeling, it is anticipated that the text will be similar to the corresponding text in the reference product labeling. Text based on the reference product labeling need not be identical to the reference product labeling and should reflect currently available information necessary for the safe and effective use of the biosimilar or interchangeable biosimilar product. Certain differences may be appropriate. For example, biosimilar or interchangeable biosimilar product labeling conforming to PLR and/or PLLR may differ from reference product labeling because the reference product labeling may not be required to conform to those requirements at the time of licensure of the biosimilar or interchangeable biosimilar product. In addition, biosimilar or interchangeable biosimilar product labeling may include information specific to the biosimilar or interchangeable biosimilar product that is necessary to inform safe and effective use, including preparation, administration, storage conditions, or safety information. This information may differ from that of the reference product labeling to reflect differences between the biosimilar or interchangeable biosimilar product and the reference product that do not preclude licensure.

[21] A 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling submitted for the proposed biosimilar or interchangeable biosimilar product have been previously licensed for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act). However, a biosimilar or interchangeable biosimilar product applicant generally may seek licensure for fewer than all conditions of use for which the reference product has been previously licensed. See Q.I.7 in the Final QA Biosimilar guidance; see also 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) (COU draft guidance), which, when final, will represent the FDA's current thinking on this topic. Even if the applicant does not intend to seek licensure for all of the reference product's licensed conditions of use, FDA expects that applicants seeking to demonstrate interchangeability will submit data and information to support a showing that the proposed interchangeable biosimilar 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. See the guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019).

A. Recommended Approaches to Product Identification[22]

In biosimilar and interchangeable biosimilar product labeling, the recommended approach to product identification depends on the context of the information being presented. FDA acknowledges that there will be variations on the general concepts outlined in this section because the recommended approach to product identification depends on the specific statements in the labeling. The illustrative examples in this section use a fictional reference product JUNEXANT (replicamab-hjxf) and a fictional biosimilar product NEXSYMEO (replicamab-cznm).

1. Recommendations for When to Use the Biosimilar or Interchangeable Biosimilar Product Name

The biosimilar or interchangeable biosimilar product name should be used in labeling text that is specific to the biosimilar or interchangeable biosimilar product or that refers solely to it, as well as for emphasis in labeling text such as directive statements and recommendations for preventing, monitoring, managing, or mitigating risks. If a biosimilar or interchangeable biosimilar product has a proprietary name, the proprietary name (e.g., NEXSYMEO) should be used in the appropriate sections (except when referring to the drug substance, as noted below). However, if the biosimilar or interchangeable biosimilar product does not have a proprietary name, its proper name (e.g., replicamab-cznm) should be used.[23]

The biosimilar or interchangeable biosimilar product's proprietary name (or, if it does not have a proprietary name, its proper name) should be used in circumstances such as the following:

- In sections where the information described is specific to the biosimilar or interchangeable biosimilar product — this may include, but is not limited to, the following labeling sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING.

- For directive statements and recommendations for preventing, monitoring, managing, or mitigating risks (e.g., "Discontinue NEXSYMEO in patients with *[adverse reaction]*") — such statements are typically included in, but are not limited to, the following labeling sections: BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS.

[22] Additional recommendations relating to product identification in the *Pediatric Use* subsection of biosimilar and interchangeable biosimilar product labeling are provided in section IV.C.3., USE IN SPECIFIC POPULATIONS, *Pediatric Use* Subsection. The recommendations for product identification described in this section (IV.A) apply to the *Pediatric Use* subsection of biosimilar and interchangeable biosimilar labeling only to the extent such recommendations do not conflict with the recommendations in section IV.C.3. See section IV.C.3 for additional information.

[23] The *proper name* is the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act (see section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k)).

When referring to the drug substance, the biosimilar or interchangeable biosimilar product's proper name, as opposed to its proprietary name, should be used. An example would be to use the biosimilar or interchangeable biosimilar product's proper name (e.g., replicamab-cznm) in the DESCRIPTION section when referring to the drug substance.

