Labeling for Biosimilar Products

Guidance for Industry

DRAFT GUIDANCE

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

March 2016
Labeling

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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
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Food and Drug Administration
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants in developing draft labeling for submission in applications for proposed biosimilar products under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)). The recommendations for prescription drug labeling in this guidance pertain only to the prescribing information (commonly referred to as the package insert), except for recommendations in section V pertaining to FDA-approved patient labeling (e.g., Patient Information, Medication Guide, and Instructions for Use).[2] Specific labeling recommendations for interchangeable biological products are not provided in this guidance (see section VIII of this guidance).

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

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148) on March 23, 2010. The BPCI Act amends the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an

[1] This guidance has been prepared by the Office of Medical Policy 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] Unless otherwise specified, the terms *biosimilar product labeling* and *labeling* as used in this guidance address only the prescribing information as described in 21 CFR 201.56 and 201.57.

FDA-licensed biological reference product (see sections 7001 through 7003 of the Affordable Care Act). Section 351(k) of the PHS Act, added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product.

Section 351(i) defines *biosimilarity* to mean "that the biological product is highly similar to the reference product[3] 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 (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

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:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); 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.

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

Under FDA regulations, prescription drug labeling must provide adequate information to enable health care practitioners to "use the drug safely and for the purposes for which it is intended";

[3] *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).

and to this end, the approved prescribing information summarizes the essential scientific information needed by health care practitioners for the safe and effective use of a drug.[4] This labeling reflects FDA's finding of safety and effectiveness[5] for the drug under the labeled conditions of use and facilitates prescribing decisions, thereby enabling the safe and effective use of drugs (including biological products) and reducing the likelihood of medication errors.

III. GENERAL PRINCIPLES FOR DRAFT LABELING OF PROPOSED BIOSIMILAR PRODUCTS (BIOSIMILAR PRODUCT LABELING)

The goal of a biosimilar product development program is to demonstrate biosimilarity between the proposed product and the reference product, not to independently establish safety and effectiveness of the proposed product. A demonstration of biosimilarity 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.[6] 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 practitioners with the essential scientific information needed to facilitate prescribing decisions for the proposed biosimilar product's labeled conditions of use (e.g., indication(s), dosing regimen(s)). Accordingly, FDA recommends that in the biosimilar product labeling, applicants incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications.[7]

Information and data from a clinical study of a proposed biosimilar product should be described in its labeling only when necessary to inform safe and effective use by a health care practitioner. As a general matter, it is FDA's view that biosimilar product labeling should not include a description of these data, given that a clinical study supporting the licensure of the biosimilar product generally would not be designed to independently demonstrate the safety and efficacy of the product, but rather to support a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product for the approved

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

[5] 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*). In this guidance, we use the terms *safety and effectiveness* and *safety, purity, and potency* interchangeably in the discussions pertaining to biosimilar products. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs Guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

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

indications.[8] Data from clinical studies designed to support a demonstration of biosimilarity are not likely to be relevant to a health care practitioner's considerations regarding safe and effective use of the biosimilar product and potentially may cause confusion, resulting in an inaccurate understanding of the risk-benefit profile of the product. For example, the endpoints used in a clinical study intended to support a demonstration of no clinically meaningful differences may not be the same endpoints studied to support approval of the reference product and may not inform prescribing decisions regarding safety and efficacy. Similarly, the subjects in such a study may be healthy volunteers or the condition of use studied may be one for which the reference product is not licensed if, with sufficient data, that population or condition of use is thought to be adequately sensitive to support designing a study to show a demonstration of no clinically meaningful differences. Hence, the patient population may be different than what was studied in the clinical trials that supported safety and effectiveness of the reference product. Accordingly, FDA believes that including data from such studies in the prescribing information would not be useful for health care practitioners.

Therefore, based on a demonstration of biosimilarity, biosimilar product labeling should include a description of the clinical data that supported safety and efficacy of the reference product as described in the FDA-approved product labeling for the reference product.

As required under 21 CFR 201.56(c)(1), 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.[9] In addition, 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.[10]

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[8] FDA posts on its Web site certain documents generated by FDA related to its review of a 351(k) application, as appropriate. For products regulated by CDER, please see Drugs@FDA (http://www.fda.gov/drugsatfda). For products regulated by CBER, please see the CBER Freedom of Information Office Electronic Reading Room (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm129132.htm). Health care practitioners and other interested parties can refer to those documents if interested in FDA's review of the data and information submitted in a 351(k) application to support biosimilarity.

