
Interpretation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009

Guidance for Industry

**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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TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	2
	A. BPCI Act	2
	B. Transition Period for Certain Biological Products	4
III.	INTERPRETATION OF THE “DEEMED TO BE A LICENSE” PROVISION	4
	A. FDA’s Interpretation of Section 7002(e) of the BPCI Act	4
	1. <i>FDA Interprets section 7002(e)(4) to be Limited to Approved Applications</i>	5
	2. <i>Removal of Biological Products from the Orange Book on March 23, 2020</i>	8
	3. <i>Exclusivity</i>	9
	B. Recommendations for Sponsors of Proposed Protein Products Intended for Submission in an Application Under Section 505 of the FD&C Act	10
	1. <i>“Stand-Alone” New Drug Applications</i>	10
	2. <i>505(b)(2) Applications</i>	11
	APPENDIX	14

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Guidance for Industry¹

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

I. INTRODUCTION

This guidance describes FDA’s interpretation of the provision of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) under which an application for a biological product approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) as of March 23, 2020, will be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) on March 23, 2020. Specifically, this guidance describes FDA’s interpretation of the “deemed to be a license” provision in section 7002(e) of the BPCI Act for biological products that are approved under section 505 of the FD&C Act as of March 23, 2020 (the transition date). This guidance also provides recommendations to sponsors of proposed protein products intended for submission in an application that may not receive final approval under section 505 of the FD&C Act on or before March 23, 2020, to facilitate alignment of product development plans with FDA’s interpretation of section 7002(e) of the BPCI Act.

Although the majority of therapeutic biological products have been licensed under section 351 of the PHS Act, some protein products historically have been approved under section 505 of the FD&C Act (see the Appendix to this guidance for examples of such products). On March 23, 2010, the BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Public Law 111-148). The BPCI Act clarified the statutory authority under which certain protein products will be regulated by amending the definition of a “biological product”² in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² 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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polypeptide),”³ and describing procedures for submission of a marketing application for certain biological products.

The BPCI Act requires that a marketing application for a “biological product” (that previously could have been submitted under section 505 of the FD&C Act) must be submitted under section 351 of the PHS Act; this requirement is subject to certain exceptions during a 10-year transition period ending on March 23, 2020 (see section 7002(e)(1)-(3) and (e)(5) of the BPCI Act and section II of this guidance). On March 23, 2020 (i.e., the transition date), an approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for the biological product under section 351 of the PHS Act (see section 7002(e)(4) of the BPCI Act). This guidance sets forth FDA’s current interpretation of section 7002(e) of the BPCI Act.

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

II. BACKGROUND

A. BPCI Act

The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the BPCI Act). The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (commonly referred to as the “Hatch-Waxman Amendments”), which established abbreviated pathways for the approval of drug products under section 505(b)(2) and 505(j) of the FD&C Act. An abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the generally larger and typically more complex structure of biological products, as well as the processes by which such

³ FDA has described its interpretation of the statutory terms “protein” and “chemically synthesized polypeptide” in the amended definition of “biological product” in guidance. See draft guidance for industry *New and Revised Draft Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)*. When final, this guidance will represent FDA’s current thinking on this topic. FDA’s guidances for industry are available on the FDA Drugs guidance web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs web guidance page. In addition, in the *Federal Register* of December 12, 2018, FDA also 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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products are manufactured. Most biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

Section 351(k) of the PHS Act, added by the BPCI Act, sets forth, among other things, the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) defines “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” (section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the standard for “interchangeability,” an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

The BPCI Act also includes, among other provisions:

- A 12-year exclusivity period from the date of first licensure of certain reference products, during which approval of a 351(k) application referencing that product may not be made effective (see section 351(k)(7) of the PHS Act)
- A 4-year exclusivity period from the date of first licensure of certain reference products, during which a 351(k) application referencing that product may not be submitted (see section 351(k)(7) of the PHS Act)
- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product (see section 351(k)(6) of the PHS Act)
- Procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act (see section 351(l) of the PHS Act)

