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# The “Deemed to be a License” Provision of the BPCI Act

## Questions and Answers Guidance for Industry

### ***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (CDER) Janice Weiner, 301-796-3475, 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)**

**December 2018  
Procedural**

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1                   **The “Deemed to be a License” Provision**  
2                   **of the BPCI Act: Questions and Answers**  
3                   **Guidance for Industry<sup>1</sup>**  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
10 for this guidance as listed on the title page.  
11

12  
13  
14 **I. INTRODUCTION**  
15

16 This draft guidance is intended to provide answers to common questions about FDA’s  
17 interpretation of the “transition” provision of the Biologics Price Competition and Innovation  
18 Act of 2009 (BPCI Act) under which an application for a biological product approved under  
19 section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) as of  
20 March 23, 2020, will be deemed to be a license for the biological product under section 351 of  
21 the Public Health Service Act (PHS Act) (42 U.S.C. 262) on March 23, 2020 (the transition  
22 date). This guidance also describes FDA’s compliance policy for the labeling of biological  
23 products that are the subject of deemed biologics license applications (BLAs). This guidance is  
24 intended to facilitate planning for the transition date and provide further clarity regarding the  
25 Agency’s interpretation of this statutory provision.  
26

27 Although the majority of therapeutic biological products have been licensed under section 351 of  
28 the PHS Act, some protein products historically have been approved under section 505 of the  
29 FD&C Act. On March 23, 2010, the BPCI Act was enacted as part of the Patient Protection and  
30 Affordable Care Act (Public Law 111-148). The BPCI Act clarified the statutory authority under  
31 which certain protein products will be regulated by amending the definition of a “biological  
32 product”<sup>2</sup> in section 351(i) of the PHS Act to include a “protein (except any chemically  
33 synthesized polypeptide),” and describing procedures for submission of a marketing application  
34 for certain “biological products.”  
35

36 The BPCI Act requires that a marketing application for a biological product (that previously  
37 could have been submitted under section 505 of the FD&C Act) must be submitted under section  
38 351 of the PHS Act; this requirement is subject to certain exceptions during a 10-year transition

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<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at FDA.

<sup>2</sup> As amended by the BPCI Act, a “biological product” is defined, in relevant part, as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings” (see section 351(i) of the PHS Act; see also 21 CFR 600.3(h)).

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39 period ending on March 23, 2020 (see section 7002(e)(1)-(3) and (e)(5) of the BPCI Act). On  
40 March 23, 2020 (i.e., the transition date), an approved application for a biological product under  
41 section 505 of the FD&C Act shall be deemed to be a license for the biological product under  
42 section 351 of the PHS Act (see section 7002(e)(4) of the BPCI Act).

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

49  
50

## **51 II. BACKGROUND**

52

### **53 A. BPCI Act**

54

55 The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure  
56 pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or  
57 interchangeable with, an FDA-licensed biological reference product (see sections 7001 through  
58 7003 of the BPCI Act). The objectives of the BPCI Act are conceptually similar to those of the  
59 Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417)  
60 (commonly referred to as the “Hatch-Waxman Amendments”), which established abbreviated  
61 pathways for the approval of drug products under section 505(b)(2) and 505(j) of the FD&C Act.  
62 An abbreviated licensure pathway for biological products can present challenges given the  
63 scientific and technical complexities that may be associated with the generally larger, and  
64 typically more complex, structure of biological products, as well as the processes by which such  
65 products are manufactured. Most biological products are produced in a living system, such as a  
66 microorganism or plant or animal cells, whereas small molecule drugs are typically  
67 manufactured through chemical synthesis.

68

69 Section 351(k) of the PHS Act, added by the BPCI Act, sets forth, among other things, the  
70 requirements for an application for a proposed biosimilar product and an application or a  
71 supplement for a proposed interchangeable product. Section 351(i) defines “biosimilarity” to  
72 mean “that the biological product is highly similar to the reference product notwithstanding  
73 minor differences in clinically inactive components” and that “there are no clinically meaningful  
74 differences between the biological product and the reference product in terms of the safety,  
75 purity, and potency of the product” (section 351(i)(2) of the PHS Act). A 351(k) application  
76 must contain, among other things, information demonstrating that the biological product is  
77 biosimilar to a reference product based upon data derived from analytical studies, animal studies,  
78 and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are  
79 unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the  
80 standard for “interchangeability,” an applicant must provide sufficient information to  
81 demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to  
82 produce the same clinical result as the reference product in any given patient and, if the  
83 biological product is administered more than once to an individual, the risk in terms of safety or  
84 diminished efficacy of alternating or switching between the use of the biological product and the

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85 reference product is not greater than the risk of using the reference product without such  
86 alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be  
87 substituted for the reference product without the intervention of the prescribing health care  
88 provider (see section 351(i)(3) of the PHS Act).

89

### **B. Transition Period for Certain Biological Products**

90

91  
92 Section 7002(e) of the BPCI Act provides that a marketing application for a biological product  
93 (that previously could have been submitted under section 505 of the FD&C Act) **must** be  
94 submitted under section 351 of the PHS Act, subject to the following exception during the  
95 transition period described below.

96

97 An application for a biological product **may** be submitted under section 505 of the FD&C Act  
98 not later than March 23, 2020, if the biological product is in a product class<sup>3</sup> for which a  
99 biological product in such product class was approved under section 505 of the FD&C Act not  
100 later than March 23, 2010.

101

102 However, an application for a biological product **may not** be submitted under section 505 of the  
103 FD&C Act if there is another biological product approved under section 351(a) of the PHS Act  
104 that could be a “reference product”<sup>4</sup> if such application were submitted under section 351(k) of  
105 the PHS Act.

106

107 An approved application for a biological product under section 505 of the FD&C Act shall be  
108 deemed to be a license for a biological product under section 351 of the PHS Act (a “deemed  
109 BLA”) on March 23, 2020. For additional information about FDA’s interpretation of this  
110 “transition” provision, please refer to FDA’s guidance for industry *Interpretation of the*  
111 *“Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of*  
112 *2009* (Transition Policy Final Guidance).

113

114

115

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<sup>3</sup> FDA has interpreted the statutory term *product class* for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period (see FDA’s guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (Biosimilars Q&A Guidance), at Q. II.2). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> The term *reference product* means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under section 351(k) (see section 351(i)(4) of the PHS Act).

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### 116 III. QUESTIONS AND ANSWERS

117

#### 118 A. Identification of Products Subject to the Transition Provision

119

#### 120 Q1. What products are affected by the transition provision? How will the holder of an 121 approved new drug application (NDA) for a biological product know if it will be 122 affected by the transition provision?

