
Guidance for Industry

Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act

DRAFT GUIDANCE

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**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)**

**August 2014
Procedural**

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2 **Reference Product Exclusivity for Biological Products**
3 **Filed Under 351(a) of the PHS Act**
4

5
6 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the
7 Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and
8 does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies
9 the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach,
10 contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate
11 FDA staff, call the appropriate number listed on the title page of this guidance.
12

13
14 **I. INTRODUCTION**
15

16 This guidance is intended to assist sponsors who are developing biological products, sponsors of
17 biologics license applications (BLAs), and other interested parties in providing information that
18 will help the Agency determine the date of first licensure for a reference product under
19 351(k)(7)(C) of the Public Health Service Act (PHS Act), as added by the Biologics Price
20 Competition and Innovation Act of 2009 (BPCI Act). Under 351(k)(7), licensure of an
21 application for a biosimilar or interchangeable product under 351(k) of the PHS Act (also known
22 as a 351(k) application) may not be made effective by FDA until the date that is 12 years after
23 the date on which the reference product referred to in the 351(k) application was first licensed
24 under section 351(a) of the PHS Act. In addition, a 351(k) application may not be submitted to
25 FDA for review until 4 years after the date of first licensure of the reference product. This
26 period of time in which a 351(k) application may not be licensed (or submitted for review) is
27 known as the reference product exclusivity² period. Thus, a decision under 351(k)(7)(C)
28 regarding the date of first licensure of a reference product submitted under 351(a) is, in effect, a
29 decision on eligibility for reference product exclusivity and on the date on which such
30 exclusivity begins to run.
31

32 Not every licensure of a biological product under 351(a) is considered a "first licensure" that
33 gives rise to its own exclusivity period. Under the terms of 351(k)(7), the dates of licensure of
34 applications for certain changes to previously licensed biological products from the same or
35 certain related sponsors are explicitly not considered the dates of first licensure for purposes of
36 giving rise to a period of reference product exclusivity. As discussed further in this guidance,
37 reference product sponsors generally have superior information about changes to previously

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 The term *exclusivity* as applied to a particular product generally refers to a statutory limitation on FDA's ability to accept for review or to license or approve certain competing products for a specified period of time. Exclusivity provisions can be found in the Federal Food, Drug, and Cosmetic Act (FD&C Act) at, among others, 505(c)(3)(E), 505(j)(5)(F), 505A(b) and (c), 527(a), and in the PHS Act at 351(k)(7).

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38 licensed products and corporate relationships to other sponsors that are relevant to a
39 determination of the date of first licensure under 351(k)(7)(C). In this guidance, we describe the
40 types of information that reference product sponsors should provide to facilitate FDA’s
41 determination of the date of first licensure for their products.

42
43 FDA’s guidance documents, including this guidance, do not establish legally enforceable
44 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
45 be viewed only as recommendations, unless specific regulatory or statutory requirements are
46 cited. The use of the word *should* in Agency guidances means that something is suggested or
47 recommended, but not required.

48 **II. BACKGROUND**

49
50
51 The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Affordable
52 Care Act) (Public Law 111–148) on March 23, 2010. The BPCI Act amends the PHS Act and
53 other statutes to create an abbreviated licensure pathway for biological products shown to be
54 biosimilar to or interchangeable with an FDA-licensed biological reference product (see sections
55 7001 through 7003 of the Affordable Care Act). Section 351(k) of the PHS Act (42 U.S.C.
56 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed
57 biosimilar product and an application or a supplement for a proposed interchangeable product.

58
59 Section 351(k)(7) of the PHS Act, entitled “Exclusivity for Reference Product,” describes
60 reference product exclusivity, the period of time in which a 351(k) sponsor is not permitted to
61 submit and FDA is not permitted to license a 351(k) application that references a reference
62 product, the single biological product licensed under section 351(a) of the PHS Act against
63 which a biological product is evaluated in a 351(k) application.³ Under this section, exclusivity
64 for the reference product is described in terms of a prohibition on acceptance or approval of an
65 application for a biosimilar or interchangeable product for a period of time starting from the date
66 of first licensure. Specifically, approval of a 351(k) application may not be made effective until
67 12 years after the date of first licensure of the reference product, which under the statute
68 excludes the date of licensure of supplements and certain other applications.⁴ A 351(k)
69 application for a biosimilar or interchangeable biological product cannot be submitted for review
70 until 4 years after the date on which the reference product was first licensed under section 351(a)
71 of the PHS Act.⁵ As provided by section 351(m) of the PHS Act, an additional six-month period
72 of exclusivity (in which a biosimilar or interchangeable biological product cannot be licensed or
73 accepted for review) will attach to the 12- and 4-year periods, respectively, if the sponsor
74 conducts pediatric studies that meet the requirements for pediatric exclusivity pursuant to section
75 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).⁶ Furthermore, a biological
76 product seeking licensure as biosimilar to or interchangeable with a reference product indicated

³ Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(4) of the PHS Act.

⁴ Sections 7002(a)(7)(A) and 7002(a)(7)(C) of the Affordable Care Act, adding sections 351(k)(7)(A) and 351(k)(7)(C) of the PHS Act.

⁵ Section 7002(a)(7)(B) of the Affordable Care Act, adding section 351(k)(7)(B) of the PHS Act.

⁶ Section 7002(g) of the Affordable Care Act, adding section 351(m) of the PHS Act. This period is referred to as the pediatric exclusivity period.

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77 for a rare disease or condition and granted 7 years of “orphan drug exclusivity” under section
78 527(a) of the FD&C Act, may not be licensed by FDA for the protected orphan indication until
79 after the expiration of the 7-year orphan drug exclusivity period or the 12-year reference product
80 exclusivity period granted under section 351(k)(7) of the PHS Act, whichever is later.⁷

81
82 Determining the date of first licensure for a reference product, in turn, determines whether a
83 particular biological product qualifies for a period of exclusivity under 351(k)(7) of the PHS Act
84 and the date on which such exclusivity, if any, will expire. Making this determination can
85 present unique challenges given the requirements of section 351(k)(7) of the PHS Act. These are
86 made more acute because of the scientific and technical complexities that may be associated with
87 the larger and typically more complex structures of biological products as compared with small
88 molecule drugs, as well as the processes by which such biological products are made. Therefore,
89 the 351(a) applicant may provide information to FDA, such as that described in this guidance or
90 other relevant information, to assist FDA with its analysis of the date of first licensure for a
91 biological product under section 351(k)(7) of the PHS Act.⁸

III. DISCUSSION

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93
94
95 A biological product submitted for licensure under section 351(a) of the PHS Act (a 351(a)
96 application) may be eligible for a period of exclusivity that commences on the date of its
97 licensure unless its date of licensure is not considered a date of first licensure because it falls
98 within an exclusion under 351(k)(7)(C). In most instances, the date of first licensure will be the
99 initial date the particular product at issue was licensed in the United States.

100
101 Under section 351(k)(7)(C) of the PHS Act, however, the date of first licensure does not include
102 the date of licensure of (and a new period of exclusivity shall not be available for) a biological
103 product licensed under section 351(a) of the PHS Act if the licensure is for:

- 104
- 105 • a supplement for the biological product that is the reference product; or
 - 106 • a subsequent application filed by the same sponsor or manufacturer of the
107 biological product (or a licensor, predecessor in interest, or other related
108 entity) for:
 - 109 ○ a change (not including a modification to the structure of the
110 biological product) that results in a new indication, route of
111 administration, dosing schedule, dosage form, delivery system,
112 delivery device, or strength; or
 - 113 ○ a modification to the structure of the biological product that does not
114 result in a change in safety, purity, or potency.⁹
- 115

⁷ Section 7002(h) of the Affordable Care Act.

⁸ This guidance document does not include an exhaustive list of information that a sponsor may submit to assist FDA in determining the date of first licensure. FDA recommends that sponsors submit any additional information regarding the date of first licensure that they think supports eligibility for exclusivity and include an explanation of its relevance.

⁹ Section 7002(a)(7)(C) of the Affordable Care Act, adding section 351(k)(7)(C) of the PHS Act.