2. Recommendations for When to Use the Reference Product Name

When clinical studies or specific data derived from studies with the reference product are described in biosimilar or interchangeable biosimilar product labeling, the reference product's proper name (e.g., replicamab-hjxf) should be used. This information would typically be included in labeling sections such as ADVERSE REACTIONS (*Clinical Trials Experience* subsection) and CLINICAL STUDIES (see Table 1 for an example of using the reference product's proper name in the *Clinical Trials Experience* subsection).

Table 1: Example of Using the Reference Product's Proper Name

Reference Product Labeling	**Biosimilar or Interchangeable Biosimilar Product Labeling**
Hypoglycemia occurred more frequently in patients treated with JUNEXANT compared to patients treated with placebo (10% versus 2%, respectively) (Study 1).	Hypoglycemia occurred more frequently in patients treated with replicamab-hjxf compared to patients treated with placebo (10% versus 2%, respectively) (Study 1).

3. Recommendations for When to Use the Core Name Followed by the Word 'Products'[24,25]

The overall benefit-risk profile of the reference product is relevant to the biosimilar or interchangeable biosimilar product, even if a particular adverse reaction or other risk included in

[24] *Core name* means the component shared among an originator biological product and any related biological product, biosimilar product, or interchangeable biosimilar product as part of the proper names of those products. Two examples of a core name are trastuzumab and adalimumab. The *proper name* for biological products generally includes a distinguishing suffix composed of four lowercase letters attached to the core name with a hyphen. Two examples of a proper name are trastuzumab-dkst and adalimumab-atto. See the guidance for industry *Nonproprietary Naming of Biological Products* (January 2017) (Naming guidance) for more information, including information regarding the meaning of the term *related biological product*. See also the draft guidance for industry *Nonproprietary Naming of Biological Products: Update* (March 2019). This draft guidance, when finalized by revising the Naming guidance, will represent the FDA's current thinking on this topic.

[25] The term *core name + products* (or *core name + product*) refers to the reference product and licensed biosimilar products, including interchangeable biosimilar products, if any, that share the same core name. To illustrate, *replicamab products* refers to the reference product replicamab-hjxf and the licensed biosimilar product, replicamab-cznm; it would not, however, include a product with two biological product components, e.g., a biological product with the proper name replicamab and drugimab-xxxx, or a drug-biologic combination product. For additional information about the naming policy, see the Naming guidance and the draft guidance for industry *Nonproprietary Naming of Biological Products: Update* (March 2019). This draft guidance, when finalized by revising the Naming guidance, will represent the FDA's current thinking on this topic.

the reference product labeling may not have been reported with the biosimilar or interchangeable biosimilar product at the time of licensure. For statements incorporated into the reference product labeling that convey information, such as risk information or what is known about the reference product's mechanism of action,[26] that is applicable to both the biosimilar or interchangeable biosimilar product and the reference product, the core name of the reference product followed by the word *products* (e.g., replicamab products) should be used in the biosimilar or interchangeable biosimilar product labeling.[27]

Therefore, in the labeling sections where the risk or other information necessary for the safe use of the product applies to both the biosimilar or interchangeable biosimilar product and the reference product (e.g., BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS (*Postmarketing Experience* subsection)), it would be appropriate to use the core name + products terminology (e.g., replicamab products) to convey, for instance, that the relevant information applies to both the biosimilar or interchangeable biosimilar product and the reference product (see section IV.B., Recommended Approaches to Content Presentation). FDA recommends using this terminology regardless of whether the adverse reaction or risk is described in the reference product labeling as one that "has occurred," "occurs," or "may occur" with the reference product.

Table 2, below, provides examples of the recommended core name + products terminology in the WARNINGS AND PRECAUTIONS section.

Table 2: Examples of the Core Name + Products Terminology

Reference Product Labeling	**Biosimilar or Interchangeable Biosimilar Product Labeling**
Treatment with JUNEXANT increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization or death.	Treatment with replicamab products increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization or death.
Hematologic adverse reactions, including neutropenia, thrombocytopenia, and anemia, have been reported with use of JUNEXANT.	Hematologic adverse reactions, including neutropenia, thrombocytopenia, and anemia, have been reported with use of replicamab products.

