

---

# Labeling for 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### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (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, 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**

# Labeling for Biosimilar Products

## Guidance for Industry

*Additional copies are available from:*

*Office of Communications  
Division of Drug Information, Division of Drug Information  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10001 New Hampshire Ave., Hillandale Bldg., 4<sup>th</sup> Floor  
Silver Spring, MD 20993-0002  
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353  
Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

*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](mailto:ocod@fda.hhs.gov)*

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**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**

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>1</b>
<b>III.</b>	<b>GENERAL PRINCIPLES FOR DRAFT LABELING OF PROPOSED BIOSIMILAR PRODUCTS (BIOSIMILAR PRODUCT LABELING) .....</b>	<b>3</b>
<b>IV.</b>	<b>SPECIFIC RECOMMENDATIONS ON CONTENT OF BIOSIMILAR PRODUCT LABELING .....</b>	<b>5</b>
	<b>A. Approaches to Product Identification .....</b>	<b>5</b>
	<b>B. Approaches to Content Presentation.....</b>	<b>7</b>
	<b>C. Approaches to Specific Sections of Biosimilar Product Labeling.....</b>	<b>8</b>
<b>V.</b>	<b>FDA-APPROVED PATIENT LABELING .....</b>	<b>10</b>
<b>VI.</b>	<b>REVISING BIOSIMILAR PRODUCT LABELING .....</b>	<b>10</b>
	<b>A. Updating Safety Information .....</b>	<b>10</b>
	<b>B. Additional Conditions of Use .....</b>	<b>11</b>
<b>VII.</b>	<b>HOW TO SUBMIT INITIAL AND REVISED LABELING .....</b>	<b>11</b>
<b>VIII.</b>	<b>INTERCHANGEABLE BIOLOGICAL PRODUCTS .....</b>	<b>12</b>

# Labeling for Biosimilar Products Guidance for Industry<sup>1</sup>

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).<sup>2</sup> 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

<sup>1</sup> 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.

<sup>2</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

41  
42 Section 351(i) defines *biosimilarity* to mean “that the biological product is highly similar to the  
43 reference product<sup>3</sup> notwithstanding minor differences in clinically inactive components” and that  
44 “there are no clinically meaningful differences between the biological product and the reference  
45 product in terms of the safety, purity, and potency of the product.”

46  
47 To meet the standard for *interchangeability*, an applicant must provide sufficient information to  
48 demonstrate biosimilarity and also to demonstrate that the biological product can be expected to  
49 produce the same clinical result as the reference product in any given patient and, if the  
50 biological product is administered more than once to an individual, the risk in terms of safety or  
51 diminished efficacy of alternating or switching between the use of the biological product and the  
52 reference product is not greater than the risk of using the reference product without such  
53 alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be  
54 substituted for the reference product without the intervention of the prescribing health care  
55 provider (see section 351(i)(3) of the PHS Act).

56  
57 An application submitted under section 351(k) of the PHS Act must contain, among other things,  
58 information demonstrating that “the biological product is biosimilar to a reference product”  
59 based upon data derived from:

- 60
- 61 • Analytical studies that demonstrate that the biological product is highly similar to the  
62 reference product notwithstanding minor differences in clinically inactive components;
  - 63
  - 64 • Animal studies (including the assessment of toxicity); and
  - 65
  - 66 • A clinical study or studies (including the assessment of immunogenicity and  
67 pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity,  
68 and potency in one or more appropriate conditions of use for which the reference product  
69 is licensed and intended to be used and for which licensure is sought for the biological  
70 product.

71  
72 FDA has the discretion to determine that an element described above is unnecessary in a 351(k)  
73 application.

74  
75 Under FDA regulations, prescription drug labeling must provide adequate information to enable  
76 health care practitioners to “use the drug safely and for the purposes for which it is intended”;

---

<sup>3</sup> *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).