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B. Transition Period for Certain Biological Products

Section 7002(e) of the BPCI Act provides that a marketing application for a “biological product” (that previously would have been submitted under section 505 of the FD&C Act) *must* be submitted under section 351 of the PHS Act, subject to the following exception during the transition period described below:

- An application for a biological product *may* be submitted under section 505 of the FD&C Act not later than March 23, 2020, if the biological product is in a product class⁴ for which a biological product in such product class was approved under section 505 of the FD&C Act not later than March 23, 2010.
 - However, an application for a biological product *may not* be submitted under section 505 of the FD&C Act if there is another biological product approved under section 351(a) of the PHS Act that could be a “reference product”⁵ if such application were submitted under section 351(k) of the PHS Act.

An approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for the biological product under section 351 of the PHS Act (a “deemed Biologics License Application (BLA)”) on March 23, 2020.

III. INTERPRETATION OF THE “DEEMED TO BE A LICENSE” PROVISION

A. FDA’s Interpretation of Section 7002(e) of the BPCI Act

Section 7002(e) of the BPCI Act is directed primarily to the submission of an application for a biological product during the transition period ending on March 23, 2020.⁶ Though the transition scheme described in section 7002(e) of the BPCI Act culminates with the “deemed to be a license” provision in section 7002(e)(4), the statute is silent regarding the process for

⁴ 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 guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act*, at Q&A II.2).

⁵ 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).

⁶ General references in this guidance to “applications” submitted or approved under section 505 of the FD&C Act also may include abbreviated new drug applications (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.

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accomplishing the transition of approved new drug applications (NDAs) to deemed BLAs, or the implications of the deeming process on pending applications.⁷

1. FDA Interprets section 7002(e)(4) to be Limited to Approved Applications

Section 7002(e)(4) of the BPCI Act provides:

An approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) shall be deemed to be a license for the biological product under such section 351 [of the PHS Act] on the date that is 10 years after the date of enactment of [the BPCI Act].

Section 7002(e)(4) is explicitly limited to an **approved** application under section 505 of the FD&C Act. Moreover, while this provision explicitly provides that an approved application under section 505 of the FD&C Act shall be deemed to be a BLA **on** the transition date, the statute does not provide a means for deeming an approved NDA to be an approved BLA prior to, or after, the transition date.⁸ Finally, section 7002(e) of the BPCI Act does not provide a basis for the Agency to treat approved NDAs for biological products as both NDAs and BLAs after such applications are deemed to be BLAs. Therefore, FDA interprets section 7002(e) of the BPCI Act to plainly mean that, on March 23, 2020, only approved NDAs will be deemed to be BLAs. After March 23, 2020, the Agency will not approve any application submitted under section 505 of the FD&C Act for a biological product subject to the transition provision that is pending or tentatively approved.^{9,10} As a corollary, applications for biological products approved

⁷ In other legislation, Congress has described the implications of transitioning applications for drug products from one statutory scheme to another, while also describing the process that would be used in effecting the transition. See, e.g., section 107(c) of the Drug Amendments of 1962 (Pub. L. 87-781) (providing that all NDAs effective on the day immediately preceding the date of enactment of the Drug Amendments of 1962 shall be deemed approved as of the enactment date, and that the provision for withdrawal of approval of an application for lack of effectiveness generally would not apply to such deemed NDAs for a period of 2 years after the enactment date); section 125 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115) (repealing section 507 of the FD&C Act and providing that an application for an antibiotic drug approved under section 507 of the FD&C Act on the day before enactment of FDAMA shall, on and after the date of enactment, be considered to be an NDA submitted and filed under section 505(b) and approved under section 505(c) or an ANDA filed and approved under 505(j)).

⁸ Compare section 7002(e)(4) of the BPCI Act with section 125 of FDAMA (providing that an approved application for the marketing of an antibiotic drug under section 507 of the FD&C Act “shall, **on and after such date of enactment**, be considered to be an application that was submitted and filed under section 505(b) . . . and approved for safety and effectiveness under section 505(c)” (emphasis added)) and FDA’s guidance for industry *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act* (“All action letters must use the 505(b) or 505(j) templates, even for drugs that originally were submitted under section 507, but are the subject of Agency action on or after November 21, 1997.”).