[26] See 21 CFR 201.57(c)(13)(i)(A).

[27] In some cases, a drug approved under section 505 of the FD&C Act (21 U.S.C. 355) or a biological product licensed under section 351 of the PHS Act (in the following examples, referred to as "DRUG-X") may be indicated for use only in conjunction with a biological product (as reflected in the INDICATIONS AND USAGE section) or may be recommended for concomitant use with a biological product (as reflected in the DOSAGE AND ADMINISTRATION section). In these situations, when describing use of DRUG-X with such biological product, the labeling for DRUG-X might identify the biological product by the reference product proper name (replicamab-hjxf) or by *core name + products* (replicamab products). If a biosimilar product or an interchangeable biosimilar product has been licensed for the relevant condition of use that has been previously approved for the reference product, FDA generally considers such labeling statements for DRUG-X identifying the biological product by the reference product proper name to include use of the biosimilar product or the interchangeable biosimilar product.

FDA recognizes that application of these recommendations depends on the context and that it may not be clear whether a statement in the reference product labeling is describing specific results from a clinical study conducted with the reference product (and so generally would be appropriate to use the reference product's proper name in the biosimilar or interchangeable biosimilar product labeling) or, for example, a risk that applies to both the biosimilar or interchangeable biosimilar product and the reference product (for which it generally would be appropriate to use core name + products in the biosimilar or interchangeable biosimilar product labeling). The recommended approach to product identification depends on the specific statement and its context.

4. Recommendations for When to Use More Than One Product Identification Approach

There may be biosimilar or interchangeable biosimilar product labeling text appropriately based on the reference product labeling in which more than one product identification approach should be used to convey information accurately. All text in biosimilar and interchangeable biosimilar product labeling, even in sections based on reference product labeling, should be carefully evaluated for the most appropriate product identification approach. In some cases, it is appropriate to use different product identification approaches, each based on its particular context of use, in the same section, as illustrated in the following example:

> Replicamab products can cause hepatotoxicity and acute hepatic failure. In clinical trials of replicamab-hjxf, 10% of patients developed elevated ALT or AST greater than three times the upper limit of normal and 5% progressed to acute hepatic failure. Evaluate serum transaminases (ALT and AST) and bilirubin at baseline and monthly during treatment with NEXSYMEO …

5. Recommendations for When the Reference Product Labeling Describes a Clinical Study Conducted With a Non-U.S.-Approved Biological Product

In rare circumstances, none of the above approaches for product identification may be appropriate. For example, if the reference product labeling describes a clinical study conducted with a non-U.S.-approved product (e.g., a clinical study conducted to support the safety, purity, and potency of the reference product was conducted with a non-U.S.-approved product, with an appropriate scientific bridge), the biosimilar or interchangeable biosimilar product labeling should incorporate the same terminology as the reference product labeling (see Table 3 for an example).

Table 3: Example of Product Identification When a Clinical Study Was Conducted With a Non-U.S.-Approved Biological Product

Reference Product Labeling	Biosimilar or Interchangeable Biosimilar Product Labeling
In an open-label, controlled clinical study (Study 1), 12% of patients treated with a non-U.S.-approved replicamab product developed infusion-related reactions.	In an open-label, controlled clinical study (Study 1), 12% of patients treated with a non-U.S.-approved replicamab product developed infusion-related reactions.

B. Recommended Approaches to Content Presentation

Biosimilar and interchangeable biosimilar product labeling should be specific to the conditions of use (e.g., indication(s), dosing regimen(s)) sought for the biosimilar or interchangeable biosimilar product and should be consistent with language previously approved for the reference product for those conditions of use.