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

77 and to this end, the approved prescribing information summarizes the essential scientific  
78 information needed by health care practitioners for the safe and effective use of a drug.<sup>4</sup> This  
79 labeling reflects FDA’s finding of safety and effectiveness<sup>5</sup> for the drug under the labeled  
80 conditions of use and facilitates prescribing decisions, thereby enabling the safe and effective use  
81 of drugs (including biological products) and reducing the likelihood of medication errors.  
82

### **III. GENERAL PRINCIPLES FOR DRAFT LABELING OF PROPOSED 85 BIOSIMILAR PRODUCTS (BIOSIMILAR PRODUCT LABELING)**

86  
87 The goal of a biosimilar product development program is to demonstrate biosimilarity between  
88 the proposed product and the reference product, not to independently establish safety and  
89 effectiveness of the proposed product. A demonstration of biosimilarity means, among other  
90 things, that FDA has determined that there are no clinically meaningful differences between the  
91 proposed product and the reference product in terms of safety, purity, and potency.<sup>6</sup> Thus,  
92 FDA’s finding of safety and effectiveness for the reference product, as reflected in its FDA-  
93 approved prescribing information, may be relied upon to provide health care practitioners with  
94 the essential scientific information needed to facilitate prescribing decisions for the proposed  
95 biosimilar product’s labeled conditions of use (e.g., indication(s), dosing regimen(s)).  
96 Accordingly, FDA recommends that in the biosimilar product labeling, applicants incorporate  
97 relevant data and information from the reference product labeling, with appropriate product-  
98 specific modifications.<sup>7</sup>  
99

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

---

<sup>4</sup> See 21 CFR 201.100 and 201.56(a)(1).

<sup>5</sup> 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>.

<sup>6</sup> Section 351(i)(2) of the PHS Act.

<sup>7</sup> Sections V and VI of this guidance describe examples of areas in which the reference product labeling and biosimilar product labeling might differ.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

121  
122 Therefore, based on a demonstration of biosimilarity, biosimilar product labeling should include  
123 a description of the clinical data that supported safety and efficacy of the reference product as  
124 described in the FDA-approved product labeling for the reference product.

125  
126 As required under 21 CFR 201.56(c)(1), biosimilar product labeling must meet the content and  
127 format requirements of the physician labeling rule (PLR) as described in 21 CFR 201.56(d) and  
128 201.57, regardless of the format of the reference product labeling.<sup>9</sup> In addition, biosimilar  
129 product labeling must meet the content and format requirements of the pregnancy and lactation  
130 labeling final rule (PLLR) as described in 21 CFR 201.57(c)(9)(i) through (iii), regardless of  
131 whether the reference product must meet these requirements.<sup>10</sup>

132

---

<sup>8</sup> 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.

<sup>9</sup> 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>.

<sup>10</sup> 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).

## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

133

### 134 **IV. SPECIFIC RECOMMENDATIONS ON CONTENT OF BIOSIMILAR PRODUCT** 135 **LABELING**

136

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

143

144 In sections of the biosimilar product labeling that are based on the reference product labeling, it  
145 is anticipated that the text will be similar. Text based on the reference product labeling need not  
146 be identical and should reflect currently available information necessary for the safe and  
147 effective use of the biosimilar product.<sup>12</sup> Certain differences between the biosimilar and  
148 reference product labeling may be appropriate. For example, biosimilar product labeling  
149 conforming to PLR and/or PLLR may differ from reference product labeling because the  
150 reference product labeling may not be required to conform to those requirements at the time of  
151 licensure of the biosimilar product. In addition, biosimilar product labeling may include  
152 information specific to the biosimilar product necessary to inform safe and effective use of the  
153 product, which could include differences such as administration, preparation, storage, or safety  
154 information that do not otherwise preclude a demonstration of biosimilarity.

155

#### 156 **A. Approaches to Product Identification**

157

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

164

---

<sup>11</sup> 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).

<sup>12</sup> 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.”).

