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# **Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009**

## **Guidance for Industry**

### ***DRAFT GUIDANCE***

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For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-7800.

**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)**

**May 2015  
Biosimilarity**

**Revision 1**

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# **Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009**

## **Guidance for Industry**

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1           **Biosimilars: Additional Questions and Answers Regarding**  
2           **Implementation of the Biologics Price Competition and**  
3           **Innovation Act of 2009**  
4           **Guidance for Industry<sup>1</sup>**  
5  
6

7  
8           This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
9           Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not  
10          binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
11          applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
12          for this guidance as listed on the title page.  
13

14  
15          **INTRODUCTION**  
16

17          This guidance provides answers to common questions from sponsors interested in developing  
18          proposed biosimilar products, biologics license application (BLA) holders, and other interested  
19          parties regarding FDA’s interpretation of the Biologics Price Competition and Innovation Act of  
20          2009 (BPCI Act). This guidance revises the 2012 draft guidance on *Biosimilars: Questions and*  
21          *Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of*  
22          *2009* to provide new and revised questions and answers. It also includes certain original  
23          questions and answers that have not yet been finalized. The questions and answers (Q&As) are  
24          grouped below in the following categories:  
25

- 26                   •        Biosimilarity or Interchangeability  
27                   •        Provisions Related to Requirement to Submit a BLA for a “Biological Product”  
28                   •        Exclusivity  
29

30          The BPCI Act amends the Public Health Service Act (PHS Act) and other statutes to create an  
31          abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to  
32          be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see  
33          sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111–148)

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<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency).

Guidance documents are available on the CDER guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and on the CBER guidance page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER or CBER guidance page.

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34 (Affordable Care Act)). On November 2 and 3, 2010, FDA held a public hearing and established  
35 a public docket to obtain input on specific issues and challenges associated with the  
36 implementation of the BPCI Act (see Docket No. FDA-2010-N-0477). This guidance describes  
37 FDA's current interpretation of certain statutory requirements added by the BPCI Act and  
38 reflects consideration of the comments concerning those requirements that were submitted to the  
39 public docket.

40  
41 This guidance is one in a series of guidances that FDA is developing to implement the BPCI Act.  
42 The guidances address a broad range of issues, including:

- 43
- 44 • Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein  
45 Product to a Reference Product
  - 46 • Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  - 47 • Biosimilars: Questions and Answers Regarding Implementation of the Biologics  
48 Price Competition and Innovation Act of 2009
  - 49 • Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors  
50 or Applicants
- 51

52 When applicable, references to information in these guidances are included in this Q&A  
53 guidance.

54  
55 The Q&A format is intended to promote transparency and facilitate development programs for  
56 proposed biosimilar products by addressing questions that may arise in the early stages of  
57 development. In addition, these Q&As respond to questions the Agency has received from  
58 prospective BLA and new drug application (NDA) applicants regarding the appropriate statutory  
59 authority under which certain products will be regulated. FDA intends to update this guidance to  
60 include additional Q&As as appropriate.<sup>2</sup> Table 1 describes the status of the draft guidance  
61 Q&As provided in this guidance and final guidance Q&As that are included in the guidance on  
62 *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price  
63 Competition and Innovation Act of 2009*. FDA has maintained the original numbering of the  
64 Q&As used in the February 2012 draft guidance. Q&As that have been finalized appear in the  
65 final guidance, and the omission of these Q&As from this revised draft guidance is marked by  
66 several asterisks between nonconsecutively numbered Q&As.  
67

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<sup>2</sup> The process by which FDA is requesting public comment on proposed Q&As and issuing new Q&As is described in the accompanying FEDERAL REGISTER notice.

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68 Table 1. Status of Draft Guidance Q&As for Comment and Final Guidance Q&As

Q&A Category	Q&A Numbers	Publication Date of Draft Guidance Q&As for Comment	Comment Period	Publication Date of Final Guidance Q&As
Part I. Biosimilarity or Interchangeability	I.1—I.8 I.11—I.12 I.15	2/15/12	2/15/12-4/16/12	April 2015
	I.13—I.14	2/15/12	2/15/12-4/16/12	
	I.9—I.10 (revised)	5/13/15	5/13/15-7/13/15	
	I.16—I.19 (new)	5/13/15	5/13/15-7/13/15	
Part II. Provisions Related To Requirement To Submit A BLA For A “Biological Product”	II.1—II.2	2/15/12	2/15/12-4/16/12	April 2015
	II.3 (new)	5/13/15	5/13/15-7/13/15	
Part III. Exclusivity	III.1 (revised)	5/13/15	5/13/15-7/13/15	
	III.2	2/15/12	2/15/12-4/16/12	April 2015

69  
70 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
71 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
72 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
73 the word *should* in Agency guidances means that something is suggested or recommended, but  
74 not required.