When a biosimilar or interchangeable biosimilar product applicant obtains licensure for fewer than all conditions of use for which the reference product is licensed, certain text in the reference product labeling related to condition(s) of use for the reference product that are not licensed for the biosimilar or interchangeable biosimilar product would generally not be included in the biosimilar or interchangeable biosimilar product labeling.[28]

However, in certain circumstances it may be necessary to include information in the biosimilar or interchangeable biosimilar product labeling relating to an indication(s) or other condition(s) of use for which the product is not licensed, to help ensure safe use (e.g., when safety information in the reference product labeling is related to use of the biosimilar or interchangeable biosimilar product and is not specific to a particular licensed indication(s) or other condition(s) of use, or when information specific to only the biosimilar or interchangeable biosimilar product's indication(s) or other condition(s) of use cannot be easily extracted).[29] Such text should be written in a manner that does not imply that the biosimilar or interchangeable biosimilar product is licensed for a reference product indication(s) or use(s) that has not been licensed for the biosimilar or interchangeable biosimilar product. In these circumstances, specific sections of labeling that could be affected include BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, and USE IN SPECIFIC POPULATIONS.

For example, for sections such as WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, the reference product labeling may pool data on adverse reactions from all the reference product clinical trials for all the indications for which the reference product is licensed. A biosimilar or interchangeable biosimilar product applicant may decide not to seek licensure for

[28] See Q.I.7 in the Final QA Biosimilar guidance; see also the COU draft guidance, which, when final, will represent the FDA's current thinking on this topic.

[29] See also 21 CFR 201.57(c)(6)(i).

all the indications or other conditions of use for which the reference product is licensed. In this case, the pooled data described in the reference product labeling should be included in the biosimilar or interchangeable biosimilar product labeling in a manner that does not imply that the biosimilar or interchangeable biosimilar product is licensed for an indication or other condition of use that has not been licensed for that product. Additionally, any text in biosimilar or interchangeable biosimilar product labeling that refers to an indication or other condition of use for which the applicant is not seeking licensure but that is included to ensure safe use of the biosimilar or interchangeable biosimilar product should be written to avoid an implication that the product has been licensed for that indication(s) or other condition(s) of use.

As an example, if information from a particular study or studies conducted with the reference product is included in the proposed biosimilar or interchangeable biosimilar product labeling, FDA recommends that the data reflect the total number of patients who received the reference product in such study or studies, and not just those who received the reference product for the indication(s) included in the proposed labeling for the biosimilar or interchangeable biosimilar product. In other words, data should reflect the analyses of such study or studies and should not be recalculated to reflect only the indication(s) for which the biosimilar or interchangeable biosimilar product is licensed, and the labeling should appropriately anonymize the indication(s) for which licensure was not sought.

To help further illustrate, the labeling of JUNEXANT states that in nine clinical trials in adult patients with rheumatoid arthritis, ulcerative colitis, or Crohn's disease, the rate of serious infection was 6.7 per 100 patient-years in 583 patients treated with JUNEXANT. If a biosimilar or interchangeable biosimilar product applicant sought licensure only for the rheumatoid arthritis and ulcerative colitis indications, the labeling should also convey that in the nine clinical trials, the rate of serious infection was 6.7 per 100 patient-years in 583 patients treated with replicamab-hjxf (i.e., the data should not be recalculated to remove the data based on adult patients with Crohn's disease, and the term *Crohn's disease* as used in the reference product labeling should be appropriately anonymized in the biosimilar or interchangeable biosimilar product labeling).

C. Recommended Approaches to Specific Sections of Biosimilar and Interchangeable Biosimilar Product Labeling

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

a. Initial U.S. approval

The initial U.S. approval in the Highlights of Prescribing Information (Highlights) is the year that the biosimilar or interchangeable biosimilar product is initially licensed. If a biological product is initially licensed as a biosimilar product, and is later licensed as an interchangeable biosimilar product, the initial approval in the Highlights is the year that the product was initially licensed in the U.S. as a biosimilar product.

b. Biosimilarity statement

For a biosimilar or an interchangeable biosimilar product, FDA recommends including a statement that the product is biosimilar to the reference product. The statement should be placed on the line immediately beneath the initial U.S. approval in the Highlights. The statement should read as follows:

> *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT'S PROPRIETARY NAME (biosimilar or interchangeable biosimilar product's proper name)]* is biosimilar* to *[REFERENCE PRODUCT'S PROPRIETARY NAME (reference product's proper name)]*.