## Contains Nonbinding Recommendations

Draft — Not for Implementation

### 165 1. When to use the biosimilar product name

166  
167 FDA recommends that the biosimilar product name be used in labeling text that is specific to the  
168 biosimilar product or refers solely to the biosimilar product. If a biosimilar product has a  
169 proprietary name, FDA recommends that the proprietary name be used in these instances; if a  
170 proprietary name is not available for the biosimilar product, the biosimilar product’s proper name  
171 should be used.<sup>13</sup>

172  
173 FDA recommends the use of the biosimilar product name in circumstances such as the following:

- 174
- 175 • In sections where the information described is specific to the biosimilar product — This  
176 includes, but is not limited to, the following sections: INDICATIONS AND USAGE,  
177 DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS,  
178 DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING.
  - 179
  - 180 • For directive statements and recommendations for preventing, monitoring, managing, or  
181 mitigating risks (e.g., “Discontinue NEXSYMEO in patients with [adverse reaction]”) —  
182 Such statements are typically included in, but are not limited to, the BOXED  
183 WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and  
184 DRUG INTERACTIONS sections.
  - 185

### 186 2. When to use the reference product name

187  
188 When clinical studies or data derived from studies with the reference product are described in  
189 biosimilar product labeling, the reference product’s proper name should be used. This  
190 information would typically be included in sections such as, but not limited to, ADVERSE  
191 REACTIONS (Clinical Trials Experience) and CLINICAL STUDIES.

192  
193 Additionally, the reference product name should be included within the biosimilarity statement  
194 as described in section IV.C.1.b of this guidance.

### 195 196 3. When to use the core name<sup>14</sup>

197  
198 The overall risk-benefit profile of the reference product is relevant to the biosimilar product,  
199 even if a particular serious adverse reaction or other risk included in the reference product  
200 labeling may not have been reported with the biosimilar product at the time of licensure. In

---

<sup>13</sup> 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)).

<sup>14</sup> 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.

## Contains Nonbinding Recommendations

Draft — Not for Implementation

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

208

209 For example, in WARNINGS AND PRECAUTIONS:

210

Reference Product Labeling	Biosimilar Product Labeling
Treatment with <i>JUNEXANT</i> increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization or death.	Treatment with <i>replicamab products</i> increases the risk of serious infections involving various organ systems and sites that may lead to hospitalization or death.

211

212

#### 4. When to use more than one product name

213

214 There may be text appropriately based on the reference product labeling where more than one of  
215 these product identification approaches should be used to accurately convey information.

216 Therefore, all text in biosimilar product labeling, even sections that have been based on reference  
217 product labeling, should be carefully evaluated for the most appropriate product identification  
218 approach. In some cases, such as the example below, two or more of the three approaches may  
219 be used.

220

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

226

#### **B. Approaches to Content Presentation**

227

228  
229 The labeling for the biosimilar product should be specific to the conditions of use (e.g.,  
230 indication(s), dosing regimen(s)) sought for the biosimilar product and should be consistent with  
231 language previously approved for the reference product for those conditions of use.

232

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

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

237 labeling.<sup>15</sup> However, in certain circumstances it may be necessary to include information in the  
238 biosimilar product labeling relating to an indication(s) for which the biosimilar product applicant  
239 is not seeking licensure, in order to help ensure safe use (e.g., when safety information in the  
240 reference product labeling is related to use of the product and is not specific to a particular  
241 approved indication(s) or when information specific to only the biosimilar product's  
242 indication(s) cannot be easily extracted).<sup>16</sup> Such text should be written in a manner that does not  
243 imply that the biosimilar product is approved for a reference product indication(s) or use(s) that  
244 has not been approved for the biosimilar product. In these circumstances, specific sections of  
245 labeling that could be affected include BOXED WARNING, CONTRAINDICATIONS,  
246 WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, and  
247 USE IN SPECIFIC POPULATIONS.