[9] See the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006). This rule is commonly referred to as the *physician labeling rule* because it addresses prescription drug labeling that is used by prescribing physicians and other health care practitioners. Also see additional labeling guidances at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

[10] See the final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (79 FR 72064, December 4, 2014). 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 PRODUCT LABELING

FDA recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The relevant data and information from the reference product labeling that should be incorporated into the biosimilar product labeling will depend on whether the applicant is seeking approval for all conditions of use (e.g., indication(s), dosing regimen(s)) or fewer than all conditions of use of the reference product for the biosimilar product.[11]

In sections of the biosimilar product labeling that are based on the reference product labeling, it is anticipated that the text will be similar. Text based on the reference product labeling need not be identical and should reflect currently available information necessary for the safe and effective use of the biosimilar product.[12] Certain differences between the biosimilar and reference product labeling may be appropriate. For example, 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 product. In addition, biosimilar product labeling may include information specific to the biosimilar product necessary to inform safe and effective use of the product, which could include differences such as administration, preparation, storage, or safety information that do not otherwise preclude a demonstration of biosimilarity.

A. Approaches to Product Identification

In biosimilar product labeling, the 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 approach to product identification will depend on the specific statements. The illustrative examples in this section use a fictional reference product JUNEXANT *(replicamab-hjxf)* and a fictional biosimilar product NEXSYMEO *(replicamab-cznm)*.

[11] A biosimilar product applicant generally may seek licensure for fewer than all conditions of use for which the reference product is licensed. The 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 product have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act).

[12] All holders of marketing applications for drugs (including biological products) have an ongoing obligation to ensure that their labeling is accurate and up to date. See, e.g., 21 CFR 201.56(a)(2) ("In accordance with . . . [21 CFR 601.12], the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.").

1. When to use the biosimilar product name

FDA recommends that the biosimilar product name be used in labeling text that is specific to the biosimilar product or refers solely to the biosimilar product. If a biosimilar product has a proprietary name, FDA recommends that the proprietary name be used in these instances; if a proprietary name is not available for the biosimilar product, the biosimilar product's proper name should be used.[13]

FDA recommends the use of the biosimilar product name in circumstances such as the following:

- In sections where the information described is specific to the biosimilar product — This includes, but is not limited to, the following 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 BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections.

2. When to use the reference product name

When clinical studies or data derived from studies with the reference product are described in biosimilar product labeling, the reference product's proper name should be used. This information would typically be included in sections such as, but not limited to, ADVERSE REACTIONS (Clinical Trials Experience) and CLINICAL STUDIES.

Additionally, the reference product name should be included within the biosimilarity statement as described in section IV.C.1.b of this guidance.

3. When to use the core name[14]

The overall risk-benefit profile of the reference product is relevant to the biosimilar product, even if a particular serious adverse reaction or other risk included in the reference product labeling may not have been reported with the biosimilar product at the time of licensure. In

[13] 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)).

[14] The *core name* is the component shared among related biological products as part of the *proper name*. Two examples of a *core name* are filgrastim and epoetin alfa. The *proper name* for biological products will include a designated suffix composed of four lowercase letters attached to the *core name* with a hyphen.

labeling sections where the risk applies to both the biosimilar product and the reference product (e.g., BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS (Postmarketing Experience)), it would be appropriate to use the core name of the reference product followed by the word "*products*" (i.e., *replicamab products*) to convey, for example, that a risk or other information necessary for the safe use of the product applies to both the biosimilar product and the reference product (see section IV.B of this guidance).

For example, in WARNINGS AND PRECAUTIONS:

Reference Product Labeling	**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.

4. When to use more than one product name

There may be text appropriately based on the reference product labeling where more than one of these product identification approaches should be used to accurately convey information. Therefore, all text in biosimilar product labeling, even sections that have been based on reference product labeling, should be carefully evaluated for the most appropriate product identification approach. In some cases, such as the example below, two or more of the three approaches may be used.

> Replicamab products can cause hepatoxicity 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 . . .

B. Approaches to Content Presentation

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

When a biosimilar product applicant obtains licensure for fewer than all conditions of use (e.g., indication(s), dosing regimen(s)) for which the reference product is licensed, certain text in the reference product labeling related to conditions of use for the reference product that are not approved for the biosimilar product would generally not be included in the biosimilar product

labeling.[15] However, in certain circumstances it may be necessary to include information in the biosimilar product labeling relating to an indication(s) for which the biosimilar product applicant is not seeking licensure, in order to help ensure safe use (e.g., when safety information in the reference product labeling is related to use of the product and is not specific to a particular approved indication(s) or when information specific to only the biosimilar product's indication(s) cannot be easily extracted).[16] Such text should be written in a manner that does not imply that the biosimilar product is approved for a reference product indication(s) or use(s) that has not been approved for the 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 group the events by type from all the reference product clinical trials for all the indications for which the reference product is licensed. In cases where the biosimilar product applicant is not seeking approval for all the indications for which the reference product is licensed, the combined data described in the reference product labeling should be included in the biosimilar product labeling in a manner that is not indication-specific. However, any text that refers to an indication for which licensure has not been sought by the biosimilar product applicant and is included to ensure safe use of the biosimilar product should be revised to avoid an implication that the biosimilar has been approved for that indication(s).