123

124 The “deemed to be a license” provision of the BPCI Act (also known as the transition provision)  
125 will apply on March 23, 2020, to approved applications for a biological product under section  
126 505 of the FD&C Act.<sup>5</sup> The BPCI Act amended the definition of a “biological product” in  
127 section 351(i) of the PHS Act to include a “protein (except any chemically synthesized  
128 polypeptide).”

129

130 FDA has previously stated its interpretation of the statutory terms “protein” and “chemically  
131 synthesized polypeptide” in the amended statutory definition of “biological product.”<sup>6</sup> As most  
132 recently explained in FDA’s draft guidance for industry *New and Revised Draft Q&As on*  
133 *Biosimilar Development and the BPCI Act (Revision 2)* (Biosimilars Q&A Draft Guidance),  
134 FDA interprets the term “protein” to mean any alpha amino acid polymer with a specific defined  
135 sequence that is greater than 40 amino acids in size.<sup>7</sup> FDA interprets the term “chemically  
136 synthesized polypeptide” to mean any alpha amino acid polymer that (1) is made entirely by  
137 chemical synthesis and (2) is greater than 40 amino acids, but less than 100 amino acids in size.  
138 A “chemically synthesized polypeptide” is not a “biological product” and will continue to be  
139 regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory  
140 definition of a “biological product” (see Q. II.1 in the Biosimilars Q&A Draft Guidance).  
141 Moreover, a drug product that contains a protein only as an inactive ingredient (e.g., a drug  
142 product formulated with human serum albumin) is not considered to be a “protein” for purposes  
143 of the statutory definition of “biological product” and the transition provision of the BPCI Act.  
144

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<sup>5</sup> General references in this guidance to “applications” submitted or approved under section 505 of the FD&C Act also may include ANDAs, to the extent applicable. An ANDA generally must contain information to demonstrate, among other things, that the proposed generic drug has the same active ingredient(s), conditions of use, dosage form, route of administration, strength, and (with certain permissible differences) labeling as the reference listed drug (section 505(j)(2)(A) of the FD&C Act). Given the complexity of protein molecules and limitations of current analytical methods, it may be difficult for manufacturers of proposed protein products to demonstrate that the active ingredient in their proposed product is the same as the active ingredient in an already approved product, and thus ANDAs are not a focus of this guidance. There are no currently marketed biological products that were approved through the ANDA pathway.

<sup>6</sup> 80 FR 24259, April 30, 2015 (announcing the availability of a guidance for industry entitled “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,” available at [www.regulations.gov](http://www.regulations.gov) (Docket No. FDA-2011-D-0611)).

<sup>7</sup> When final, this guidance will represent the FDA’s current thinking on this topic. In addition, in the *Federal Register* of December 12, 2018, FDA has issued a proposed rule to amend its regulation that defines “biological product” to incorporate changes made by the BPCI Act, and to provide its interpretation of the statutory terms “protein” and “chemically synthesized polypeptide.” When final, this regulation will codify FDA’s interpretation of these terms.

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145 Examples of biological products approved under the FD&C Act are listed in the Appendix to the  
146 Transition Policy Final Guidance. To enhance transparency and facilitate planning for the  
147 transition date, FDA is posting on the FDA web site  
148 ([www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm)) a preliminary list  
149 of approved applications for biological products under the FD&C Act (as of May 31, 2018) that  
150 will be affected by the transition provision, and FDA intends to periodically update the list  
151 before the transition date (see Q3 below).

152

153 **Q2. Does the holder of an approved NDA for a biological product on FDA’s list need to**  
154 **take any affirmative steps for its NDA to be deemed a BLA?**

155

156 FDA interprets the transition provision to mean that the holder of an approved application for a  
157 biological product does not need to take any affirmative steps for its NDA to be deemed a BLA.  
158 Specifically, FDA interprets section 7002(e)(4) of the BPCI Act to mean that an approved  
159 application under the FD&C Act for the biological product will be “deemed to be a license” for  
160 the biological product on the transition date by operation of the statute.

161

162 The statute is silent regarding the process for accomplishing the transition of approved NDAs to  
163 deemed BLAs. FDA intends to send a letter to such application holders on March 23, 2020,  
164 advising that the approved NDA was deemed to be a BLA at 12:00 am Eastern Daylight Time  
165 (EDT) on March 23, 2020, and no longer exists as an NDA. (If the NDA is approved on March  
166 23, 2020, the approved NDA will be deemed to be a BLA immediately after approval.) In the  
167 letter, FDA also will notify the application holder that it has been issued a license that authorizes  
168 the application holder to manufacture the biological product within the meaning of section 351 of  
169 the PHS Act and to introduce the biological product or deliver the biological product for  
170 introduction into interstate commerce (see Q6 below).

171

172 To enhance transparency and facilitate planning for the transition date, FDA is posting on the  
173 FDA website a preliminary list of approved applications for biological products under the FD&C  
174 Act (as of May 31, 2018) that will be affected by the transition provision, and FDA intends to  
175 periodically update the list before the transition date (see Q1 above). Biological products  
176 approved in NDAs that are deemed to be BLAs will be removed from *FDA’s Approved Drug*  
177 *Products With Therapeutic Equivalence Evaluations* (the Orange Book) on March 23, 2020, and  
178 will be listed in FDA’s *Lists of Licensed Biological Products with Reference Product Exclusivity*  
179 *and Biosimilarity or Interchangeability Evaluations* (the Purple Book) on or shortly after the  
180 March 23, 2020 transition date.

181

182 **Q3. Who should an application holder contact if it believes that its approved NDA**  
183 **should or should not be included on FDA’s preliminary list of approved applications**  
184 **for biological products that will be affected by the transition provision?**

185

186 If an application holder or other person reviews, on FDA’s website, the preliminary list of  
187 approved applications for biological products under the FD&C Act that will be affected by the  
188 transition provision and believes that an approved NDA should be added to the list or should not  
189 be included on the list, the application holder or other person should submit a comment to the  
190 public docket established for this guidance and the preliminary list. For information on



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191 submission of comments to the public docket, please refer to the Federal Register (FR) Notice of  
192 Availability of this guidance.