If a biosimilar or an interchangeable biosimilar product does not have a proprietary name, the statement should refer only to its proper name. The asterisk should appear as a footnote symbol inserted after the word *biosimilar*. For example, for the fictitious biosimilar product NEXSYMEO (replicamab-cznm) and the fictitious reference product JUNEXANT (replicamab-hjxf), the statement should read as follows:

> NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf).

The footnote should appear at the end of the Highlights (but above the revision date)[30] and state the following:

> *Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT'S PROPRIETARY NAME]* has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

To have a consistent approach with all biosimilar and interchangeable biosimilar product labeling, the biosimilarity statement as well as the associated footnote in the Highlights should appear in regular font (not bold font). The font of the biosimilarity statement in the Highlights should be at least eight points, but the associated biosimilarity footnote in the Highlights should be six points.

2. INDICATIONS AND USAGE Section

Information in the INDICATIONS AND USAGE section should be specific to the licensed indication(s) for the biosimilar or interchangeable biosimilar product and should be consistent with information previously approved for the reference product. The biosimilar or interchangeable biosimilar product labeling should include text from the reference product

[30] The revision date must be placed at the end of the Highlights (see 21 CFR 201.57(a)(15)). The footnote should be placed after the Patient Counseling Information statement (if applicable).

labeling regarding any Limitations of Use relevant to the biosimilar or interchangeable biosimilar product's indication(s). See section IV.B., Recommended Approaches to Content Presentation, for recommendations regarding text that refers to an indication for which licensure has not been sought by the biosimilar or interchangeable biosimilar product applicant.

3. USE IN SPECIFIC POPULATIONS, Pediatric Use Subsection[31]

In general, pediatric use information should be discussed in the *Pediatric Use* subsection and included in other sections of labeling as appropriate.[32] In general, the pediatric use statements are framed in terms of whether or not safety and effectiveness of a drug or biological product in pediatric patients have been established based on supporting studies with that drug or biological product.[33]

A licensed biosimilar or interchangeable biosimilar product is expected to be as safe and effective as its reference product for the conditions of use for which it is licensed. Biosimilar and interchangeable biosimilar product applicants are not required to independently reestablish safety and effectiveness. Although, in general, a 351(k) application is required to include data from a clinical study or studies,[34] the studies (if any) that are relevant to the *Pediatric Use* subsection generally would have been conducted with the reference product, not the biosimilar or interchangeable biosimilar product.[35] This is because a biosimilar or interchangeable biosimilar product applicant can, as appropriate, provide a scientific justification to support licensure under section 351(k) of the PHS Act for nonstudied indications (including pediatric indications) or other conditions of use. The scientific justification to support such licensure is typically based on all available data and information in the biosimilar or interchangeable biosimilar product application (including, in general, the demonstration of biosimilarity and, if applicable, interchangeability, and consideration of the mechanism of action, pharmacokinetics,

[31] The recommendations in this section of the guidance provide additional guidance specific to biosimilar and interchangeable biosimilar products on the content of pediatric use information in the *Pediatric Use* subsection of labeling. See footnote 5 of the guidance for industry *Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling* (March 2019) (Pediatric Labeling guidance).

[32] See 21 CFR 201.57(c)(9)(iv). See also the Pediatric Labeling guidance.

[33] Although in general pediatric use statements are framed in this manner, the types of information to support a labeling change need not have been conducted by or on behalf of the applicant. See the final rule, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling," (1994 rule) published December 13, 1994 (59 FR 64240, 64246).

[34] See section 351(k)(2)(A)(i)(I)(cc) and (k)(2)(A)(ii) of the PHS Act.