⁹ Tentative approval means that an NDA or ANDA otherwise meets the requirements for approval under the FD&C Act but cannot be approved until the expiration of an applicable period of patent and/or exclusivity protection. A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA or ANDA (see 21 CFR 314.105; see also 21 CFR 314.107).

¹⁰ The fact that section 7002(e)(2) of the BPCI Act permits submission of an application under section 505 of the FD&C Act “not later than” the transition date does not change this conclusion. Section 7002(e)(2) is not

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under section 505 of the FD&C Act will no longer exist as NDAs and will be replaced by approved BLAs under section 351 of the PHS Act.¹¹

Accordingly, an original 505(b)(2) application (including a resubmission) for a biological product that relies, at least in part, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product will receive a complete response if the application is pending at the end of the day (11:59 pm Eastern Daylight Time (EDT)) on Friday, March 20, 2020, because the NDA for the listed drug relied upon will no longer exist at midnight on Monday, March 23, 2020. An original application (including a resubmission) for a biological product that has been submitted as a 505(b)(1) application (i.e., a "stand-alone" NDA) or a 505(b)(2) application that does not rely, to any extent, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product (e.g., a 505(b)(2) application that relies on non-product-specific published literature) and is pending at the end of the day (11:59 pm EDT) on March 23, 2020, will receive a complete response.¹² Such applications may, for example, be withdrawn and submitted under section 351(a) or 351(k) of the PHS Act, as appropriate. We provide an overview of key dates/times below and recommendations to minimize the impact on development programs for any proposed biological products intended for submission under section 505 of the FD&C Act that may not be able to receive final approval by March 23, 2020.

inconsistent with the interpretation set forth here because, among other things, Congress presumably is aware that approval decisions can take a variable amount of time, and thus did not settle on a date by which such submissions would no longer be permitted. Moreover, if Congress meant to allow for pending applications submitted under section 505 of the FD&C Act to be deemed BLAs after the transition, it knew how to do so explicitly. See section 125 of FDAMA, *supra* note 8.

¹¹ See FDA's draft guidance for industry *The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers* (Transition Q&A Draft Guidance) for additional information, including whether an approved application for a biological product under section 505 of the FD&C Act will be deemed a license for the biological product under section 351(a) or 351(k) of the PHS Act and administrative issues associated with the transition (including BLA numbers and user fee questions). When final, that guidance will represent FDA's current thinking on this topic.

¹² An applicant who seeks to obtain final approval of a tentatively approved NDA for a biological product on or before March 23, 2020, would need to submit an amendment requesting final approval. FDA recommends that the amendment should be submitted by a date that allows adequate time for FDA review and approval before March 23, 2020. Please refer to the recommended timeframes provided in the tentative approval letter and any applicable guidance for further information and contact the relevant review division with any questions (including questions about whether an inspection may be needed). An amendment requesting final approval of a tentatively approved application should provide the legal/regulatory basis for the request for final approval and should include a copy of any relevant court action, written consent to approval by the patent owner or exclusive patent licensee, or waiver of exclusivity by the relevant NDA holder, as appropriate, that has not been submitted previously to FDA under 21 CFR 314.107(e). In addition to a safety update, the amendment should identify whether there are any changes in the conditions under which the product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and, as applicable, Risk Evaluation and Mitigation Strategy (REMS). Any changes require FDA review before final approval and the goal date for FDA review will be set accordingly.