193

194 **Q4. How will FDA notify the sponsor of a proposed biological product who seeks to**  
195 **obtain approval under section 505 of the FD&C Act that the planned application**  
196 **would need to be approved under the FD&C Act on or before March 23, 2020?**

197

198 FDA provided notice to sponsors of proposed biological products intended for submission in an  
199 application under section 505 of the FD&C Act that they will be affected by the transition  
200 provision through FDA’s draft guidance for industry *Implementation of the “Deemed to be a*  
201 *License” Provision of the Biologics Price Competition and Innovation Act of 2009* (Transition  
202 Policy Draft Guidance) and the Biosimilars Q&A Guidances. In the Biosimilars Q&A  
203 Guidances, FDA stated its interpretation of the statutory terms “protein” and “chemically  
204 synthesized polypeptide” in the amended definition of “biological product” (see Q1 above). In  
205 the Transition Policy Final Guidance, FDA provides recommendations to sponsors of proposed  
206 protein products intended for submission in an application that may not receive final approval  
207 under section 505 of the FD&C Act on or before March 23, 2020, to facilitate alignment of  
208 product development plans with FDA’s interpretation of section 7002(e) of the BPCI Act. FDA  
209 recommends that sponsors of development programs for proposed protein products evaluate  
210 whether a planned submission under section 505 of the FD&C Act would allow adequate time  
211 for approval of the application prior to March 23, 2020, considering, among other things,  
212 whether the submission may require a second cycle of review and, for certain types of  
213 applications, whether unexpired patents or exclusivity may delay final approval. If a sponsor is  
214 unsure whether its proposed product may receive approval under the FD&C Act by March 23,  
215 2020, the sponsor should consider submitting a BLA under section 351(a) or 351(k) of the PHS  
216 Act instead. For additional information, please see the Transition Policy Final Guidance.

217

218 **B. Applications for Biological Products Submitted Under Section 505 of the**  
219 **FD&C Act on or Before the Transition Date**

220

221 **Q5. When will the holder of an approved NDA for a biological product receive the BLA**  
222 **number that will be used for its deemed BLA?**

223

224 FDA intends to assign the same application number used for the approved NDA to the deemed  
225 BLA on the March 23, 2020, transition date. As a hypothetical example, NDA 012345 would be  
226 deemed to be BLA 012345 on the transition date. This approach is intended to minimize burden  
227 on holders of approved applications for biological products under the FD&C Act who are  
228 preparing submissions to their applications around the transition date and to facilitate the  
229 administrative conversion of any pending supplements to such applications (see the Transition  
230 Policy Final Guidance for additional information regarding such supplements). The use of a  
231 predictable application numbering system for deemed BLAs is also expected to facilitate  
232 preparation and submission of 351(k) BLAs that seek to rely upon a reference product licensed  
233 in a deemed 351(a) BLA. The FDA letter that notifies the application holder that its approved  
234 NDA is deemed to be a BLA on the transition date will include the product’s BLA number.

235

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236 **Q6. When will the holder of an approved NDA for a biological product receive the**  
237 **license number that will apply to its deemed BLA(s)?**  
238

239 The FDA letter that notifies the application holder that its approved NDA is deemed to be an  
240 approved BLA will include the U.S. license number assigned to the application holder. Each  
241 establishment that is listed in the approved NDA as currently involved in the manufacture of the  
242 biological product on the transition date will be considered a licensed establishment on that date  
243 (see section 7002(e)(4) of the BPCI Act). FDA does not intend to conduct pre-license  
244 inspections to manufacture the transitioning biological product because FDA interprets section  
245 7002(e)(4) of the BPCI Act to mean that an approved application under the FD&C Act for the  
246 biological product will be “deemed to be a license” on the transition date by operation of the  
247 statute. Moreover, the establishments will have been inspected in connection with the previously  
248 approved NDAs under the FD&C Act (see Q16 below for information on establishment  
249 inspections related to certain supplements to a deemed 351(a) BLA).

250  
251 FDA issues only one U.S. license number per BLA holder, regardless of the number of licensed  
252 biological products manufactured by that BLA holder under separate BLAs. Accordingly, if an  
253 NDA holder is also a BLA holder and has been assigned a U.S. license number for another  
254 biological product, the NDA holder will not be issued a different U.S. license number when its  
255 approved NDA for a biological product is deemed to be a BLA on the transition date.  
256

257 Section 351(a)(1)(B)(ii) of the PHS Act requires that each package of a biological product is  
258 plainly marked with, among other things, the applicable license number of the manufacturer of  
259 the biological product in order for the biological product to be introduced or delivered for  
260 introduction into interstate commerce. To minimize possible disruption in the distribution of  
261 biological products in the United States and to minimize burden on holders of deemed BLAs,  
262 FDA intends to adopt a compliance policy for the labeling of biological products that are the  
263 subject of deemed BLAs (see Q14 and section IV below for additional information on the  
264 compliance policy for labeling of biological products in deemed BLAs).  
265

266 **Q7. Will an approved NDA for a biological product be deemed to be a 351(a) BLA or a**  
267 **351(k) BLA?**  
268

269 FDA interprets the transition provision, along with the applicable provisions of the FD&C Act  
270 and the PHS Act, to mean that an approved NDA, including an application submitted through the  
271 pathway described by section 505(b)(2) of the FD&C Act (505(b)(2) application), will be  
272 deemed to be a 351(a) BLA on the transition date.  
273

274 Section 7002(e) of the BPCI Act is directed primarily to the submission of an application for a  
275 biological product during the transition period ending on March 23, 2020 and is silent regarding  
276 whether an approved NDA will be deemed to be a 351(a) BLA or a 351(k) BLA. The Agency’s  
277 interpretation that an NDA submitted under section 505(b)(1) of the FD&C Act will be deemed  
278 to be a 351(a) BLA is based on the shared requirement that both types of applications contain  
279 full reports of investigations of safety and effectiveness (or, for a 351(a) BLA, safety, purity, and  
280 potency). We expect that the measures FDA has taken to minimize differences in the review and  
281 approval of products in marketing applications submitted under section 351(a) of the PHS Act

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282 and section 505(b)(1) of the FD&C Act will facilitate implementation of the statutory provision  
283 under which an approved NDA will be deemed to be a BLA.

284  
285 A 505(b)(2) application is an NDA that contains full reports of investigations of safety and  
286 effectiveness, where at least some of the information required for approval comes from studies  
287 not conducted by or for the applicant and for which the applicant has not obtained a right of  
288 reference or use (e.g., FDA’s finding of safety and/or effectiveness for a listed drug or published  
289 literature). As noted above, the Agency’s interpretation that an approved 505(b)(2) application  
290 will be deemed to be a 351(a) BLA reflects the shared requirement that both types of  
291 applications contain full reports of investigations of safety and effectiveness (or, for a 351(a)  
292 BLA, safety, purity, and potency). This approach also reflects the Agency’s view that it is more  
293 appropriate to regulate a biological product approved through the 505(b)(2) pathway that may be  
294 intended to differ in certain respects (e.g., different strength, dosage form, or route of  
295 administration or approved conditions of use) from a previously approved product under the  
296 statutory and regulatory framework for 351(a) BLAs, as these differences are not permitted  
297 under the statutory framework for 351(k) BLAs. Moreover, FDA’s approval of a 505(b)(2)  
298 application reflects the Agency’s evaluation of the data against a different statutory standard than  
299 a determination of biosimilarity or interchangeability under section 351(k) of the PHS Act.