75  
76 **BACKGROUND**

77  
78 The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI  
79 Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to,  
80 or interchangeable with, an FDA-licensed biological reference product. The objectives of the  
81 BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term  
82 Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the “Hatch-Waxman Act”),  
83 which established abbreviated pathways for the approval of drug products under the Federal  
84 Food, Drug, and Cosmetic Act (FD&C Act).<sup>3</sup> The implementation of an abbreviated licensure  
85 pathway for biological products can present challenges given the scientific and technical  
86 complexities that may be associated with the larger and typically more complex structure of  
87 biological products, as well as the processes by which such products are manufactured. Most  
88 biological products are produced in a living system such as a microorganism, or plant or animal  
89 cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

90  
91 Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the  
92 requirements for an application for a proposed biosimilar product and an application or a  
93 supplement for a proposed interchangeable product. Section 351(i) defines *biosimilarity* to mean

<sup>3</sup> See section 505(b)(2) and 505(j) of the FD&C Act (21 U.S.C. 355(b)(2) and 355(j)).

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94 “that the biological product is highly similar to the reference product notwithstanding minor  
95 differences in clinically inactive components” and that “there are no clinically meaningful  
96 differences between the biological product and the reference product in terms of the safety,  
97 purity, and potency of the product” (see section 351(i)(2) of the PHS Act). A 351(k) application  
98 must contain, among other things, information demonstrating that the biological product is  
99 biosimilar to a reference product based upon data derived from analytical studies, animal studies,  
100 and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are  
101 unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the  
102 additional standard of “interchangeability,” an applicant must provide sufficient information to  
103 demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to  
104 produce the same clinical result as the reference product in any given patient and, if the  
105 biological product is administered more than once to an individual, the risk in terms of safety or  
106 diminished efficacy of alternating or switching between the use of the biological product and the  
107 reference product is not greater than the risk of using the reference product without such  
108 alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be  
109 substituted for the reference product without the intervention of the prescribing healthcare  
110 provider (see section 351(i)(3) of the PHS Act).

111

112 The BPCI Act also includes, among other provisions:

- 113 • A 12-year exclusivity period from the date of first licensure of the reference product,  
114 during which approval of a 351(k) application referencing that product may not be made  
115 effective (see section 351(k)(7) of the PHS Act);
- 116 • A 4-year exclusivity period from the date of first licensure of the reference product,  
117 during which a 351(k) application referencing that product may not be submitted (see  
118 section 351(k)(7) of the PHS Act);
- 119 • An exclusivity period for the first biological product determined to be interchangeable  
120 with the reference product for any condition of use, during which a second or subsequent  
121 biological product may not be determined interchangeable with that reference product  
122 (see section 351(k)(6) of the PHS Act);
- 123 • An exclusivity period for certain biological products for which pediatric studies are  
124 conducted in accordance with a written request (see section 351(m) of the PHS Act);
- 125 • A transition provision for biological products that have been or will be approved under  
126 section 505 of the FD&C Act (21 U.S.C. 355) before March 23, 2020 (see section  
127 7002(e) of the Affordable Care Act); and
- 128 • A provision stating that a 351(k) application for a biosimilar product contains a “new  
129 active ingredient” for purposes of the Pediatric Research Equity Act (PREA) (see section  
130 505B(n) of the FD&C Act).

131

132 The BPCI Act also establishes procedures for identifying and resolving patent disputes involving  
133 applications submitted under section 351(k) of the PHS Act.