[35] Although a biosimilar product that has not been determined to be interchangeable is considered to have a *new active ingredient* for purposes of the Pediatric Research Equity Act (PREA) (see section 505B(*l*) of the FD&C Act), in general, biosimilar product applicants can satisfy PREA requirements without conducting a clinical study with pediatric subjects, as described in the Final QA Biosimilar guidance. See Q.I.16 in the Final QA Biosimilar guidance.

immunogenicity, and toxicity for each indication (including pediatric indications)), and FDA's finding of safety and effectiveness for other licensed indications for the reference product.[36]

Accordingly, the following statements, which adequately characterize the available data on pediatric use (including when none is available) for the proposed biosimilar or interchangeable biosimilar product, are examples of pediatric use statements that the Agency recommends including in the *Pediatric Use* subsection of biosimilar or interchangeable biosimilar product labeling. The recommendations for product identification described in section IV.A., Recommended Approaches to Product Identification, apply to the *Pediatric Use* subsection of biosimilar and interchangeable biosimilar product labeling only to the extent such recommendations do not conflict with the recommendations in this section of the guidance. The recommendations in this section are intended to balance the objectives of ensuring that product labeling adequately describes data on pediatric use (including when no such data exists) and the unique considerations for biosimilar or interchangeable biosimilar products described above.

The following scenarios in Table 4, which provide context for the examples of recommended pediatric use statements, parallel those described in the guidance for industry *Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling*. For illustrative purposes, these examples use the fictitious biosimilar product NEXSYMEO (replicamab-cznm) and the fictitious reference product JUNEXANT (replicamab-hjxf).[37]

[36] See the guidances for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015) and *Considerations in Demonstrating Interchangeability with a Reference Product* (May 2019).

[37] There may be situations when the biosimilar or interchangeable biosimilar product is not licensed for a pediatric indication even though its reference product is licensed for such a pediatric indication because a biosimilar or interchangeable biosimilar product applicant generally may obtain licensure for fewer than all of the conditions of use for which the reference product is licensed. See the COU draft guidance, which, when final, will represent the FDA's current thinking on this topic. In these situations, it may be appropriate to use an alternative pediatric use statement. See 21 CFR 201.57(c)(9)(iv)(G).

Table 4: Examples of Pediatric Use Statements

Scenario for the Reference Product	Reference Product Labeling	Biosimilar or Interchangeable Biosimilar Product Labeling
Evidence supports the safety and effectiveness for an indication in pediatric patients	The safety and effectiveness of JUNEXANT (for Indication Y) have been established in pediatric patients aged 6 months and older. Use of JUNEXANT for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 6 months and older.	The safety and effectiveness of NEXSYMEO (for Indication Y) have been established in pediatric patients aged 6 months and older. Use of NEXSYMEO for this indication is supported by NEXSYMEO's approval as a biosimilar to replicamab-hjxf and evidence from adequate and well-controlled studies of replicamab-hjxf in adults with additional pharmacokinetic and safety data of replicamab-hjxf in pediatric patients aged 6 months and older.
The evidence does not support the safety and effectiveness for an indication in pediatric patients. Results of studies conducted in that population with the reference product were either negative* or inconclusive.	The safety and effectiveness of JUNEXANT have not been established in pediatric patients (for Indication Y). Effectiveness was not demonstrated in two adequate and well-controlled studies conducted in 120 JUNEXANT-treated pediatric patients, aged 6 months to younger than 17 years for Indication Y.	The safety and effectiveness of NEXSYMEO have not been established in pediatric patients (for Indication Y). Effectiveness was not demonstrated in two adequate and well-controlled studies conducted in 120 pediatric patients treated with replicamab-hjxf, aged 6 months to younger than 17 years for Indication Y.
There is no evidence available to support safety and effectiveness for any indication in pediatric patients	The safety and effectiveness of JUNEXANT have not been established in pediatric patients.	The safety and effectiveness of NEXSYMEO have not been established in pediatric patients.
Contraindicated for use in pediatric patients based on available evidence	JUNEXANT is contraindicated in pediatric patients because of deaths observed in a juvenile animal study with administration of replicamab-hjxf to juvenile rats at clinically relevant doses.	NEXSYMEO is contraindicated in pediatric patients because of deaths observed in a juvenile animal study with administration of replicamab-hjxf to juvenile rats at clinically relevant doses.