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Table: Overview of Key Dates/Times Related to the Statutory Transition Provision

Date/Time	Relevant Application Type	Event
Friday, March 20, 2020, 11:59 pm (EDT)	Pending 505(b)(2) applications that rely, at least in part, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product	Deadline for any pending 505(b)(2) application of this type to be approved under the FD&C Act.
Monday, March 23, 2020, 12:00 am (EDT)	Approved NDAs for biological products	Approved NDAs for biological products are deemed to be BLAs, and cease to exist as NDAs.
Monday, March 23, 2020, 12:01 am (EDT)	351(k) BLA that relies on a deemed BLA for its reference product	A 351(k) BLA can be submitted for a proposed biosimilar or a proposed interchangeable to a biological reference product that is the subject of a deemed BLA.
Monday, March 23, 2020, during hours in which FDA is open for business	Approved NDAs for biological products	FDA intends to send a letter to each holder of an approved NDA for a biological product that advises that the approved NDA has been deemed to be a BLA by operation of the statute, and no longer exists as an NDA. FDA intends to update the Orange Book to remove biological product listings.
Monday, March 23, 2020, 11:59 pm (EDT)	Pending 505(b)(1) applications and pending 505(b)(2) applications that do not rely, to any extent, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product	Deadline for any pending 505(b)(1) application or any pending 505(b)(2) application of this type to be approved under the FD&C Act. An NDA approved on March 23, 2020, will be deemed to be a BLA immediately after approval under the FD&C Act.

FDA intends to assist applicants who may be affected by section 7002(e) of the BPCI Act, where feasible and appropriate. For example, during the review of a BLA submitted after the transition date under section 351(a) or 351(k) of the PHS Act for a proposed biological product that was previously submitted, but not approved, in an application under section 505 of the FD&C Act, FDA intends to consider any previously conducted scientific review by the Agency of such previous application under the FD&C Act, to the extent that such review is relevant to, and consistent with, applicable requirements of section 351 of the PHS Act.

An application generally includes all amendments and supplements to the application.¹³ We recognize that there may be one or more supplements submitted to an approved NDA for a biological product before March 23, 2020, that is pending on March 23, 2020. Such supplements may include a prior approval supplement (e.g., an efficacy supplement,¹⁴ a labeling supplement,

¹³ See 21 CFR 314.3(b) (definition of *application*).

¹⁴ An efficacy supplement is a supplement to an approved NDA proposing to make one or more related changes from among the following changes to product labeling: (1) Add or modify an indication or claim; (2) Revise the dose or dose regimen; (3) Provide for a new route of administration; (4) Make a comparative efficacy claim naming

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or a manufacturing supplement), a supplement for changes being effected (CBE) in 30 days (for certain chemistry, manufacturing, and controls changes), or a supplement for changes being effected upon receipt by the Agency of the supplement (for certain safety-related labeling changes or any other labeling change that FDA specifically requests to be submitted in a CBE supplement).¹⁵ At the time that FDA deems the approved NDA for a biological product to be a BLA on the transition date, FDA intends to also administratively convert any pending supplement to such approved NDA to a pending supplement to the deemed BLA, and to review such supplements under applicable standards for BLAs. For example, a pending “stand-alone” efficacy supplement to a “stand-alone” NDA¹⁶ (e.g., a supplement intended to address a post-approval requirement or post-approval commitment) will be administratively converted to a pending efficacy supplement to the corresponding deemed 351(a) BLA on the transition date and reviewed under applicable standards for 351(a) BLAs. Similarly, a pending CBE supplement to an application submitted under the FD&C Act will be administratively converted to a pending CBE supplement to the deemed BLA on the transition date, irrespective of whether the change described in the CBE supplement has been implemented before or after the transition date. The Agency also intends to maintain the same goal date, where applicable, for completion of its review of such supplements.

2. Removal of Biological Products from the Orange Book on March 23, 2020

FDA intends to remove biological products that have been approved in NDAs from FDA’s *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book)¹⁷ on March 23, 2020, based on the Agency’s position that these products are no longer “listed drugs” and such NDAs may not be relied upon by a 505(b)(2) applicant (or ANDA applicant) for approval. After March 23, 2020, FDA will not approve any NDA (or ANDA), including those that are pending or tentatively approved, for a biological product.