134

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135 **QUESTIONS AND ANSWERS**

136 **I. BIOSIMILARITY OR INTERCHANGEABILITY**

137  
138

\* \* \* \* \*

139 ***Q. I.9. Is a clinical study to assess the potential of the biological product to delay***  
140 ***cardiac repolarization (a QT/QTc study) or a drug-drug interaction study***  
141 ***generally needed for licensure of a proposed biosimilar product? [Revised]***  
142

143 **A. I.9.** (Revised Proposed Answer): In general, a proposed biosimilar product may rely  
144 upon the reference product’s clinical evaluation of QT/QTc interval prolongation  
145 and proarrhythmic potential and drug-drug interactions. If such studies were not  
146 required for the reference product, then these data generally would not be needed  
147 for licensure of the proposed biosimilar product. However, if the BLA holder for  
148 the reference product has been required to conduct postmarket studies or clinical  
149 trials under section 505(o)(3) of the FD&C Act to assess or identify a certain risk  
150 related to a QT/QTc study or a drug-drug interaction study and those studies have  
151 not yet been completed, then FDA may impose similar postmarket requirements  
152 on the biosimilar applicant in appropriate circumstances.  
153

154 ***Q. I.10. How long and in what manner should sponsors retain reserve samples of the***  
155 ***biological products used in comparative clinical PK and/or PD studies intended***  
156 ***to support a 351(k) application? [Revised]***  
157

158 **A. I.10.** (Revised Proposed Answer): Reserve samples establish the identity of the  
159 products tested in the actual study, allow for confirmation of the validity and  
160 reliability of the results of the study, and facilitate investigation of further follow-  
161 up questions that arise after the studies are completed. FDA recommends that the  
162 sponsor of a proposed biosimilar product retain reserve samples for at least 5  
163 years following a comparative clinical PK and/or PD study of the reference  
164 product and the proposed biosimilar product (or other clinical study in which PK  
165 or PD samples are collected with the primary objective of assessing PK similarity)  
166 that is intended to support a submission under section 351(k) of the PHS Act. For  
167 a 3-way PK similarity study, samples of both comparator products should be  
168 retained, in addition to samples of the proposed biosimilar product.  
169

170 For most protein therapeutics, FDA recommends that a sponsor retain the  
171 following quantities of product and dosage units, which are expected to be  
172 sufficient for evaluation by state of the art analytical methods:  
173

- 174 • A minimum of 10 dosage units each of the proposed biosimilar, reference  
175 product and, if applicable, comparator product, depending on the amount of  
176 product within each unit. In general, this should provide for a total product

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177 mass of equal to or greater than 200 mg in a volume equal to or greater than  
178 10 mL.

- 179 • For multi-site studies, 3 or more dosage units each of the proposed biosimilar,  
180 reference product, and, if applicable, comparator product, at the site where the  
181 highest number of patients enrolled, and 1 or more dosage units from the next  
182 highest enrolling sites until the minimum recommended total number of  
183 retained samples is met.

184  
185 FDA recommends that the sponsor contact the review division to discuss the  
186 appropriate quantities of reserve samples in the following situations:

- 187  
188 • A product mass of equal to or greater than 200 mg in a volume equal to or  
189 greater than 10 mL requires a large number of dosage units.  
190 • Biologics other than protein therapeutics.  
191 • A product intended for multi-dose administration.

192  
193 \* \* \* \* \*

194  
195 ***Q. I.13. What constitutes “publicly-available information” regarding FDA’s previous***  
196 ***determination that the reference product is safe, pure, and potent to include in a***  
197 ***351(k) application?***

198  
199 A. I.13. (Proposed Answer): “Publicly-available information” in this context generally  
200 includes the types of information found in the “action package” for a BLA (see  
201 section 505(1)(2)(C) of the FD&C Act). However, FDA notes that submission of  
202 publicly available information composed of less than the action package for the  
203 reference product BLA will generally not be considered a bar to submission or  
204 approval of an acceptable 351(k) application.

205  
206 FDA intends to post on the Agency’s Web site publicly available information  
207 regarding FDA’s previous determination that certain biological products are safe,  
208 pure, and potent in order to facilitate biosimilar development programs and  
209 submission of 351(k) applications. We note, however, that the publicly available  
210 information posted by FDA in this context does not necessarily include all of the  
211 information that would otherwise be disclosable in response to a Freedom of  
212 Information Act request.