C. Approaches to Specific Sections of Biosimilar Product Labeling

1. HIGHLIGHTS OF PRESCRIBING INFORMATION (Highlights)

a. Initial U.S. approval

The initial U.S. approval date in Highlights is the year that the biosimilar product is licensed.

b. Biosimilarity statement

FDA recommends inclusion of a statement, on the line immediately beneath the initial U.S. approval date in Highlights, that the product is biosimilar to the reference product. It should read as follows:

[15] See Q.I.7 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

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

> [BIOSIMILAR PRODUCT'S PROPRIETARY NAME (biosimilar product's proper name)] is biosimilar* to [REFERENCE PRODUCT'S PROPRIETARY NAME (reference product's proper name)] for the indications listed. (1)

The asterisk should appear as a footnote symbol inserted after the word "biosimilar." The end of the statement should include a cross-reference to the INDICATIONS AND USAGE section "(1)" in the Full Prescribing Information, which contains more detailed information.

For example, for the fictitious product NEXSYMEO, the statement should read:

> NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf) for the indications listed. (1)

The footnote should appear at the end of Highlights (but above the Revision Date) and state:

> *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.

2. INDICATIONS AND USAGE

Information in INDICATIONS AND USAGE should be specific to the approved indications for the biosimilar product and should be consistent with language previously approved for the reference product for those indications. The biosimilar product labeling should include text from the reference product labeling regarding any Limitations of Use relevant to the biosimilar product's indication(s) (see section IV.B of this guidance for recommendations regarding text that refers to an indication for which licensure has not been sought by the biosimilar product applicant).

3. ADVERSE REACTIONS, Immunogenicity

Immunogenicity information for therapeutic protein products is usually placed in a subsection in the ADVERSE REACTIONS section entitled *Immunogenicity*. To help health care practitioners interpret the significance of the information, the following (or a similar) statement should be included as the first paragraph in the subsection, preceding the immunogenicity data based on the reference product labeling:

> As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to [reference

product's proper name] in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

V. FDA-APPROVED PATIENT LABELING

If a Medication Guide is required, applicants must follow existing Medication Guide regulations for biosimilar product labeling.[17] If Instructions for Use (IFU) is necessary, the IFU for the proposed 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 accurately describe the biosimilar product. If other changes are proposed beyond those necessary to accurately describe the biosimilar product, FDA recommends that applicants discuss proposed changes with the Agency and the potential need for additional data that might support 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 applicants should seek FDA input on the proposed IFU when the human factors study protocol is submitted for FDA review. A full and final review of proposed 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.

VI. REVISING BIOSIMILAR PRODUCT LABELING

A. Updating Safety Information

During the lifecycle 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 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. As with any biological product, a biosimilar product application holder must promptly review all adverse drug experience information obtained or otherwise received from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological studies/postmarketing adverse event surveillance, reports in the scientific literature, and unpublished scientific papers; and the biosimilar product application holder must comply with applicable reporting and recordkeeping requirements (see 21 CFR 600.80).

When new information becomes available that causes information in labeling to be inaccurate, the application holder must take steps to change the content of its product labeling, in accordance

[17] See 21 CFR part 208.

with 21 CFR 601.12. All holders of marketing applications for biological products have an ongoing obligation to ensure their labeling is accurate and up to date.[18] A biological product is misbranded, in violation of the Federal Food, Drug, and Cosmetic Act (FD&C 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 (see 21 U.S.C. 331(a) through (b) and 352(a), (f), and (j)).

B. Additional Conditions of Use

FDA recognizes that a biosimilar product application holder may be interested in seeking approval for an additional condition(s) of use after product licensure in the following scenarios:

- The biosimilar product applicant originally obtained licensure for fewer than all the conditions of use for which the reference product is licensed and is seeking approval for one or more of the remaining approved conditions of use of the reference product.

- The biologics license application (BLA) holder for the reference product received approval for a new condition of use for the reference product after the original licensure of the biosimilar product.

The biosimilar product applicant may seek licensure for an additional condition(s) of use of the reference product in these scenarios by submitting an efficacy 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. For more information on how to support licensure of the biosimilar product for an additional condition(s) of use for which the reference product is licensed, please refer to the guidance documents on biosimilar product development on FDA's Web site.[19]

VII. HOW TO SUBMIT INITIAL AND REVISED LABELING

New BLAs and supplement submissions for biosimilar product labeling should include the following:

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

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

[19] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm

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

- A clean version of the proposed biosimilar product labeling

VIII. INTERCHANGEABLE BIOLOGICAL PRODUCTS

FDA continues to consider the types of data and information that would support a demonstration that a biological product is interchangeable with a reference product. Any specific recommendations for labeling for interchangeable biological products, including any interchangeability statement similar to the biosimilarity statement described in section IV.C.1.b of this guidance, will be provided in future guidance.