300

301 **Q8. Will an approved NDA for a biological product that has been discontinued from**  
302 **marketing be deemed to be a BLA?**

303

304 Section 7002(e)(4) states that an “approved application for a biological product under section  
305 505 of the [FD&C Act]” will be deemed to be a BLA on the transition date. Accordingly, FDA  
306 interprets the statute to mean that an approved NDA for a biological product that has been  
307 discontinued from marketing, but for which FDA has not withdrawn approval of the application,  
308 will be deemed to be a BLA on the transition date. The holder of an NDA for a discontinued  
309 product must comply with applicable statutory and regulatory requirements for its application  
310 before the transition date, and after its application is deemed to be a BLA. These requirements  
311 include, for example, postmarketing reporting of adverse drug experiences and, if appropriate,  
312 the submission of proposed revisions to product labeling. If the holder of a deemed BLA for a  
313 biological product that has been discontinued from marketing seeks to reintroduce the product to  
314 the market, the BLA holder should consult with the relevant FDA review division before  
315 submitting a supplement to the deemed BLA, to discuss any data and information that may be  
316 needed.

317

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318 **Q9. How will the transition on March 23, 2020, affect the annual program fee for an**  
319 **approved NDA for a biological product?**  
320

321 Under section 736(a)(2) of the FD&C Act, persons named as the applicant in a human drug  
322 application (which refers to an NDA or a 351(a) BLA, subject to applicable statutory exceptions)  
323 are assessed annual prescription drug program fees. A prescription drug program fee is assessed  
324 each fiscal year for each prescription drug product identified in a human drug application  
325 approved as of October 1 of the fiscal year, with certain exceptions described by statute. For  
326 more information about the prescription drug program fee, consult the FDA guidance *Assessing*  
327 *User Fees Under the Prescription Drug User Fee Amendments of 2017*.  
328

329 In general, sponsors of biological products (1) for which annual prescription drug program fees  
330 are assessed prior to the transition and (2) that are deemed to be licensed under section 351(a) of  
331 the PHS Act on the transition date will continue to be assessed prescription drug program fees  
332 for such products after the transition, subject to applicable statutory requirements and exceptions.  
333

334 **Q10. If an applicant withdraws an NDA that is tentatively approved on or before the**  
335 **transition date, or otherwise pending with FDA, and submits an application for the**  
336 **same product under section 351(a) of the PHS Act, will an additional PDUFA**  
337 **application fee be assessed?**  
338

339 An applicant (or the applicant's licensee, assignee, or successor) will not be charged a  
340 Prescription Drug User Fee Act (PDUFA) application fee for the submission of an application  
341 under section 351(a) of the PHS Act if all of the following circumstances are satisfied (see  
342 section 736(a)(1)(C) of the FD&C Act):  
343

- 344 • The applicant previously submitted an NDA for the same product and paid the associated  
345 PDUFA application fee for the NDA.  
346
- 347 • The NDA was accepted for filing. (Note that an NDA for a biological product will not be  
348 accepted for filing after the transition date.)  
349
- 350 • The NDA was not approved or was withdrawn (without a waiver).  
351

352 For questions regarding user fees, please contact the User Fee Staff at  
353 [CDERCollections@fda.hhs.gov](mailto:CDERCollections@fda.hhs.gov) or 301-796-7900.  
354

355 **Q11. If the applicant withdraws an NDA that is tentatively approved on or before the**  
356 **transition date, or otherwise pending with FDA, and submits an application for the**  
357 **same product under section 351(k) of the PHS Act, will a BsUFA application fee be**  
358 **assessed?**  
359

360 An application for licensure of a biological product under section 351(k) of the PHS Act meets  
361 the definition of a "biosimilar biological product application" in section 744G(4) of the FD&C  
362 Act, with certain exceptions. Under section 744H(a)(2) of the FD&C Act, a biosimilar  
363 biological product application fee is assessed to the applicant at the time of submission of a

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364 biosimilar biological product application, unless an exception applies under section  
365 744H(a)(2)(D). Certain applicants may be eligible for a small business waiver of the biosimilar  
366 biological product application fee under section 744H(d)(1) of the FD&C Act. If an applicant  
367 withdraws an NDA that is tentatively approved or pending on or before the transition date and  
368 later submits a biosimilar biological product application under section 351(k) of the PHS Act, the  
369 applicant would be assessed a biosimilar biological product application fee for the 351(k)  
370 application, unless a small business waiver has been granted or the applicant previously  
371 submitted a biosimilar biological product application for the same product and meets the other  
372 criteria for the exception described in section 744H(a)(2)(D) of the FD&C Act. For more  
373 information about the biosimilar biological product application fee, consult the FDA guidance,  
374 *Assessing User Fees Under the Biosimilar User Fee Amendments of 2017*.

375  
376 **Q12. Will approved NDAs that are deemed to be BLAs remain within the same review**  
377 **office/division in CDER? Will pending NDAs that are withdrawn and submitted as**  
378 **BLAs be reviewed within the same CDER review office/division?**  
379

380 In general, approved NDAs that are deemed to be BLAs will remain within the same review  
381 office/division within CDER's Office of New Drugs (OND) after the transition date. Similarly,  
382 pending NDAs that are withdrawn and submitted as BLAs will be reviewed within the same  
383 OND review office/division.

384  
385 With respect to the product quality assessment, review responsibilities within CDER's Office of  
386 Pharmaceutical Quality (OPQ) for products composed of amino acid polymers are in the process  
387 of being (re)assigned based on certain characteristics of the molecule, rather than the regulatory  
388 pathway, with the expectation that the reassignments will be completed by the transition date.  
389 Accordingly, on the transition date, we expect to maintain the assigned OPQ review offices for  
390 approved NDAs that are deemed BLAs, as well as pending NDAs that are withdrawn and  
391 submitted as BLAs.

392  
393 **C. Statutory and Regulatory Requirements for BLAs**  
394

395 **Q13. Will the holder of a deemed 351(a) BLA be subject to requirements under the PHS**  
396 **Act and FDA regulations for BLAs that are different from requirements for NDAs? If so,**  
397 **when will the requirements apply to deemed BLAs?**  
398

399 The holder of a deemed 351(a) BLA will be subject to applicable requirements under the PHS  
400 Act and FDA regulations. In general, FDA anticipates that a holder of an NDA for a biological  
401 product that is being deemed a 351(a) BLA will experience minimal disruption due to  
402 differences in requirements under the FD&C Act and PHS Act. FDA has taken measures to  
403 minimize differences in the review and approval of products required to have licensed BLAs  
404 under section 351(a) of the PHS Act and products required to have approved NDAs under  
405 section 505(b)(1) of the FD&C Act (see section 123(f) of the Food and Drug Administration  
406 Modernization Act of 1997 (FDAMA) (Public Law 105-115). However, there are certain  
407 statutory and regulatory requirements for biological products regulated under the PHS Act that  
408 differ from requirements for drug products regulated under the FD&C Act. FDA is committed to  
409 working with application holders to minimize any potential burden.

