Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Janice Weiner at 301-796-3601 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2016
Procedural

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance describes FDA's approach to implementation 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) on or before 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 have been or will be approved under section 505 of the FD&C Act on or before March 23, 2020. 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 changed the statutory authority under which certain

[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.

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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 polypeptide)."[3]

The BPCI Act requires that a marketing application for a "biological product" 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, 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 Act"), which established abbreviated pathways for the approval of drug products under section 505(b)(2) and 505(j) of the FD&C Act. The implementation of an abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger

[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)).

[3] FDA has interpreted the statutory terms "protein" and "chemically synthesized polypeptide" to implement the amended definition of "biological product." As explained in FDA's guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (Biosimilars Q&A Guidance), the term "protein" means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size. The term "chemically synthesized polypeptide" means any alpha amino acid polymer that (1) is made entirely by chemical synthesis and (2) is less than 100 amino acids in size. A "chemically synthesized polypeptide," as defined, is not a "biological product" and will be regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory definition of a "biological product" (see Q&A II.1 in the Biosimilars Q&A Guidance).

and typically more complex structure of biological products, as well as the processes by which such 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 additional standard of "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 the reference product, 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 the reference product, 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)

B. Transition Period for Certain Biological Products

Section 7002(e) of the BPCI Act provides that a marketing application for a "biological product" ***must*** be submitted under section 351 of the PHS Act, subject to the following exception during a transition period ending on March 23, 2020:

- 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 class[4] 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 a biological product under section 351 of the PHS Act on March 23, 2020.

III. IMPLEMENTATION 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 to the requirements for submission of an application for a biological product during the transition period ending on March 23, 2020. The linchpin of the transition scheme described in section 7002(e) of the BPCI Act is the "deemed to be a license" provision in section 7002(e)(4); however, the statute is silent regarding implementation.[6]

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[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 Q&A II.2 in the Biosimilars Q&A Guidance).

[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] In other legislation, Congress has described the implications of transitioning applications for drug products from one statutory scheme to another and has provided for the process that would be used in effecting the transition (see section 107(c) of the Drug Amendments of 1962 (Public Law 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 two years after the enactment date); see also section 125 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 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))).

Section 7002(e)(4) 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].

FDA interprets this provision to mean that on March 23, 2020, applications for biological products that have been approved under section 505 of the FD&C Act will no longer exist as New Drug Applications (NDAs) (or, as applicable, Abbreviated New Drug Applications (ANDAs)) and will be replaced by approved Biologics License Applications (BLAs) under section 351(a) or 351(k) of the PHS Act, as appropriate.[7] The "deemed to be a license" provision takes effect "on the date that is 10 years after the date of enactment of this [BPCI] Act." Section 7002(e)(4) of the BPCI Act does not provide a mechanism to transition an approved application under section 505 to an approved BLA under the PHS Act prior to March 23, 2020, or after March 23, 2020.[8]

Section 7002(e)(4) also is explicitly limited to an ***approved*** application under section 505 of the FD&C Act. FDA interprets this provision to mean that the Agency will not approve any application under section 505 of the FD&C Act for a biological product subject to the transition provisions that is pending or tentatively approved[9] "on" March 23, 2020, even though section 7002(e)(2) of the BPCI Act expressly permits submission of an application under section 505 of the FD&C Act "not later than" March 23, 2020, if certain criteria are met.[10] Therefore, an application for a protein product that has been submitted under section 505 of the FD&C Act and is pending on March 23, 2020, will not be able to be approved. Such an application may, for

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[7] FDA intends to provide additional guidance regarding its approach for determining 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 for handling administrative issues associated with the transition (including BLA numbers and user fee questions).

[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 due to an unexpired period of orphan drug exclusivity, or that a 505(b)(2) application 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).

[10] See King v. Burwell, 135 S.Ct. 2480, at 2492 (2015) ("The Affordable Care Act contains more than a few examples of inartful drafting.").

example, be withdrawn and resubmitted under section 351(a) or 351(k) of the PHS Act, as appropriate. We recognize that this interpretation could have a significant impact on development programs for any proposed protein products intended for submission under section 505 of the FD&C Act that are not able to receive final approval by March 23, 2020, and provide recommendations to sponsors below.