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116 The exclusions noted above indicate that Congress did not intend for every biological product
117 licensed under section 351(a) of the PHS Act to be eligible for a separate period of reference
118 product exclusivity. Because of these exclusions, for each product licensed under section 351(a)
119 of the PHS Act that may serve as a reference product for a biosimilar application, FDA must
120 make a determination regarding the date of first licensure.
121

122 Thus, for instance, FDA must determine whether an application is considered a “subsequent
123 application filed by the same sponsor or manufacturer of the biological product (or a licensor,
124 predecessor in interest, or other related entity).” For such applications, FDA must determine
125 whether a particular application is for a “modification to the structure” of a biological product
126 previously licensed by such an entity. If FDA concludes that a particular application filed by a
127 relevant entity includes a “modification to the structure” of a previously licensed biological
128 product that was the subject of a 351(a) application filed by the same sponsor or manufacturer, or
129 its licensor, predecessor in interest, or other related entity, FDA must also determine whether
130 such a structural modification would result in a “change in safety, purity, or potency.”
131

132 A sponsor may submit the information described in section IV of this guidance document to
133 assist FDA in determining the date of first licensure for a biological product to determine
134 whether the product is eligible for its own period of exclusivity or is subject to an exclusion
135 described in 351(k)(7)(C). If the sponsor cannot adequately characterize the biological product,
136 FDA recommends that the sponsor consult FDA for additional guidance.
137

A. “Licensor, Predecessor in Interest, or Other Related Entity”

138
139
140 Section 351(k)(7)(C) of the PHS Act excludes from the date of first licensure the date of
141 approval of supplements and certain subsequent applications filed by the same sponsor or a
142 licensor, predecessor in interest, or other entity that is “related” to the sponsor of a previously
143 licensed biological product. The Agency has experience in construing other provisions that
144 require examination of the relationships between business entities to determine eligibility of a
145 new drug application for exclusivity.¹⁰ For example, in the context of 3-year new drug product
146 exclusivity, the Agency has included studies conducted or funded by the applicant’s predecessor
147 in interest in any assessment of eligibility for exclusivity. It has construed the term “predecessor
148 in interest” to mean an entity (e.g., a corporation) that the sponsor has taken over, merged with,
149 or purchased, or from which the sponsor has purchased all rights to the drug [reference
150 product].¹¹ Also, the Agency has construed a predecessor in interest to include an entity which
151 has granted to the applicant exclusive rights to a new drug application or the data upon which
152 exclusivity is based, which may include licensors, assignors, and joint venture partners,
153 depending on the circumstances of the case.¹²
154

¹⁰ Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act (requiring that a study be “conducted or sponsored by the applicant” to qualify for 3-year new drug product exclusivity).

¹¹ 21 CFR 314.108(a); see also 21 CFR 314.50(j)(4)(iii).

¹² See the final rule entitled “Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions” (patent and exclusivity final rule), published in the Federal Register of October 3, 1994 (59 FR 50338 at 50359 and 50362). Sections 21 CFR 314.108(a) and 314.50(j)(4)(iii) also state that the purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition of predecessor in interest.

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155 With respect to 351(k)(7)(C), the Agency intends to interpret the term “predecessor in interest”
156 as it does in the 3-year new drug product exclusivity context.¹³ It will consider any entity that
157 the sponsor has taken over, merged with, or purchased, or that has granted the sponsor exclusive
158 rights to market the biological product under the 351(a) application, or had exclusive rights to the
159 data underlying that application to be a predecessor in interest for purposes of the first licensure
160 provisions at section 351(k)(7)(C) of the PHS Act.

161
162 The Agency intends to consider a “licensor” under the BPCI Act to be any entity that has granted
163 the sponsor a license to market the biological product, regardless of whether such license is
164 exclusive. This term would include, for instance, entities that continue to retain rights to
165 develop, manufacture, or market the biological product, and/or rights to intellectual property that
166 covers the biological product.

167
168 Although the BPCI Act does not define the term “other related entity,” the Agency generally will
169 consider an applicant to be a “related entity” in this context if (1) either entity owns, controls, or
170 has the power to own or control the other entity (either directly or through one or more other
171 entities) or (2) the entities are under common ownership or control. The Agency also may find
172 that two parties are related entities for purposes of the BPCI Act if the entities are or were
173 engaged in certain commercial collaborations relating to the development of the biological
174 product(s) at issue.¹⁴ In analyzing whether the relationship between the parties would result in a
175 finding that they were “other related entities,” the Agency expects to consider not only
176 ownership and control of the investigational new drug application (IND) and the BLA, but also
177 the level of collaboration between the entities during the development program as a whole.