Moreover, with the exception of orphan drug exclusivity and pediatric exclusivity, the exclusivity provisions of the FD&C Act serve to limit the submission or approval of applications under section 505 of the FD&C Act, but not under section 351 of the PHS Act. Section 7002(e) of the BPCI Act provides that no applications for biological products may be submitted under section 505 of the FD&C Act after the transition date. Accordingly, on March 23, 2020, any unexpired period of exclusivity associated with an approved NDA for a biological product subject to section 7002(e) of the BPCI Act (e.g., 5-year exclusivity or 3-year exclusivity) would

another drug product; (5) Significantly alter the intended patient population; (6) Change the marketing status from prescription to over-the-counter use; (7) Provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of part 314; or (8) Incorporate other information based on at least one adequate and well-controlled clinical study (21 CFR 314.3(b)).

¹⁵ See generally 21 CFR 314.70.

¹⁶ See section III.B.1 of this guidance for information on “stand-alone” NDAs. There may be additional considerations for a pending 505(b)(2) efficacy supplement to a stand-alone NDA and a pending 505(b)(2) efficacy supplement to a 505(b)(2) application.

¹⁷ Biological products approved in NDAs that are deemed to be BLAs will be listed in FDA’s *Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations* (the Purple Book) on or shortly after the March 23, 2020, transition date.

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cease to have any effect, and any patents listed in the Orange Book would no longer be relevant for purposes of determining the timing of approval of a 505(b)(2) application (or ANDA). However, any unexpired period of orphan drug exclusivity would continue to apply to the biological product for the protected use after the transition date, because orphan drug exclusivity can block the approval of a drug approved under section 505 of the FD&C Act or a biological product licensed under section 351 of the PHS Act (see section 527 of the FD&C Act (21 U.S.C. 360cc)). Similarly, any unexpired period of pediatric exclusivity associated with an approved NDA for a biological product would continue to apply to a deemed 351(a) BLA on and after March 23, 2020, provided that the conditions in section 351(m) of the PHS Act are met. Any post-approval requirements or post-approval commitments, including any pediatric assessments necessary to comply with the Pediatric Research Equity Act (PREA) (Public Law 108-155), also would transfer to the deemed BLA.

3. *Exclusivity*

FDA interprets section 7002(e) of the BPCI Act and section 351 of the PHS Act to mean that an approved NDA for a biological product that will be *deemed* to be “licensed” under section 351(a) of the PHS Act on March 23, 2020, can be a reference product for a proposed biosimilar product or a proposed interchangeable product (see section 351(i)(4) of the PHS Act). However, a biological product that was first approved in an NDA under section 505 of the FD&C Act and deemed “licensed” under section 351(a) of the PHS Act on March 23, 2020, will not have been “first licensed under subsection (a)” for purposes of section 351(k)(7) of the PHS Act. Thus, such a biological product will not be eligible for exclusivity under section 351(k)(7)(A) and (B) of the PHS Act.

Section 351(k)(7)(A) and (B) of the PHS Act describe a 12-year exclusivity period during which FDA may not approve a 351(k) application and a 4-year exclusivity period during which an applicant may not submit a 351(k) application (“reference product exclusivity”). Except as provided in section 351(k)(7)(C) of the PHS Act, these periods begin on “the date on which the reference product was first licensed under subsection (a) [referring to section 351(a) of the PHS Act].” However, section 351(k)(7)(C) of the PHS Act provides that reference product exclusivity shall not apply to a license for or approval of:

- A supplement for the biological product that is the reference product; or
- A subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) under the conditions set forth in section 351(k)(7)(C) of the PHS Act.¹⁸

Nothing in the Biologics Price Competition and Innovation Act suggests that Congress intended for biological products approved under section 505 of the FD&C Act — some of which were approved decades ago — to obtain a 12-year period of reference product exclusivity upon being

¹⁸ See section 351(k)(7)(C) of the PHS Act and FDA’s guidance for industry *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*. When final, this guidance will represent FDA’s current thinking on this topic.