248  
249 For example, for sections such as WARNINGS AND PRECAUTIONS and ADVERSE  
250 REACTIONS, the reference product labeling may group the events by type from all the  
251 reference product clinical trials for all the indications for which the reference product is licensed.  
252 In cases where the biosimilar product applicant is not seeking approval for all the indications for  
253 which the reference product is licensed, the combined data described in the reference product  
254 labeling should be included in the biosimilar product labeling in a manner that is not indication-  
255 specific. However, any text that refers to an indication for which licensure has not been sought  
256 by the biosimilar product applicant and is included to ensure safe use of the biosimilar product  
257 should be revised to avoid an implication that the biosimilar has been approved for that  
258 indication(s).

259

### **C. Approaches to Specific Sections of Biosimilar Product Labeling**

261

#### **1. HIGHLIGHTS OF PRESCRIBING INFORMATION (Highlights)**

263

##### **a. Initial U.S. approval**

265

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

267

##### **b. Biosimilarity statement**

269

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

273

---

<sup>15</sup> 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*.

<sup>16</sup> See also 21 CFR 201.57(c)(6)(i).

## Contains Nonbinding Recommendations

Draft — Not for Implementation

274 [BIOSIMILAR PRODUCT’S PROPRIETARY NAME (biosimilar product’s proper  
275 name)] is biosimilar\* to [REFERENCE PRODUCT’S PROPRIETARY NAME  
276 (reference product’s proper name)] for the indications listed. (1)  
277

278 The asterisk should appear as a footnote symbol inserted after the word “biosimilar.” The end of  
279 the statement should include a cross-reference to the INDICATIONS AND USAGE section  
280 “(1)” in the Full Prescribing Information, which contains more detailed information.  
281

282 For example, for the fictitious product NEXSYMEO, the statement should read:  
283

284 NEXSYMEO (replicamab-cznm) is biosimilar\* to JUNEXANT (replicamab-hjxf) for the  
285 indications listed. (1)  
286

287 The footnote should appear at the end of Highlights (but above the Revision Date) and state:  
288

289 \*Biosimilar means that the biological product is approved based on data demonstrating  
290 that it is highly similar to an FDA-approved biological product, known as a reference  
291 product, and that there are no clinically meaningful differences between the biosimilar  
292 product and the reference product.  
293

### 294 2. INDICATIONS AND USAGE 295

296 Information in INDICATIONS AND USAGE should be specific to the approved indications for  
297 the biosimilar product and should be consistent with language previously approved for the  
298 reference product for those indications. The biosimilar product labeling should include text from  
299 the reference product labeling regarding any Limitations of Use relevant to the biosimilar  
300 product’s indication(s) (see section IV.B of this guidance for recommendations regarding text  
301 that refers to an indication for which licensure has not been sought by the biosimilar product  
302 applicant).  
303

### 304 3. ADVERSE REACTIONS, Immunogenicity 305

306 Immunogenicity information for therapeutic protein products is usually placed in a subsection in  
307 the ADVERSE REACTIONS section entitled *Immunogenicity*. To help health care practitioners  
308 interpret the significance of the information, the following (or a similar) statement should be  
309 included as the first paragraph in the subsection, preceding the immunogenicity data based on the  
310 reference product labeling:  
311

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

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

320

321

### **V. FDA-APPROVED PATIENT LABELING**

322

323  
324 If a Medication Guide is required, applicants must follow existing Medication Guide regulations  
325 for biosimilar product labeling.<sup>17</sup> If Instructions for Use (IFU) is necessary, the IFU for the  
326 proposed biosimilar product should incorporate relevant information from the IFU for the  
327 reference product and present the information in a similar manner. The proposed IFU may differ  
328 from the IFU for the reference product where, for example, modified language or images are  
329 needed to accurately describe the biosimilar product. If other changes are proposed beyond  
330 those necessary to accurately describe the biosimilar product, FDA recommends that applicants  
331 discuss proposed changes with the Agency and the potential need for additional data that might  
332 support such changes. Additionally, if there are plans to conduct a human factors study and the  
333 applicant intends to submit a protocol for FDA's review, the applicants should seek FDA input  
334 on the proposed IFU when the human factors study protocol is submitted for FDA review. A full  
335 and final review of proposed product labeling, including the IFU, will occur in the context of the  
336 planned 351(k) application and may be informed by any human factors study findings submitted  
337 or other relevant data included in the application.