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410  
411 Labeling requirements for deemed BLAs, including certain differences between the requirements  
412 in the PHS Act and FD&C Act, are further described in Q15 below. The Agency’s compliance  
413 policy for the labeling of biological products that are the subject of deemed BLAs is described in  
414 section IV below.

415  
416 Biological products that are deemed to be licensed under section 351 of the PHS Act on March  
417 23, 2020, will be subject to chemistry, manufacturing, and controls (CMC) requirements  
418 applicable to products regulated under the PHS Act beginning on March 23, 2020. Holders of  
419 deemed BLAs should be aware that there are certain CMC-related requirements that differ  
420 between the PHS Act and FD&C Act. However, as further described in Q16 below, the burden  
421 related to these differences is expected to be minor.

422  
423 **Q14. Will the holder of a deemed BLA need to update the product labeling to conform to**  
424 **labeling requirements for BLAs?**

425  
426 The holder of a deemed BLA will need to revise the product labeling to conform to labeling  
427 requirements for biological products regulated under section 351 of the PHS Act. However,  
428 FDA acknowledges that holders of deemed BLAs may need time to revise their labeling to  
429 conform to such requirements and may not be able to make these revisions until receiving the  
430 information provided in the letter from FDA on the transition date. Accordingly, FDA generally  
431 does not intend to enforce these labeling requirements for deemed BLAs until March 23, 2025.  
432 The Agency’s compliance policy for the labeling of biological products that are the subject of  
433 deemed BLAs is described in section IV below. FDA recommends, in order to facilitate the  
434 implementation of the proposed revisions within that timeframe, that the holder of the deemed  
435 BLA submit a prior approval supplement (PAS) with proposed revised product labeling between  
436 March 23, 2020 (when the approved application under section 505 of the FD&C Act for the  
437 biological product is deemed to be a BLA), and March 23, 2022.

438  
439 Most labeling requirements for container labels, carton labeling, and prescribing information are  
440 the same for biological products currently regulated under the FD&C Act as they are for  
441 biological products regulated under the PHS Act. However, there are certain labeling  
442 requirements under the PHS Act and regulations for BLAs that differ from requirements under  
443 the FD&C Act and regulations for NDAs.

444  
445 The PHS Act requires that each “package” of a biological product is plainly marked with, among  
446 other things, “the proper name of the biological product contained in the package” and “the  
447 name, address, and applicable license number of the manufacturer of the biological product” in  
448 order for the biological product to be introduced or delivered for introduction into interstate  
449 commerce (see section 351(a)(1)(B) of the PHS Act; 21 CFR 610.61, 610.63, 610.64 and  
450 201.1(m)). The “package” means the “immediate carton, receptacle, or wrapper, including all  
451 labeling matter therein and thereon, and the contents of the one or more enclosed containers. If  
452 no package, as defined in the preceding sentence, is used, the container shall be deemed to be the  
453 package” (21 CFR 600.3(cc)).

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455 The holder of the deemed BLA will be required to revise product labeling (e.g., container labels,  
456 carton labeling, and prescribing information) so that biological products introduced or delivered  
457 for introduction into interstate commerce on or after March 23, 2020, are labeled with the proper  
458 name of the biological product, the name and address of the manufacturer (if not already  
459 provided), and the license number and otherwise conform to labeling requirements for biological  
460 products regulated under section 351 of the PHS Act (see section IV below for information about  
461 the Agency’s compliance policy). The FDA letter that notifies the application holder that its  
462 approved NDA is deemed to be a BLA on the transition date will provide the U.S. license  
463 number assigned to the application holder. The license authorizes the application holder to  
464 manufacture the biological product within the meaning of section 351 of the PHS Act and to  
465 introduce the biological product or deliver the biological product for introduction into interstate  
466 commerce. FDA will designate the *proper name* of the biological product in the license (see 21  
467 CFR 600.3(k) and Q21 below).

468  
469 There are additional requirements for the container labels and carton labeling for a biological  
470 product regulated under section 351 of the PHS Act (see 21 CFR 610.61; see also 21 CFR  
471 610.62 for requirements applicable to biological products that do not fall within the specified  
472 categories of biological products described in 21 CFR 601.2 (“non-specified biological  
473 products”). In the table below, we provide an overview of key changes from NDA labeling  
474 requirements for container labels and carton labeling that will apply to biological products in  
475 deemed BLAs.  
476

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477 Table. Selected Requirements for Container Labels and Carton Labeling for Biological Products

Labeling Information	Change From NDA Labeling Requirements That Will Apply to Biological Products in Deemed BLAs
New Information	
<b>Proper Name</b>	<p>Container labels and carton labeling must include the <i>proper name</i> of the biological product designated by FDA in the license (see 21 CFR 610.60(a)(1) and 610.61(a)).</p> <p>For non-specified biological products (e.g., pancrelipase, urofollitropin), the regulations provide more specific requirements for the position and prominence of the proper name, and the legibility of information on the package and container label (see 21 CFR 610.62).</p>
<b>Manufacturer Name and Address and License Number</b>	<p>The name and address of the manufacturer (i.e., the license holder) must appear on container labels and carton labeling in the format specified by the regulations (see 21 CFR 610.60(a)(2) and 610.61(b); see 21 CFR 610.63 for labeling requirements for divided manufacturing responsibility).</p> <ul style="list-style-type: none"> <li>• For containers capable of bearing only a partial label, only the proper name, the lot number or other lot identification, and the name of the manufacturer is required (see 21 CFR 610.60(c)).</li> <li>• The name and address of the distributor of the biological product may appear in addition to the name and address of the manufacturer. The qualifying phrases used for a distributor are the same for drug and biological products (compare 21 CFR 201.1(h)(5) with 21 CFR 610.64).</li> </ul> <p>Container labels and carton labeling must also include the license number of the manufacturer of the biological product (see 21 CFR 610.60(a)(2) and 610.61(b)).</p>
Information That May Currently Appear in Approved Prescribing Information	
<b>Preservative</b>	<p>Carton labeling must include the name of the preservative used (which already appears in the statement of ingredients on the carton of biological products approved under the FD&amp;C Act) and its concentration (see 21 CFR 610.61(e)).</p> <p>If no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” must appear on the carton labeling (see 21 CFR 610.61(e)).</p>
<b>Potency Statement</b>	<p>Carton labeling must include the minimum potency of product expressed in terms of official standard of potency (compare 21 CFR 610.61(r) with 21 CFR 201.51(a)).</p> <p>If potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency” must appear on the carton labeling (see 21 CFR 610.61(r)).</p>
<b>Source of the Product When a Factor in Safe Administration</b>	<p>Carton labeling must include the source of the product when a factor in safe administration, such as products made from sources that may be allergenic (see 21 CFR 610.61(p)).</p>

478  
479 Certain requirements for container labels and carton labeling (see, e.g., 21 CFR 610.60(a)(5) and  
480 (c), and 21 CFR 610.61(j)) can be addressed by including a statement that refers to the  
481 prescribing information and by including the required information in the prescribing information  
482 (see, e.g., 21 CFR 610.61(l), (n), and (q)).