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deemed to be licensed under section 351(a) of the PHS Act. Reference product exclusivity recognizes the fact that the sponsor of an eligible reference product generated (and submitted for review) the data and information required to obtain a license under section 351(a) of the PHS Act and limits competition from biosimilar and interchangeable products for a limited period of time. The biological products that will be deemed to have BLAs on the transition date, however, have already obtained marketing approval under a different statutory authority. Allowing such products to obtain a separate 12-year period of reference product exclusivity would inappropriately impede biosimilar or interchangeable product competition in several product classes.

Recognizing these principles, FDA interprets section 7002(e) of the BPCI Act together with section 351(k)(7) of the PHS Act such that section 351(k)(7)(A)-(B) of the PHS Act applies only to products that have undergone review and licensing under section 351(a), and not to biological products that will be deemed licensed under section 351(a) of the PHS Act on the transition date. At the same time, FDA interprets the limitations on eligibility for reference product exclusivity in section 351(k)(7)(C) of the PHS Act to apply to any “reference product,” without regard to whether such product was “first licensed under subsection (a)” or instead deemed to be a license under section 7002(e) of the BPCI Act. Nothing in the BPCI Act suggests that Congress intended holders of deemed BLAs to be able to circumvent the statutory limitations on eligibility for a 12-year period of reference product exclusivity through subsequent submissions simply because the previous reference product was deemed to be licensed under section 7002(e). Therefore, FDA interprets section 351(k)(7) of the PHS Act together with section 7002(e) of the BPCI Act such that section 351(k)(7)(C) will operate to bar supplements to deemed BLAs and, where applicable, subsequent BLAs from being eligible for their own periods of reference product exclusivity.

B. Recommendations for Sponsors of Proposed Protein Products Intended for Submission in an Application Under Section 505 of the FD&C Act

Sponsors of development programs for proposed protein products should evaluate whether a planned submission under section 505 of the FD&C Act would allow adequate time for approval of the application prior to March 23, 2020, considering, among other things, whether the submission may require a second cycle of review and, for certain types of applications, whether unexpired patents or exclusivity may delay final approval. FDA’s recommendations for sponsors are based on whether a “stand-alone” or abbreviated development program is planned.

1. “Stand-Alone” New Drug Applications

An application submitted under section 505(b)(1) of the FD&C Act (i.e., a “stand-alone” NDA) contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use. Sponsors of a proposed protein product intended for submission in an NDA under section 505(b)(1) of the FD&C Act should consider submitting a BLA under section 351(a) of the PHS Act. A 351(a) BLA for a biological product can be submitted before, on, or after March 23, 2020. Sponsors can contact

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the relevant review division within the Office of New Drugs in FDA's CDER with any questions about a BLA submission.¹⁹

2. *505(b)(2) Applications*

A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., FDA's finding of safety and/or effectiveness for a listed drug or published literature). A 505(b)(2) application that seeks to rely on a listed drug must contain adequate data and information to demonstrate that the proposed product is sufficiently similar to the listed drug to justify reliance, in part, on FDA's finding of safety and/or effectiveness for the listed drug. Any aspects of the proposed product that differ from the listed drug must be supported by adequate data and information to support the safety and effectiveness of the proposed product.

Congress did not provide an approval pathway under the PHS Act that directly corresponds to section 505(b)(2) of the FD&C Act. Accordingly, there are additional considerations for sponsors of proposed protein products intended for submission in a 505(b)(2) application or a 505(b)(2) efficacy supplement, and sponsors may contact the relevant review division with any questions. If a sponsor anticipates that a planned 505(b)(2) application or 505(b)(2) efficacy supplement may not receive final approval before the transition date (e.g., due to the need for a second cycle of review, applicable unexpired exclusivity or listed patents, or a stay of approval due to patent infringement litigation), the sponsor should consider the following options:

- Modifying the development program to support submission of an application or efficacy supplement under section 351(a) of the PHS Act (i.e., a "stand-alone" BLA) before or after March 23, 2020. This may involve, for example, obtaining a right of reference from the application holder for the listed drug on which the proposed 505(b)(2) application or 505(b)(2) efficacy supplement would have relied or conducting studies with the proposed product to provide the scientific data that otherwise would have been relied upon to support approval of the application or the change proposed in the supplement, as applicable.²⁰
- Modifying the development program to support submission of a 351(k) BLA for a proposed biosimilar product or a proposed interchangeable product at such time as there is a biological product licensed under section 351(a) of the PHS Act that could be a reference product.