Section 7002(e) of the BPCI Act does not explicitly provide a basis for the Agency to treat approved NDAs or ANDAs for biological products as both NDAs and BLAs after such applications are deemed to be BLAs on March 23, 2020. Thus, FDA intends to remove NDAs (and, as applicable, ANDAs) for biological products from FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) 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 pending or tentatively approved 505(b)(2) application (or ANDA) for a biological product that relied on an approved NDA that was deemed to be a BLA on March 23, 2020.

Moreover, with the exception of orphan drug 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 March 23, 2020. Under the interpretation described above, the Agency will not approve any applications for biological products under section 505 of the FD&C Act that are pending or tentatively approved after March 23, 2020. Accordingly, 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, 3-year exclusivity, or pediatric exclusivity) would 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 drug for the protected use after March 23, 2020, because orphan drug exclusivity can be granted to and 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)). 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 BLA.

Finally, FDA interprets section 7002(e) of the BPCI Act and section 351(k)(7) of the PHS Act to mean that an approved application for a biological product under section 505 of the FD&C Act that will be *deemed* to be a license for the biological product 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, and thus will not receive a period of exclusivity under section

351(k)(7)(A) and (B) of the PHS Act.[11] 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 that begin on "the date on which the reference product was first licensed under subsection (a) [referring to section 351(a) of the PHS Act]." Nothing in the BPCI Act suggests that Congress intended to grant biological products approved under section 505 of the FD&C Act — some of which were approved decades ago — a period of exclusivity upon being deemed to have a license under the PHS Act that would impede biosimilar or interchangeable product competition in several product classes until the year 2032. Therefore, FDA interprets section 7002(e) of the BPCI Act together with section 351(k)(7) of the PHS Act such that the phrase "the date on which the reference product was first licensed under subsection (a)" in section 351(k)(7)(A) and (B) of the PHS Act does not apply to biological products that will be deemed to have a license under section 351(a) of the PHS Act on March 23, 2020.

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 NDA (or, as applicable, ANDA) 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 proposed protein products intended for submission in an NDA under section 505(b)(1) of the FD&C Act should consider submitting an application under section 351(a) of the PHS Act. Sponsors can contact the relevant review division within the Office of New Drugs in FDA's CDER with any questions about a BLA submission.[12]

[11] The applicability of section 351(k)(7)(A) and (B) of the PHS Act to BLA supplements and subsequent applications filed by the same sponsor or manufacturer after March 23, 2020, will be governed by section 351(k)(7)(C) of the PHS Act.

[12] 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, for sponsors of proposed protein products who intend to submit a BLA, it should be noted that a Type II Drug Master File (DMF) for a drug substance, drug substance intermediate, or drug product would not be acceptable for a BLA because a license holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. FDA is considering a mechanism that, in limited circumstances, would allow holders of approved applications under section 505 of the FD&C Act that reference a type II DMF to continue to reference the DMF after the application is deemed to be a license under the PHS Act on March 23, 2020. Other types of contract manufacturing arrangements

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. The timing of approval for a 505(b)(2) application is subject to applicable patent and marketing exclusivity protections.

Congress did not provide an approval pathway under the PHS Act that precisely 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. If a sponsor anticipates that a planned 505(b)(2) application may not receive final approval on or before March 23, 2020 (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 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 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.[13]

- 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.

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:

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can be considered if the sponsor does not intend to manufacture the product for licensure (see FDA's guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics*). For additional information regarding other requirements for BLAs, including potency assays and manufacturing processes, manufacturing facilities, and inspection information, please contact the relevant review division.

[13] 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.

- 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)

- seeks licensure for a condition(s) of use (e.g., indication, dosing regimen) previously approved for the reference product[14]

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 submit comparative data with a listed drug that subsequently is deemed to be licensed under section 351(a) of the PHS Act.[15]

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

[14] See section 351(k) of the PHS Act; see also, generally, FDA's guidance documents on biosimilar products.

[15] Considerations similar to those described for 505(b)(2) applications would apply to any applications submitted under section 505(j) during the transition period.

Appendix

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

chorionic gonadotropin products
desirudin products
hyaluronidase products
insulin products, insulin mix products, and insulin analog products (e.g., insulin aspart, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro products)
pancrelipase products
pegvisomant products
somatropin products
thyrotropin alfa products