213  
214 ***Q. I.14. Can an applicant obtain a determination of interchangeability between its***  
215 ***proposed product and the reference product in an original 351(k) application?***

216  
217 A. I.14. (Proposed Answer): Yes. Under the BPCI Act, FDA can make a determination  
218 of interchangeability in a 351(k) application or any supplement to a 351(k)  
219 application. An interchangeable product must be shown to be biosimilar to the  
220 reference product and meet the other standards described in section 351(k)(4) of

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221 the PHS Act. At this time, it would be difficult as a scientific matter for a  
222 prospective biosimilar applicant to establish interchangeability in an original  
223 351(k) application given the statutory standard for interchangeability and the  
224 sequential nature of that assessment. FDA is continuing to consider the type of  
225 information sufficient to enable FDA to determine that a biological product is  
226 interchangeable with the reference product.

227  
228 ***Q. I.16. How can a proposed biosimilar product applicant fulfill the requirement for***  
229 ***pediatric assessments under the Pediatric Research Equity Act (PREA)? [New]***  
230

231 A. I.16. (Proposed Answer): Applicants for proposed biosimilar products should address  
232 PREA requirements based upon the nature and extent of pediatric information in  
233 the reference product labeling.

234  
235 As a preliminary matter, we note that there are differences in the use of the term  
236 “extrapolation” in the context of a proposed biosimilar product under the BPCI  
237 Act and in the context of PREA. Under the BPCI Act, if a biosimilar applicant  
238 fulfills the requirements for demonstrating its product is biosimilar to a reference  
239 product in one condition of use for which the reference product is licensed (e.g.,  
240 an indication for an adult population), information regarding the safety, purity,  
241 and potency of the reference product in one or more additional conditions of use  
242 for which the reference product is licensed (e.g., the same indication in the  
243 pediatric population) may be extrapolated to the proposed biosimilar product if  
244 sufficient scientific justification for extrapolation is provided by the applicant (see  
245 question and answer I.11 in FDA’s guidance for industry on *Biosimilars:*  
246 *Questions and Answers Regarding Implementation of the Biologics Price*  
247 *Competition and Innovation Act of 2009*). In this context, extrapolation occurs  
248 across drug products (i.e., from the reference product to the proposed biosimilar  
249 product).

250  
251 Under PREA, a single sponsor with a single drug or biological product or drug or  
252 biological product line may conduct studies in an indication in one population  
253 (e.g., adults or older pediatric populations) and extrapolate efficacy findings to  
254 satisfy, in part, PREA requirements regarding use of that same product or product  
255 line in additional populations (e.g., younger pediatric populations). In this  
256 context, “extrapolation” occurs in a single product or product line without relying  
257 on studies comparing the product to an approved product and without conducting  
258 a full complement of additional studies in those additional populations. Under  
259 PREA, extrapolation of efficacy (but not safety or dosing) from adult populations  
260 to pediatric populations in a single drug or biological product or drug or  
261 biological product line may be permitted if the adult and pediatric indications are  
262 the same indication and the course of the disease and the effects of the drug are  
263 sufficiently similar in adult and pediatric patients. Extrapolation from one  
264 pediatric age group to another pediatric age group for a single drug or biological

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265 product or drug or biological product line also may be appropriate to fulfill a  
266 PREA requirement under these circumstances. However, under PREA,  
267 extrapolation of dosing or safety from adult populations to pediatric populations  
268 in a single drug or biological product or drug or biological product line generally  
269 is not permitted and will not satisfy a PREA requirement.

270  
271 In the discussion that follows, the term “extrapolation” generally refers to  
272 extrapolation from the reference product to the proposed biosimilar product under  
273 the BPCI Act, not to extrapolation from adults or older pediatric populations to  
274 younger pediatric populations within a single product or product line under  
275 PREA.

- 276  
277 • Adequate pediatric information in reference product labeling  
278  
279 If the labeling for the reference product contains adequate pediatric  
280 information (information reflecting an adequate pediatric assessment) with  
281 respect to an indication for which a biosimilar applicant seeks licensure in  
282 adults, the biosimilar applicant may fulfill PREA requirements by  
283 satisfying the statutory requirements for showing biosimilarity and  
284 providing an adequate scientific justification under the BPCI Act for  
285 extrapolating the pediatric information from the reference product to the  
286 proposed biosimilar product. See question and answer I.11 in FDA’s  
287 guidance for industry on *Biosimilars: Questions and Answers Regarding*  
288 *Implementation of the Biologics Price Competition and Innovation Act of*  
289 *2009* for additional information on extrapolation under the BPCI Act.

290  
291 If the submitted scientific justification for extrapolation under the BPCI  
292 Act is inadequate, a biosimilar applicant must submit appropriate data to  
293 fulfill applicable PREA requirements.