¹⁹ FDA has taken measures to minimize differences in the review and approval of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FD&C Act (see section 123(f) of FDAMA). However, certain differences continue to exist. For additional information on how FDA intends to address these issues, see the Transition Q&A Draft Guidance or contact the relevant review division. When final, this guidance will represent FDA's current thinking on this topic.

²⁰ FDA has issued guidance for industry on *Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs* and is considering how the concepts described in the guidance would apply to proposed pancreatic enzyme products submitted under the PHS Act.

Contains Nonbinding Recommendations

Sponsors evaluating whether a proposed product could be submitted under section 351(k) of the PHS Act should consider whether they would be able to provide information demonstrating that, among other things, the proposed product:

- Is “highly similar” to a single reference product licensed under section 351(a) of the PHS Act, and that there are “no clinically meaningful differences” between the proposed product and the reference product in terms of safety, purity, and potency;
- Has the same route of administration, dosage form, and strength as the reference product;
- Utilizes the same mechanism(s) of action as the reference product for the proposed condition(s) of use (but only to the extent that the mechanism(s) of action are known); and
- Seeks licensure for a condition(s) of use (e.g., indication, dosing regimen) previously approved for the reference product.²¹

A sponsor of a proposed biological product that could meet the requirements for a proposed biosimilar and other applicable requirements would be able to submit a 351(k) BLA that cites the listed drug as its reference product after the NDA for the listed drug is deemed to be a BLA (or after another product that could be a reference product for the proposed product is licensed under section 351(a) of the PHS Act). Sponsors that intend to adapt their development programs to meet the requirements for a submission under section 351(k) of the PHS Act can request meetings with FDA, including a Biosimilar Biological Product Development (BPD) Type 3 meeting, before March 23, 2020, to support the development and review of a proposed biosimilar product or a proposed interchangeable product. Such meetings may be based on relevant comparative data with a listed drug that is the “intended reference product” (i.e., the listed drug that is intended to be the reference product after the NDA for such drug is deemed to be licensed under section 351(a) of the PHS Act).

Proposed products that are intended to differ in certain respects (e.g., different dosage forms, routes of administration, strengths, or conditions of use) from a previously approved product likely would need to be submitted under section 351(a) of the PHS Act and meet applicable statutory and regulatory requirements for a 351(a) BLA. Such products likely would be unable to use the 351(k) pathway to abbreviate their development program due to lack of a reference product or the inability to meet the statutory requirements for a proposed biosimilar product.

A sponsor may contact the relevant review division within the Office of New Drugs in FDA’s CDER to request advice on a product-specific basis regarding the development of a protein product intended for submission in an application under the FD&C Act (during the transition

²¹ See section 351(k) of the PHS Act; see also, generally, FDA’s guidance documents on biosimilar products.

Contains Nonbinding Recommendations

period described in section 7002(e) of the BPCI Act) or under section 351(a) or 351(k) of the PHS Act, as appropriate.²²

²² For information on requesting a formal meeting regarding the development of a proposed biosimilar product intended for submission under section 351(k) of the PHS Act, see FDA's draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*. For information on requesting a formal meeting regarding the development of a biological product intended for submission in an NDA before March 23, 2020, or in a 351(a) BLA, see FDA's draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, these guidances will represent FDA's current thinking on these topics.

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APPENDIX

Examples of Biological Products That Have Been Approved Under the FD&C Act

chorionic gonadotropin products
desirudin products
follitropin products, urofollitropin products, and menotropins products
hyaluronidase products
imiglucerase products
insulin products, insulin mix products, and insulin analog products (e.g., insulin aspart, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro products)
mecasermin products
pancrelipase products
pegademase products
pegvisomant products
sacrosidase products
somatropin products
taliglucerase alfa products and velaglucerase alfa products
thyrotropin alfa products