* In this context, study results are considered negative when they strongly suggest that the product would be ineffective or unsafe. See the guidance for industry *Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling*.

4. CLINICAL PHARMACOLOGY, Immunogenicity Subsection[38]

In accordance with FDA's recommendation that biosimilar and interchangeable biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate modifications, the Agency has the following recommendations with respect to incorporating relevant immunogenicity data and information from the reference product labeling:[39]

- For a reference product with labeling consistent with FDA's recommendations as described in the Immunogenicity Labeling draft guidance, when finalized,[40] the biosimilar or interchangeable biosimilar product labeling generally should follow the same content and format recommendations described in that guidance. The biosimilar or interchangeable biosimilar product labeling should also incorporate the appropriate modifications recommended in this guidance (e.g., the approaches to product identification in section IV.A., Recommended Approaches to Product Identification).

- If the reference product labeling is not consistent with FDA's recommendations as described in the Immunogenicity Labeling draft guidance, when finalized, FDA recommends that the biosimilar or interchangeable biosimilar product applicant incorporate relevant immunogenicity data and information from the reference product labeling, with appropriate modifications (e.g., the approaches to product identification in section IV.A., Recommended Approaches to Product Identification).

Under either scenario, if immunogenicity information is included in the reference product labeling, the Agency generally recommends including the following paragraph in the biosimilar or interchangeable biosimilar product labeling, preceding the presentation of the immunogenicity data:

> The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of

[38] See the draft guidance for industry *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* (February 2022) (Immunogenicity Labeling draft guidance); this draft guidance, when final, will represent the FDA's current thinking on this topic. The Immunogenicity Labeling draft guidance, when finalized, will provide recommendations on incorporating immunogenicity information into the labeling of certain biological products licensed under section 351(a) of the PHS Act and of select drug products that have immunogenicity assessments. The Immunogenicity Labeling draft guidance also references the guidance for industry *Labeling for Biosimilar Products* and acknowledges the Agency's intent to issue additional guidance on the content and format of immunogenicity data in the labeling of biological products licensed under section 351(k) of the PHS Act. The recommendations in this section are intended to provide such additional guidance.

[39] Less commonly, FDA may determine that immunogenicity studies were unnecessary for a reference product and, therefore, the reference product labeling does not include an *Immunogenicity* subsection. In that instance, the labeling for the biosimilar or interchangeable biosimilar product should also not include an *Immunogenicity* subsection.

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

anti-drug antibodies in other studies, including those of *[proper name of reference product]* or of other *[core name]* products.

If the methodology for the immunogenicity evaluation of the reference product precluded an assessment of the incidence of anti-drug antibodies, FDA recommends that the biosimilar or interchangeable biosimilar product applicant contact the relevant review division (additionally, the Agency anticipates that it would generally be appropriate for the biosimilar or interchangeable biosimilar product labeling to omit the above paragraph in such circumstances).

Additionally, the biosimilar or interchangeable biosimilar product labeling should incorporate relevant immunogenicity information contained within other sections of the reference product labeling (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL STUDIES) with appropriate modifications and with use of cross-references between related information.

V. FDA-APPROVED PATIENT LABELING OF BIOSIMILAR AND INTERCHANGEABLE BIOSIMILAR PRODUCTS

If a Medication Guide is required, applicants for biosimilar and interchangeable biosimilar products must follow existing Medication Guide regulations.[41] If the FDA-approved patient labeling for the reference product includes Patient Information (also known as a Patient Package Insert), the applicant should develop Patient Information for the biosimilar or interchangeable biosimilar product, incorporating relevant information from the Patient Information for the reference product, with appropriate modifications.