B. “Modification to the Structure of the Biological Product”

178
179
180
181 The statute specifies that the date of first licensure excludes (and, therefore, a new period of
182 exclusivity will not run from) the date of approval of an application for a change that results in a
183 new indication, route of administration, dosing schedule, dosage form, delivery system, delivery
184 device, or strength unless that change includes a “modification to the structure of the biological
185 product” and such modification results in a change in safety, purity, or potency. It is thus
186 essential to first determine whether a new product includes a modification to the structure of a
187 previously licensed product to assess whether the licensure of the new product is a first licensure
188 that triggers its own period of exclusivity.

189
190 Therefore, a sponsor seeking to assist FDA in determining the date of first licensure for a
191 reference product licensed under 351(a), should describe the structural similarities and
192 differences between its proposed product and any previously licensed biological product that was
193 the subject of a 351(a) application filed by the same sponsor or manufacturer (or its licensor,
194 predecessor in interest, or other related entity). For protein products, described structural
195 differences should include, as appropriate, any differences in amino acid sequence, glycosylation
196 patterns, tertiary structures, post-translational events (including any chemical modifications of

¹³ Patent and exclusivity final rule (59 FR 50338 at 50362).

¹⁴ This generally would not include service contracts, unless such contracts reflect common ownership or development of the product(s) at issue.

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197 the molecular structure such as pegylation), and infidelity of translation or transcription, among
198 others. In determining whether a biological product includes a modification to the structure of a
199 previously licensed biological product, FDA also will consider the principal structural molecular
200 features of both products and whether the modified product affects the same molecular target as
201 the previously licensed product. If a sponsor employs a cell line modified from that used to
202 manufacture the previously licensed product (for example, one employing a modified gene
203 construct) to manufacture a new product, modification of the structure will not simply be
204 presumed. Instead, a sponsor seeking to demonstrate that this new product is nevertheless
205 eligible for its own period of exclusivity should first demonstrate that the product has been
206 structurally modified. Any demonstration that the structure has been modified should be
207 followed by a demonstration that the change has resulted in a change in safety, purity, or
208 potency, as explained in section III.C below.

C. “Result[s] in Change in Safety, Purity, or Potency”

211
212 Section 351(k)(7)(C)(ii)(II) of the PHS Act excludes from the date of first licensure the dates of
213 approval of those modifications to the structure of the previously licensed product that do not
214 “result in a change in safety, purity, or potency.”¹⁵ The determination of whether a structural
215 modification results in a change in safety, purity, or potency will be made case-by-case and will
216 generally need to be based on data submitted by the sponsor. The supporting information
217 provided should include measurable effects (typically demonstrated in preclinical or clinical
218 studies and shown by relevant methods such as bioassays) clearly describing how the
219 modification resulted in a change in safety, purity, or potency compared to the previously
220 licensed product. Supporting information can include references to the data and information
221 submitted in the 351(a) application of the previously licensed product. Evidence that a change
222 resulted in a change in safety, purity, or potency may include evidence that the change will result
223 in a meaningful benefit to public health, such as a therapeutic advantage or other substantial
224 benefit when compared to the previously licensed biological product.

225
226 In cases where FDA determines that a proposed biological product includes a modification to the
227 structure of a previously licensed biological product, FDA generally will presume that the
228 modification has resulted in a change to the proposed product’s safety, purity, or potency if the
229 sponsor of the proposed product demonstrates that it affects a different molecular target than the
230 original product. A molecular target can be any molecule in the body whose activity is modified
231 by the product, resulting in a desirable therapeutic effect. Such molecular targets can include
232 receptors, enzymes, ion channels, structural or membrane transport proteins, nucleic acids, and
233 pathogens, among others.

234

¹⁵ 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 that 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>.