- 294  
295 • Lack of adequate pediatric information in reference product labeling  
296  
297 If the labeling for the reference product does not contain adequate  
298 pediatric information for one or more indications for which a biosimilar  
299 applicant seeks licensure in adults, and applicable PREA requirements  
300 were deferred for the reference product for those indications, a biosimilar  
301 applicant should request a deferral of PREA requirements for those  
302 indications.  
303  
304 If PREA requirements were waived for the reference product sponsor for  
305 those indications, and if the biosimilar applicant believes that its proposed  
306 product meets the requirements for a full or partial waiver of PREA  
307 requirements under section 505B(a)(4) of the FD&C Act, the biosimilar  
308 applicant should request a full or partial waiver for those indications.

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309  
310 If a biosimilar applicant believes that none of the situations described above  
311 applies to its proposed product, the applicant should contact FDA for further  
312 information.

313  
314 ***Q. I.17. When should a proposed biosimilar product applicant submit an initial***  
315 ***pediatric study plan (PSP)? [New]***  
316

317 A. I.17. (Proposed Answer): Section 505B(e) of the Federal Food, Drug, and Cosmetic  
318 Act (FD&C Act), as amended by Section 506 of the Food and Drug  
319 Administration Safety and Innovation Act (FDASIA), requires applicants subject  
320 to the Pediatric Research Equity Act (PREA) to submit an initial pediatric study  
321 plan (PSP) no later than 60 calendar days after the date of an end-of-Phase 2  
322 (EOP2) meeting, or at another time agreed upon by FDA and the applicant. This  
323 provision of FDASIA has an effective date of January 5, 2013. FDA has issued  
324 draft guidance on the PSP process, including the timing of PSP submission, as  
325 required by section 505B(e)(7) of the FD&C Act.

326  
327 Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process for  
328 reaching agreement between an applicant and FDA on an initial PSP that lasts up  
329 to 210 days. Given the potential length of this process, and in the absence of an  
330 EOP2 meeting for a proposed biosimilar product, FDA recommends that if a  
331 sponsor has not already initiated a comparative clinical study intended to address  
332 the requirements under section 351(k)(2)(A)(i)(I)(cc) of the Public Health Service  
333 (PHS) Act, the sponsor should submit an initial PSP as soon as feasible, but no  
334 later than 210 days before initiating such a study. This is intended to provide  
335 adequate time to reach agreement with FDA on the initial PSP before the study is  
336 initiated. Depending on the details of the clinical program, it may be appropriate  
337 to submit an initial PSP earlier in development. FDA encourages the sponsor to  
338 meet with FDA to discuss the details of the planned development program before  
339 submission of the initial PSP.

340  
341 The initial PSP must include an outline of the pediatric study or studies that a  
342 sponsor plans to conduct (including, to the extent practicable, study objectives  
343 and design, age groups, relevant endpoints, and statistical approach); any request  
344 for a deferral, partial waiver, or full waiver, if applicable, along with any  
345 supporting documentation; and should also include any previously negotiated  
346 pediatric plans with other regulatory authorities. For additional guidance on  
347 submission of the PSP, including a PSP Template, please refer to:  
348 [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm)  
349 [/ucm049867.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm). After the initial PSP is submitted, a sponsor must work with  
350 FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3)  
351 of the FD&C Act. It should be noted that requested deferrals or waivers in the  
352 initial PSP will not be formally granted or denied until the product is licensed.

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***Q. I.18 For biological products intended to be injected, how can an applicant demonstrate that its proposed biosimilar product has the same “dosage form” as the reference product? [New]***

A. I.18. (Proposed Answer): Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the *dosage form* of the proposed biosimilar or interchangeable product is the same as that of the reference product. For purposes of implementing this statutory provision, FDA considers the *dosage form* to be the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. In the context of proposed biosimilar products intended to be injected, FDA considers, for example, “injection” (e.g., a solution) to be a different dosage form from “for injection” (e.g., a lyophilized powder). Thus, if the reference product is an “injection,” an applicant could not obtain licensure of a proposed biosimilar “for injection” even if the applicant demonstrated that the proposed biosimilar product, when constituted or reconstituted, could meet the other requirements for an application for a proposed biosimilar product.

For purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act, FDA also considers emulsions and suspensions of products intended to be injected to be distinct dosage forms. Liposomes, lipid complexes, and products with extended-release characteristics present special scenarios due to their unique composition, and prospective applicants seeking further information should contact FDA.

It should be noted, however, that this interpretation regarding the same dosage form is for purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act only. For example, this interpretation should not be cited by applicants seeking approval of a new drug application under section 505(c) of the FD&C Act or licensure of a BLA under section 351(a) of the PHS Act for purposes of determining whether separate applications should be submitted and assessed separate fees for different dosage forms. For more information about the prescription drug user fee *bundling policy*, see FDA’s guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>.

***Q. I.19. If a non-U.S.-licensed product is proposed for importation and use in the U.S. in a clinical investigation intended to support a proposed biosimilar development program (e.g., a bridging clinical PK and/or PD study), is a separate IND required for the non-U.S.-licensed product? [New]***

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396 A. I.19. (Proposed Answer): No, a sponsor may submit a single IND for its proposed  
397 biosimilar development program, and may submit information supporting the  
398 proposed clinical investigation with the non-U.S.-licensed comparator product  
399 under the same IND. This scenario may occur, for example, if a sponsor seeks to  
400 use data from a clinical study comparing its proposed biosimilar product to a non-  
401 U.S.-licensed product to address, in part, the requirements under section  
402 351(k)(2)(A) of the PHS Act, and proposes to conduct a clinical PK and/or PD  
403 study in the U.S. with all three products (i.e., the proposed biosimilar product, the  
404 U.S.-licensed reference product, and the non-U.S.-licensed product) to support  
405 establishment of a bridge to the U.S.-licensed reference product and scientific  
406 justification for the relevance of these comparative data to an assessment of  
407 biosimilarity.  
408

409 A non-U.S.-licensed comparator product is considered an investigational new  
410 drug in the United States, and thus would require an IND for importation and use  
411 in the United States (see 21 CFR 312.110(a)). If a sponsor intends to conduct a  
412 clinical investigation in the United States using a non-U.S.-licensed comparator  
413 product, the IND requirements in 21 CFR part 312 also would apply to this  
414 product (see, e.g., 21 CFR 312.2).  
415

416 With respect to chemistry, manufacturing, and controls (CMC) information, a  
417 sponsor should submit to the IND as much of the CMC information required by  
418 21 CFR 312.23(a)(7) as is available. However, FDA recognizes that a sponsor  
419 may not be able to obtain all of the CMC information required by 21 CFR  
420 312.23(a)(7) for a non-U.S.-licensed comparator product for which it is not the  
421 manufacturer. In these circumstances, the sponsor can request that FDA waive  
422 the requirement for complete CMC information on the non-U.S.-licensed  
423 comparator product (21 CFR 312.10). The IND must include, as part of the  
424 waiver request, at least one of the following:  
425

- 426 • A sufficient explanation why compliance with the complete requirements of  
427 21 CFR 312.23(a)(7) is unnecessary or cannot be achieved,
- 428 • Information that will satisfy the purpose of the requirement by helping to  
429 ensure that the investigational drug will have the proper identity, strength,  
430 quality, and purity, or
- 431 • Other information justifying a waiver.  
432

433 Information that is relevant to whether the investigational drug will have the  
434 proper identity, strength, quality, and purity may include, for example,  
435 information indicating whether the investigational drug has been licensed by a  
436 regulatory authority that has similar scientific and regulatory standards as FDA  
437 (e.g., International Conference on Harmonisation (ICH) countries). This should  
438 include, to the extent possible, summary approval information and current product  
439 labeling made public by the foreign regulatory authority. In addition, a sponsor

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440 should also provide information on the conditions and containers that will be used  
441 to transport the drug product to the US clinical site(s) and information on the  
442 relabeling and repackaging operations that will be used to relabel the drug product  
443 vials for investigational use. (This should include information on how exposure  
444 of the product to light and temperature conditions outside of the recommended  
445 storage conditions will be prevented. A risk assessment on the impact the  
446 relabeling operations may have on drug product stability should also be included.)  
447

448 The sponsor should consult with the appropriate FDA review division regarding  
449 the CMC information necessary to support the proposed clinical trial.  
450