If the FDA-approved patient labeling for the reference product includes Instructions for Use (IFU),[42] the IFU for the proposed biosimilar or interchangeable biosimilar product should incorporate relevant information from the IFU for the reference product and present the information in a similar manner. The proposed IFU may differ from the IFU for the reference product where, for example, modified language or images are needed to describe the biosimilar or interchangeable biosimilar product accurately. If other changes are proposed beyond those necessary to describe the biosimilar or interchangeable biosimilar product accurately, applicants should discuss proposed changes with the Agency, including whether additional data or a written justification would be needed to provide adequate support for such changes. Additionally, if there are plans to conduct a human factors study and the applicant intends to submit a protocol for FDA's review, the applicant should seek FDA input on the proposed IFU for the biosimilar or interchangeable biosimilar product when the human factors study protocol is submitted for FDA review. A full and final review of proposed biosimilar or interchangeable biosimilar product labeling, including the IFU, will occur in the context of the planned 351(k) application and may be informed by any human factors study findings submitted or other relevant data included in the application.

[41] See 21 CFR part 208.

[42] See the guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2022).

VI. REVISING BIOSIMILAR AND INTERCHANGEABLE BIOSIMILAR PRODUCT LABELING

A. Updating Information, Including Safety Information

During the life cycle of a biological product, changes in the labeling may be necessary to provide updated information needed for the safe and effective use of the product. As the reference product and biosimilar or interchangeable biosimilar product are used more widely or under diverse conditions, new information may become available. This may include new risks or new information about known risks.

A biosimilar or interchangeable biosimilar product license holder must comply with applicable requirements regarding adverse experience review, reporting, and record keeping.[43]

When new information becomes available that causes information in labeling to be inaccurate, false, or misleading, the biosimilar or interchangeable biosimilar product license holder must take steps to change the content of its product labeling, in accordance with 21 CFR 601.12.[44] All holders of marketing applications for biological products have an ongoing obligation to ensure their labeling is accurate and up to date.[45] A biological product is misbranded, in violation of the Federal Food, Drug, and Cosmetic Act, when its labeling is false or misleading; does not provide adequate directions for use and adequate warnings; or prescribes, recommends, or suggests a dosage, manner, frequency, or duration of use of the drug that is dangerous to health.[46]

B. Adding Conditions of Use

FDA recognizes that a biosimilar or interchangeable biosimilar product license holder may be interested in seeking licensure for an additional condition(s) of use after product licensure, including in the following scenarios:

- The biosimilar or interchangeable biosimilar product license holder originally obtained licensure for fewer than all of the conditions of use for which the reference product has been previously licensed and is seeking licensure for one or more of the remaining licensed conditions of use of the reference product.

[43] See 21 CFR 600.80.

[44] See, for example, 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" (21 CFR 201.56(a)(2)).

[45] Ibid.

[46] See 21 U.S.C. 331(a) through (b) and 352(a), (f), and (j).

- The reference product license holder obtained licensure for a new condition of use for the reference product after the original licensure of the biosimilar or interchangeable biosimilar product, and the biosimilar or interchangeable biosimilar license holder is seeking to add that condition of use.

The biosimilar or interchangeable biosimilar product license holder may seek licensure for an additional condition(s) of use of the reference product in these scenarios by submitting a prior approval supplement(s) to the 351(k) application that contains the necessary data and information, including draft labeling revised to include the additional condition(s) of use sought.[47]

VII. HOW TO SUBMIT INITIAL AND REVISED BIOSIMILAR AND INTERCHANGEABLE BIOSIMILAR PRODUCT LABELING

New 351(k) applications and supplement submissions for biosimilar and interchangeable biosimilar product labeling should include the following:

- A clean version of reference product labeling that was used to develop the biosimilar or interchangeable biosimilar product labeling

- A tracked-changes and annotated version of proposed biosimilar or interchangeable biosimilar product labeling explaining the differences from the reference product labeling

- A clean version of the proposed biosimilar or interchangeable biosimilar product labeling

[47] See 21 CFR 601.12. For additional recommendations on how to support licensure for an additional condition(s) of use for which the reference product has been previously approved, refer to the guidance documents on biosimilar and interchangeable biosimilar product development on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. See also the COU draft guidance, which, when final, will represent the FDA's current thinking on this topic.