483  
484 There also are certain differences in the content of prescribing information for biological  
485 products regulated under the PHS Act. The key differences for the prescribing information for a  
486 biological product regulated under the PHS Act are that the labeling must include the proper  
487 name of the biological product, including any appropriate descriptors (see 21 CFR 201.57(a)(2)),  
488 and the manufacturer name, address, and license number (see 21 CFR 610.60(a)(2) and  
489 610.61(b)). Conforming revisions also would need to be made to FDA-approved patient  
490 labeling. In addition, for biological products that are required to meet the content and format



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491 requirements of the Physician Labeling Rule (PLR) as described in 21 CFR 201.56(d) and  
492 201.57, the year used for the Initial U.S. Approval included in the Highlights of Prescribing  
493 Information (Highlights) differs for a biological product under the FD&C Act (i.e., the year of  
494 initial U.S. approval of the new molecular entity) and the PHS Act (i.e., the year of initial U.S.  
495 approval of the new biological product). Accordingly, the Initial U.S. Approval in the Highlights  
496 may need to be revised to reflect the year in which the first NDA for the biological product(s)  
497 described in the labeling was initially approved.

498  
499 The date of initial approval of the NDA (and not the date on which the NDA is deemed to be a  
500 BLA) and the date(s) of approval of efficacy supplement(s) will continue to govern the  
501 applicability of the labeling content and format requirements described by 21 CFR 201.56(d) and  
502 201.57. For NDAs that are not required to have labeling in PLR format, application holders may  
503 consider voluntarily converting the labeling to PLR format because the PLR format represents a  
504 more useful and modern approach for communicating information on the safe and effective use  
505 of products and makes prescription information more accessible for use with electronic  
506 prescribing tools and other electronic information resources.

507  
508 The holder of a deemed BLA for a biological product should submit all proposed revisions to  
509 product labeling necessary to conform to labeling requirements for biological products regulated  
510 under section 351 of the PHS Act (i.e., container labels, carton labeling, prescribing information,  
511 and patient labeling) together in the same PAS. To facilitate identification of the type of  
512 submission for the Agency, the applicant should mark clearly on the cover letter, “Deemed BLA  
513 Labeling Revisions.”

514  
515 **Q15. Are there different requirements related to CMC that will apply to a biological**  
516 **product in a deemed 351(a) BLA?**

517  
518 Certain CMC requirements and recommendations applicable to biological products regulated  
519 under the PHS Act may differ in some respects from CMC requirements and recommendations  
520 applicable to biological products regulated under the FD&C Act. However, FDA expects that in  
521 many instances the practical implications of such differences on holders of deemed BLAs will be  
522 minimal because the CMC requirements under both the PHS Act and the FD&C Act address  
523 many of the same types of CMC considerations for ensuring quality biological products. For  
524 example, FDA anticipates that most biological products subject to the transition provision, upon  
525 being deemed BLAs, will meet the related general BLA requirements (e.g., potency, sterility,  
526 purity, and identity) under the PHS Act based on the products having been previously approved  
527 under the FD&C Act.

528  
529 The holders of deemed BLAs may be required to report or provide different information than is  
530 required for biological products under the FD&C Act. In the sections below, we highlight a few  
531 such requirements, namely lot release, biological product distribution reports, and notification of  
532 manufacturing problems involving distributed products.

533  
534 Additionally, as with all biological products, FDA may recommend changes to the control  
535 strategy throughout the product life cycle to modernize control strategies, to address product-  
536 specific issues, and to help ensure that biological products remain safe, pure, and potent for their

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537 approved conditions of use. Furthermore, as with all biological products, these changes may be  
538 recommended as a result of postapproval or surveillance inspections, which are independent of a  
539 submission and generally expected to be similar for a biological product whether approved in an  
540 NDA prior to the transition date or licensed in a BLA. For inspections related to CMC  
541 supplements see Q16 below.

542  
543 FDA is committed to working with application holders to minimize any potential burden, and  
544 encourages application holders with any CMC-related questions to contact OPQ/Office of  
545 Program and Regulatory Operations (OPRO) at [CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov).

### 546 547 *1. Lot Release*

548  
549 FDA may require that a BLA holder submit samples and CMC data for each lot of product for  
550 FDA review and release (see 21 CFR 610.2). However, FDA generally does not anticipate that  
551 lot release requirements will apply for biological products approved in NDAs that are deemed to  
552 be BLAs.

553  
554 In 1995, FDA announced the elimination of lot-by-lot release for licensed well-characterized  
555 therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products (see  
556 “Interim Definition and Elimination of Lot-by-Lot Release For Well-Characterized Therapeutic  
557 Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products; Notice,” 60 FR  
558 63048; December 8, 1995). FDA subsequently amended 21 CFR 601.2 to specify, instead of the  
559 term “well characterized biotechnology product,” the categories of products to which lot-by-lot  
560 release would not be necessary (see “Elimination of Establishment License Application for  
561 Specified Biotechnology and Specified Synthetic Biological Products,” 61 FR 24227, May 14,  
562 1996). Most of the biological products subject to the transition provision will meet the  
563 description of products for which lot-by-lot release is not required. Furthermore, for biological  
564 products that do not fall into the categories specified in 21 CFR 601.2, FDA generally does not  
565 anticipate that lot-by-lot release will be needed. As stated in the 1995 FR notice, “once a  
566 company has demonstrated its ability to consistently produce acceptable lots, and has procedures  
567 in place that will prevent the release of lots that do not meet release specifications, it is not  
568 necessary for FDA to verify that each manufactured lot is acceptable for release” (60 FR 63048-  
569 49). FDA generally considers application holders for biological products subject to the transition  
570 provision as having demonstrated the “ability to consistently produce acceptable lots” and as  
571 having “procedures in place that will prevent the release of lots that do not meet release  
572 specifications” based on product history.

### 573 574 *2. Product Distribution Reports*

575  
576 FDA anticipates that all biological product application holders will have adequate records of the  
577 product distributed to the market. Although the frequency and content of distribution reporting  
578 required for products regulated under the FD&C Act and PHS Act differ, FDA expects these  
579 differences will present minimal burden to holders of deemed BLAs.