338

339

### **VI. REVISING BIOSIMILAR PRODUCT LABELING**

340

341

342

#### **A. Updating Safety Information**

343  
344 During the lifecycle of a biological product, changes in the labeling may be necessary to provide  
345 updated information needed for the safe and effective use of the product. As the reference  
346 product and biosimilar product are used more widely or under diverse conditions, new  
347 information may become available. This may include new risks or new information about  
348 known risks. As with any biological product, a biosimilar product application holder must  
349 promptly review all adverse drug experience information obtained or otherwise received from  
350 any source, foreign or domestic, including information derived from commercial marketing  
351 experience, postmarketing clinical investigations, postmarketing epidemiological  
352 studies/postmarketing adverse event surveillance, reports in the scientific literature, and  
353 unpublished scientific papers; and the biosimilar product application holder must comply with  
354 applicable reporting and recordkeeping requirements (see 21 CFR 600.80).

355

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

---

<sup>17</sup> See 21 CFR part 208.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

358 with 21 CFR 601.12. All holders of marketing applications for biological products have an  
359 ongoing obligation to ensure their labeling is accurate and up to date.<sup>18</sup> A biological product is  
360 misbranded, in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when its  
361 labeling is false or misleading; does not provide adequate directions for use and adequate  
362 warnings; or prescribes, recommends, or suggests a dosage, manner, frequency, or duration of  
363 use of the drug that is dangerous to health (see 21 U.S.C. 331(a) through (b) and 352(a), (f),  
364 and (j)).

365

### **B. Additional Conditions of Use**

366

367  
368 FDA recognizes that a biosimilar product application holder may be interested in seeking  
369 approval for an additional condition(s) of use after product licensure in the following scenarios:  
370

371

- The biosimilar product applicant originally obtained licensure for fewer than all the  
372 conditions of use for which the reference product is licensed and is seeking approval for  
373 one or more of the remaining approved conditions of use of the reference product.  
374

375

- The biologics license application (BLA) holder for the reference product received  
376 approval for a new condition of use for the reference product after the original licensure  
377 of the biosimilar product.  
378

379

380 The biosimilar product applicant may seek licensure for an additional condition(s) of use of the  
381 reference product in these scenarios by submitting an efficacy supplement(s) to the 351(k)  
382 application that contains the necessary data and information, including draft labeling revised to  
383 include the additional condition(s) of use sought. For more information on how to support  
384 licensure of the biosimilar product for an additional condition(s) of use for which the reference  
385 product is licensed, please refer to the guidance documents on biosimilar product development  
386 on FDA's Web site.<sup>19</sup>

387

388

## **VII. HOW TO SUBMIT INITIAL AND REVISED LABELING**

389

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

392

- A clean version of reference product labeling that was used to develop the biosimilar  
393 product labeling  
394

395

---

<sup>18</sup> 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.”).

<sup>19</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

- 396 • A tracked changes and annotated version of proposed biosimilar product labeling
- 397 explaining the differences from the reference product labeling
- 398
- 399 • A clean version of the proposed biosimilar product labeling
- 400
- 401

**VIII. INTERCHANGEABLE BIOLOGICAL PRODUCTS**

402  
403  
404 FDA continues to consider the types of data and information that would support a demonstration  
405 that a biological product is interchangeable with a reference product. Any specific  
406 recommendations for labeling for interchangeable biological products, including any  
407 interchangeability statement similar to the biosimilarity statement described in section IV.C.1.b  
408 of this guidance, will be provided in future guidance.  
409