451 As applicable to all investigational drugs, FDA reminds sponsors that the  
452 investigator brochure (IB) for studies to be conducted under the IND should be  
453 carefully prepared to ensure that it is not misleading, erroneous, or materially  
454 incomplete, which can be a basis for a clinical hold (see 21 CFR 312.42(b)(1)(iii)  
455 and (b)(2)(i)). For example, the term *reference product* should be used in the IB  
456 only to refer to the single biological product licensed under section 351(a) of the  
457 Public Health Service Act against which the proposed biosimilar product is  
458 evaluated for purposes of submitting a 351(k) application. The IB and study  
459 protocol(s) should use consistent nomenclature that clearly differentiates the  
460 proposed biosimilar product from the reference product. The IB and study  
461 protocol(s) also should clearly describe whether the comparator used in each  
462 study is the US-licensed reference product or a non-U.S.-licensed comparator  
463 product, and use consistent nomenclature that clearly differentiates these  
464 products. If a non-U.S.-licensed comparator product is being used in a study  
465 conducted in the United States, the IB and study protocol(s) should clearly convey  
466 that the product is not FDA-approved and is considered an investigational new  
467 drug in the United States. The IB and study protocol(s) also should avoid  
468 conclusory statements regarding regulatory determinations (e.g., “comparable,”  
469 “biosimilar,” “highly similar”) that have not been made.  
470

## 471 **II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A** 472 **“BIOLOGICAL PRODUCT”**

473  
474  
475

\* \* \* \* \*

476 ***Q. II.3. What type of marketing application should be submitted for a proposed***  
477 ***antibody-drug conjugate? [New]***  
478

479 **A. II.3. (Proposed Answer):** As described in further detail below, a BLA should be  
480 submitted for a proposed monoclonal antibody that is linked to a drug (antibody-  
481 drug conjugate). FDA considers an antibody-drug conjugate to be a combination

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482 product composed of a biological product constituent part and a drug constituent  
483 part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857-49858; August 25, 2005).

484  
485 CDER is the FDA center assigned to regulate antibody-drug conjugates,  
486 irrespective of whether the biological product constituent part or the drug  
487 constituent part is determined to have the primary mode of action (see section  
488 503(g) of the FD&C Act; see, e.g., Transfer of Therapeutic Biological Products to  
489 the Center for Drug Evaluation and Research (June 30, 2003), available at  
490 [http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.](http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm)  
491 [htm](http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm); Intercenter Agreement Between the Center for Drug Evaluation and  
492 Research and the Center for Biologics Evaluation and Research (October 31,  
493 1991), available at  
494 [http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.](http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm)  
495 [htm](http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm)).

496  
497 To enhance regulatory clarity and promote consistency, CDER considered several  
498 factors to determine the appropriate marketing application type for antibody-drug  
499 conjugates, including the relative significance of the safety and effectiveness  
500 questions raised by the constituent parts, particularly the highly specific molecular  
501 targeting by the antibody to a cell type, cellular compartment, or other marker at  
502 the site of action (as distinguished from mere alteration of systemic  
503 pharmacokinetics).

504  
505 In light of such factors, CDER considers submission of a BLA under section 351  
506 of the PHS Act to provide the more appropriate application type for antibody-drug  
507 conjugates.

508  
509 Sponsors seeking to submit a BLA for a proposed antibody-drug conjugate should  
510 contact CDER's Office of New Drugs at 301-796-0700 for further information.  
511

### 512 **III. EXCLUSIVITY**

513  
514 ***Q. III.1. Can an applicant include in its 351(a) BLA submission a request for reference***  
515 ***product exclusivity under section 351(k)(7) of the PHS Act?***

516  
517 A. III.1. (Proposed Answer): Yes. FDA is continuing to review the reference product  
518 exclusivity provisions of section 351(k)(7) of the PHS Act and has published a  
519 draft guidance addressing certain exclusivity issues (see FDA's draft guidance for  
520 industry on *Reference Product Exclusivity for Biological Products Filed Under*  
521 *Section 351(a) of the PHS Act*, available at  
522 [http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf)  
523 [guidances/ucm407844.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf)). An applicant may include in its BLA submission a  
524 request for reference product exclusivity under section 351(k)(7) of the PHS Act,

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525 and FDA will consider the applicant’s assertions regarding the eligibility of its  
526 proposed product for exclusivity. The draft guidance describes the types of  
527 information that reference product sponsors should provide to facilitate FDA’s  
528 determination of the date of first licensure for their products.  
529