580  
581 Application holders of biological products affected by the transition provision should be aware  
582 that 21 CFR 600.81, which covers product distribution reporting for licensed BLAs, requires

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583 submission of more granular distribution data than is required for approved NDAs under 21 CFR  
584 314.81. However, FDA anticipates that affected application holders will generally already have  
585 the distribution information specified in 21 CFR 600.81. Additionally, 21 CFR 600.81 requires  
586 reporting every 6 months, in contrast to annual reporting. However, holders of deemed BLAs  
587 may request at any time, including within the first 6 months of being deemed a BLA, a waiver to  
588 provide product distribution reports annually (e.g., to align with the timing of the holder's  
589 Annual Report) rather than every 6 months (21 CFR 600.90). The requirements for a waiver  
590 request are described in 21 CFR 600.90.

591

### 592 3. *Notification of Manufacturing Problems Involving Distributed Products*

593

594 Regardless of whether a biological product has been approved under the FD&C Act or licensed  
595 under the PHS Act, application holders are required to report certain events that have the  
596 potential to affect the safety, purity, or potency of a distributed product. Under the FD&C Act,  
597 reporting of such events is through a field alert report (FAR) (see 21 CFR 314.81(b)(1)), while  
598 under the PHS Act, reporting is through a biological product deviation reports (BPDR) (see 21  
599 CFR 600.14). FDA expects the change in reporting between FAR and BPDR will present  
600 minimal burden to holders of deemed BLAs.

601

602 In particular, we note that under 21 CFR 600.14, application holders for biological products  
603 approved under the FD&C Act will be required, once the product is deemed to be licensed under  
604 a BLA, to report on events with the potential to affect the safety, purity, or potency of a  
605 distributed product by submission of BPDRs to CDER. Additionally, the BPDR is to be  
606 submitted as soon as possible but within 45 calendar days of acquiring information reasonably  
607 suggesting that a reportable event has occurred (rather than within 3 calendar days as is required  
608 in the case of a FAR).

609

#### 610 **Q16. What is required for CMC changes submitted in a PAS or changes being effected** 611 **supplements submitted to deemed 351(a) BLAs?**

612

613 FDA requires applicants or application holders of biological products—whether approved under  
614 the FD&C Act or licensed under the PHS Act—to notify FDA about each change in the  
615 conditions established in an approved application. The types of reporting categories for  
616 biological products generally are the same for an NDA (see 21 CFR 314.70) and for a BLA (see  
617 21 CFR 601.12), and in both cases, the applicant or application holder is expected to demonstrate  
618 that the postchange product continues to be of acceptable quality as it may relate to the safety or  
619 effectiveness of the product. Overall, the nature and type of data required to support such a  
620 demonstration has historically been similar for biological products approved under the FD&C  
621 Act or licensed under the PHS Act.

622

623 However, there are limited differences with respect to the timing and evaluation of certain data in  
624 submissions, and verification of these data during the review cycle and inspection varies. For  
625 example, validation data would be required to be submitted in BLA supplements to support  
626 certain postapproval changes (21 CFR 601.12).

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628 Application holders that intend to propose manufacturing changes are encouraged to contact  
629 OPQ/OPRO at [CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov). FDA is committed to working with  
630 application holders to minimize any potential burden.

631

### 632 1. *Data Necessary To Support a Process or Manufacturing Site Change*

633

634 Supplements to applications for biological products subject to the transition provision that  
635 remain under review after the transition date, including supplements submitted prior to the  
636 transition date, must comply with 21 CFR 601.12 and other applicable regulations. Applicants  
637 should also consult relevant guidances for biological products. A supplement submitted to a  
638 deemed BLA to support process or manufacturing site changes must contain, for the lots  
639 manufactured using the postchange process, manufacturing process validation data (see 21 CFR  
640 601.12). Specifically, process validation for a BLA should be performed at commercial  
641 manufacturing scale, prior to submission of a supplement. Process validation information should  
642 be included in the supplement as this may affect submission and implementation timelines of the  
643 changes for commercial distribution.

644

645 A supplement requesting approval of a proposed change to the manufacturing site for a  
646 biological product also must assess the effects of the change and contain sufficient information to  
647 support the safety, purity, and potency of material manufactured with the change (21 CFR  
648 601.12(a)(2); compare 21 CFR 314.70). In assessing the effects of the change, information  
649 demonstrating comparability of the pre and postchange material should also be submitted,  
650 consistent with the International Conference on Harmonisation Guideline on *Comparability of*  
651 *Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, Q5E*  
652 and the recommendations below.

653

#### 654 • Comparability data.

655

656 - The type and amount of data needed to support a comparability exercise depends on  
657 the extent of the changes and the potential risk to product quality. A robust control  
658 strategy for drug substance and drug product is critical in generating comparability  
659 data. For example, a potency assay that is accurate, precise, and reliable will  
660 facilitate the review of manufacturing changes. In some cases, in addition to the  
661 typical battery of release tests, extended characterization may be necessary for  
662 comparison, in particular for process changes that may affect purity, potency, or  
663 safety of the product.

664

#### 665 • Batch analysis data.

666

#### 667 • Appropriate stability data.

668

669 - Generally, limited real-time stability data for the postchange product and  
670 comparability study results, including stability data under accelerated and stressed  
671 storage conditions, are sufficient to leverage existing stability data to support the shelf  
672 life of the postchange product.

673

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674 As with all biological products, FDA may recommend changes to the control strategy throughout  
675 the product life cycle to modernize outdated assays, to address product-specific issues, and to  
676 help ensure that biological products remain safe, pure, and potent for their approved conditions  
677 of use.

678  
679 2. *Facility Inspections Related to Certain Supplements to a Deemed 351(a) BLA*  
680

681 Whether a biological product is regulated under the FD&C Act or the PHS Act, application  
682 holders for biological products should be ready for FDA inspections to assure such compliance  
683 with the conditions of approval.

684  
685 After March 23, 2020, supplements submitted to deemed BLAs, including supplements  
686 submitted prior to the transition date but with an action date after the transition date, must  
687 comply with the inspection requirements as specified in the relevant regulations in 21 CFR part  
688 600.

689  
690 In particular, supplements for site changes where facilities are added to the license or  
691 supplements for major manufacturing changes may be subject to an inspection. FDA intends to  
692 contact the holder of a deemed BLA to schedule an inspection during the review of the  
693 supplement. After March 23, 2020, holders of deemed BLAs that submit a site change or major  
694 manufacturing change supplement are advised that, as with the holder of any BLA, they should  
695 be ready for an inspection while in operation and manufacturing the product for which the  
696 change is requested during the supplement review timeframe.

697  
698 **Q17. Can the application holder for a deemed 351(a) BLA for a biological product**  
699 **originally approved through the 505(b)(2) pathway submit a supplement that relies,**  
700 **in part, on another licensed biological product?**

701  
702 Supplements to a deemed 351(a) BLA must meet the requirements of section 351(a) of the PHS  
703 Act and contain all required data and information necessary to demonstrate the safety, purity, and  
704 potency of the change to the biological product proposed in the supplement. The holder of a  
705 deemed BLA for a biological product originally approved through the 505(b)(2) pathway may  
706 not, for example, submit an efficacy supplement to the deemed 351(a) BLA that relies on FDA's  
707 finding of safety, purity, and potency for a related biological product for the indication or other  
708 condition of use for which approval is sought.