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235 If the modified product affects the same molecular target as the previously licensed product, its
236 sponsor should provide data to show that the changes in structure result in a change in safety,
237 purity, or potency of the modified product when compared to the previously licensed product. If
238 a sponsor can provide such data, FDA may determine that the date of licensure of the modified
239 product is the date of first licensure as set forth in section 351(k)(7)(C) of the PHS Act.
240

241 If the sponsor does not demonstrate that a modification in the structure results in a change in
242 safety, purity, or potency compared to the previously licensed product, or that the modified
243 product affects a different molecular target than the previously licensed product (resulting in a
244 presumption that there is a change in safety purity or potency), the date of licensure of the
245 modified product generally would not be the date of first licensure, and that product would
246 therefore not be eligible for its own period of exclusivity.
247

248 Under 351(k)(7)(C)(ii)(I) of the PHS Act, the date of approval of a change to a previously
249 licensed product from the same sponsor (or a licensor, predecessor in interest, or other related
250 entity) that does not include a modification to the structure of the sponsor's original product but
251 which results in a new indication, route of administration, dosing schedule, dosage form,
252 delivery system, delivery device, or strength is excluded from the date of first licensure; and an
253 application for such a change is not eligible for its own period of exclusivity.
254

255 IV. SUGGESTED INFORMATION FOR 351(a) APPLICANTS TO PROVIDE TO 256 FDA

257
258 FDA recommends that a sponsor include information such as that described in this guidance at
259 the time the 351(a) application is submitted or, in the case of an already licensed 351(a)
260 application, as correspondence to the application.¹⁶ Alternatively, this information can be
261 submitted as an amendment to the 351(a) application. However, the determination of the date of
262 first licensure and of eligibility for exclusivity may not always be made at the time of licensure,
263 particularly if the determination presents complicated scientific, legal, or factual issues; if the
264 information to support such a determination is submitted late in the review cycle; if such
265 information is incomplete; or if FDA requests additional information to make its determination.
266

267 To assist FDA in evaluating the date of first licensure as described in section 351(k)(7)(C) of the
268 PHS Act, FDA suggests that sponsors provide the following information:
269

- 270 1. A list of all licensed biological products that are structurally related to the biological
271 product that is the subject of the 351(a) application being considered. This list should
272 include products that share some of the same principal molecular structural features of
273 the product being considered, but generally can be limited to products that affect the

¹⁶ The Agency recommends, however, that any exclusivity request be placed specifically in the electronic common technical document (eCTD) Module 1.3.5.3 (the Exclusivity Claim section of Module 1, Administrative Information) of the application.

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274 same molecular target.¹⁷ Products that target different epitopes of the same molecular
275 target should be included. Where specific molecular targets have not been defined, this
276 list should include products that share the narrowest target that can be characterized.
277 This may be a pathway, cell type, tissue, or organ system. If this assessment results in
278 the conclusion that no product that has the same molecular target or shares some of the
279 same principal molecular structural features has been licensed, a sponsor should provide
280 an adequate justification to support the assertion that there are no previously licensed
281 products that are relevant for purposes of determining the date of first licensure.

- 282
- 283 2. Of those licensed biological products identified in item 1 above, a list of those for which
284 the sponsor or one of its affiliates, including any licensors, predecessors in interest, or
285 related entities,¹⁸ are the current or previous license holder.
286
 - 287 3. Description of the structural differences between the proposed product and any products
288 identified in item 2 above. For protein products, this should include, but is not limited to,
289 changes in amino acid sequence, differences due to post-translational events, infidelity of
290 translation or transcription, differences in glycosylation patterns or tertiary structure, and
291 differences in biological activities.¹⁹
292
 - 293 4. Evidence of the change in safety, purity, and/or potency between the proposed product
294 and any products identified in item 2 above. This should include, but is not limited to, a
295 description of how the structural differences identified in item 3 above relate to changes
296 in safety, purity, and/or potency.
297

298 Any other information and data that would assist the FDA in making a determination regarding
299 the date of first licensure for a 351(a) application should also be included.

300

V. PUBLICATION OF DECISION

302

303 FDA is reviewing options for making information publicly available regarding reference product
304 exclusivity and dates of first licensure. Once a method is determined, plans to communicate this
305 information will be provided on FDA's Web site.

¹⁷ See, for example, 21 CFR 316.3(b)(13) and its definition of "same drug" as it relates to orphan drug products and the description of structural differences of large molecule drug products.

¹⁸ In compiling this list, "predecessor in interest," "licensor," and "other related entity" should be defined as described in section III.A of this guidance.

¹⁹ Biological activities can be an important measure of structural changes.