709  
710 This requirement also applies to a pending 505(b)(2) efficacy supplement to a stand-alone NDA  
711 and to a pending 505(b)(2) efficacy supplement to a 505(b)(2) application that will be  
712 administratively converted to a pending efficacy supplement to the corresponding deemed 351(a)  
713 BLA on the transition date. To obtain approval of the administratively converted supplement  
714 under section 351(a) of the PHS Act, the applicant generally will need to amend the supplement  
715 to provide the scientific data necessary to meet the requirements of section 351(a) of the PHS  
716 Act, or a right of reference to such data, for the change proposed in the supplement.  
717

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718 **Q18. Can a biological product approved in an NDA that is deemed to be a 351(a) BLA on**  
719 **the transition date subsequently be a “reference product” for a proposed biosimilar**  
720 **or interchangeable product?**

721  
722 A biological product approved in an NDA (including a 505(b)(2) application) that is deemed  
723 licensed under section 351(a) of the PHS Act may be a reference product for a 351(k) BLA. The  
724 term “reference product” is defined as the single biological product licensed under section 351(a)  
725 of the PHS Act against which a biological product is evaluated in an application submitted under  
726 section 351(k) of the PHS Act (see section 351(i)(4) of the PHS Act).

727  
728 Sponsors currently may request advice from FDA regarding proposed biosimilar or  
729 interchangeable product development programs that identify a biological product approved under  
730 section 505 of the FD&C Act as the intended reference product. A sponsor would be able to  
731 submit a 351(k) BLA that cites the biological product approved under section 505 of the FD&C  
732 Act as its reference product after the NDA for the biological product is deemed to be a 351(a)  
733 BLA.

734  
735 **Q19. Can an application holder for a biological product that is the subject of a “deemed”**  
736 **351(a) BLA seek a determination of biosimilarity or interchangeability under**  
737 **section 351(k) of the PHS Act to another biological product licensed under section**  
738 **351(a) of the PHS Act?**

739  
740 Any person (including an application holder for a biological product that is the subject of a  
741 “deemed” 351(a) BLA) may seek to establish the biosimilarity or interchangeability under  
742 section 351(k) of the PHS Act of a proposed biosimilar or interchangeable product to a  
743 biological product licensed or deemed licensed under section 351(a) of the PHS Act. FDA  
744 intends to work with applicants to address scientific or regulatory issues that may arise in the  
745 context of these 351(k) development programs, and to provide additional procedural information.  
746 Any sponsor or applicant may contact the relevant review division within the Office of New  
747 Drugs in FDA’s CDER to request advice on a 351(k) development program.

748  
749 **D. Transition of Biological Products from the Orange Book to the Purple Book**

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751 **Q20. Will any therapeutic equivalence evaluations for biological products previously**  
752 **listed in the Orange Book be reflected in the Purple Book?**

753  
754 No, the Purple Book does not include therapeutic equivalence evaluations as reflected in the  
755 Orange Book. The Purple Book identifies, among other things, whether a biological product  
756 licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to, or  
757 interchangeable with, an FDA-licensed biological reference product.

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## *Contains Nonbinding Recommendations*

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### **E. Designation of Proper Name**

#### **Q21. What will be the proper name for a biological product that has been approved in an NDA that is deemed to be a BLA?**

The *proper name* is the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act (section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k)). FDA intends to provide additional guidance regarding the nonproprietary name for biological products previously approved under section 505 of the FD&C Act that are deemed licensed under section 351(a) of the PHS Act.

### **IV. COMPLIANCE POLICY FOR REQUIREMENTS RELATED TO LABELING**

To minimize possible disruption to the distribution of biological products that are the subject of the transition provision and to minimize burden on holders of deemed BLAs, FDA generally does not intend to enforce certain labeling requirements for biological products regulated under section 351 of the PHS Act for the labeling of biological products that are the subject of deemed BLAs until March 23, 2025. The compliance policy set forth in this draft guidance would apply only as described below.

FDA generally does not intend to take action against holders of deemed BLAs for biological products that are introduced or delivered for introduction into commerce between March 23, 2020, and March 22, 2025, for which the package is not marked with:

- The proper name of the biological product contained in the package (provided that the current packaging is plainly marked with the established name of the biological product);
- The name and address of the manufacturer of the biological product (provided that the current packaging is plainly marked with the name and place of business of the manufacturer, packer, or distributor as required in 21 CFR 201.1);
- The applicable license number; or
- Other information required by 21 CFR 610.60 through 610.64, for which there is not a corresponding requirement under 21 CFR 201.1.

FDA also generally does not intend to take action against holders of deemed BLAs for biological products that are introduced or delivered for introduction into commerce between March 23, 2020, and March 22, 2025, for which the content and format of labeling required by 21 CFR 201.56, 201.57, 201.80, and/or 208.20, as applicable, does not include the following information:

- The proper name of the biological product, including any appropriate descriptors (provided that the current labeling uses the established name of the biological product);

## ***Contains Nonbinding Recommendations***

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- 804 • The name and address of the manufacturer of the biological product (provided that the  
805 current labeling includes the name and place of business of the manufacturer, packer, or  
806 distributor as required by 21 CFR 201.1);  
807
- 808 • The applicable license number; or  
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- 810 • For biological products with approved labeling in the format described by 21 CFR  
811 201.56(d) and 201.57 (PLR format), the year of Initial U.S. Approval of the new  
812 biological product (provided that the current labeling includes the year of Initial U.S.  
813 Approval of the new molecular entity).  
814

815 If the holder of a deemed BLA for a biological product submits a supplement with proposed  
816 revisions to product labeling during the compliance period and the required BLA-specific  
817 labeling revisions to container labels, carton labeling, and prescribing information referenced in  
818 this guidance have not already been made, such revisions would need to be made before the  
819 supplement could be approved (see, e.g., 21 CFR 610.60). A changes-being-effected (CBE-0)  
820 supplement may be submitted prior to submission of a prior approval supplement that includes  
821 the BLA-specific labeling revisions. However, the prior approval supplement would need to be  
822 approved before or concurrent with approval of the CBE-0 supplement. FDA also notes that the  
823 timing of BLA-specific revisions to the prescribing information should be coordinated with the  
824 corresponding revisions to the container labels and carton labeling for the biological product to  
825 ensure consistency among the different types of product labeling.  
826

827 Under this approach, holders of deemed BLAs may coordinate BLA-specific labeling updates  
828 with their plans for other proposed revisions to product labeling.  
829