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DRAFT GUIDANCE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)

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Questions and Answers
Guidance for Industry

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The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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This draft guidance is intended to provide answers to common questions about FDA's interpretation of the "transition" provision of the Biologics Price Competition and Innovation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 (the transition date). This guidance also describes FDA's compliance policy for the labeling of biological products that are the subject of deemed biologics license applications (BLAs). This guidance is intended to facilitate planning for the transition date and provide further clarity regarding the Agency's interpretation of this statutory provision.

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. 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 polypeptide)," 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

[1] 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.

[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)).

period ending on March 23, 2020 (see section 7002(e)(1)-(3) and (e)(5) of the BPCI Act). 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).

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 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).

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 could 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 class[3] 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"[4] 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 (a "deemed BLA") on March 23, 2020. For additional information about FDA's interpretation of this "transition" provision, please refer to FDA's guidance for industry *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (Transition Policy Final Guidance).

[3] 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.

[4] 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).

III. QUESTIONS AND ANSWERS

A. Identification of Products Subject to the Transition Provision

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

The "deemed to be a license" provision of the BPCI Act (also known as the transition provision) will apply on March 23, 2020, to approved applications for a biological product under section 505 of the FD&C Act.[5] The BPCI Act amended the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)."

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

[5] 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.

[6] 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 (Docket No. FDA-2011-D-0611)).

[7] 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.

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

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

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

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

To enhance transparency and facilitate planning for the transition date, FDA is posting on the FDA website a preliminary list of approved applications for biological products under the FD&C Act (as of May 31, 2018) that will be affected by the transition provision, and FDA intends to periodically update the list before the transition date (see Q1 above). Biological products approved in NDAs that are deemed to be BLAs will be removed from *FDA's Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) on March 23, 2020, and 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.

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

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

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

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

FDA provided notice to sponsors of proposed biological products intended for submission in an application under section 505 of the FD&C Act that they will be affected by the transition provision through FDA's draft guidance for industry *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (Transition Policy Draft Guidance) and the Biosimilars Q&A Guidances. In the Biosimilars Q&A Guidances, FDA stated its interpretation of the statutory terms "protein" and "chemically synthesized polypeptide" in the amended definition of "biological product" (see Q1 above). In the Transition Policy Final Guidance, FDA 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. FDA recommends that sponsors of development programs for proposed protein products 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. If a sponsor is unsure whether its proposed product may receive approval under the FD&C Act by March 23, 2020, the sponsor should consider submitting a BLA under section 351(a) or 351(k) of the PHS Act instead. For additional information, please see the Transition Policy Final Guidance.

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

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

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

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

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

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

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

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

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

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 and is silent regarding whether an approved NDA will be deemed to be a 351(a) BLA or a 351(k) BLA. The Agency's interpretation that an NDA submitted under section 505(b)(1) of the FD&C Act will be deemed to be a 351(a) BLA is based on the shared requirement that both types of applications contain full reports of investigations of safety and effectiveness (or, for a 351(a) BLA, safety, purity, and potency). We expect that the measures FDA has taken to minimize differences in the review and approval of products in marketing applications submitted under section 351(a) of the PHS Act

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

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). As noted above, the Agency's interpretation that an approved 505(b)(2) application will be deemed to be a 351(a) BLA reflects the shared requirement that both types of applications contain full reports of investigations of safety and effectiveness (or, for a 351(a) BLA, safety, purity, and potency). This approach also reflects the Agency's view that it is more appropriate to regulate a biological product approved through the 505(b)(2) pathway that may be intended to differ in certain respects (e.g., different strength, dosage form, or route of administration or approved conditions of use) from a previously approved product under the statutory and regulatory framework for 351(a) BLAs, as these differences are not permitted under the statutory framework for 351(k) BLAs. Moreover, FDA's approval of a 505(b)(2) application reflects the Agency's evaluation of the data against a different statutory standard than a determination of biosimilarity or interchangeability under section 351(k) of the PHS Act.

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

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

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

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

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

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

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

- The applicant previously submitted an NDA for the same product and paid the associated PDUFA application fee for the NDA.

- The NDA was accepted for filing. (Note that an NDA for a biological product will not be accepted for filing after the transition date.)

- The NDA was not approved or was withdrawn (without a waiver).

For questions regarding user fees, please contact the User Fee Staff at CDERCollections@fda.hhs.gov or 301-796-7900.

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

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

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

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

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

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

C. Statutory and Regulatory Requirements for BLAs

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

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

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

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

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

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

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

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

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

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

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
Proper Name	Container labels and carton labeling must include the *proper name* of the biological product designated by FDA in the license (see 21 CFR 610.60(a)(1) and 610.61(a)). 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).
Manufacturer Name and Address and License Number	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). • 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)). • 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). 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)).
	Information That May Currently Appear in Approved Prescribing Information
Preservative	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&C Act) and its concentration (see 21 CFR 610.61(e)). 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)).
Potency Statement	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)). 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)).
Source of the Product When a Factor in Safe Administration	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)).

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

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

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

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

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

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

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

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

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

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

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

1. Lot Release

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

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

2. Product Distribution Reports

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

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

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

3. Notification of Manufacturing Problems Involving Distributed Products

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

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

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

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

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

Application holders that intend to propose manufacturing changes are encouraged to contact OPQ/OPRO at CDER-OPQ-Inquiries@fda.hhs.gov. FDA is committed to working with application holders to minimize any potential burden.

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

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

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

- Comparability data.
  - The type and amount of data needed to support a comparability exercise depends on the extent of the changes and the potential risk to product quality. A robust control strategy for drug substance and drug product is critical in generating comparability data. For example, a potency assay that is accurate, precise, and reliable will facilitate the review of manufacturing changes. In some cases, in addition to the typical battery of release tests, extended characterization may be necessary for comparison, in particular for process changes that may affect purity, potency, or safety of the product.
- Batch analysis data.
- Appropriate stability data.
  - Generally, limited real-time stability data for the postchange product and comparability study results, including stability data under accelerated and stressed storage conditions, are sufficient to leverage existing stability data to support the shelf life of the postchange product.

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

2. Facility Inspections Related to Certain Supplements to a Deemed 351(a) BLA

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

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

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

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

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

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

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

A biological product approved in an NDA (including a 505(b)(2) application) that is deemed licensed under section 351(a) of the PHS Act may be a reference product for a 351(k) BLA. The term "reference product" is defined as 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) of the PHS Act (see section 351(i)(4) of the PHS Act).

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

Q19. Can an application holder for a biological product that is the subject of a "deemed" 351(a) BLA seek a determination of biosimilarity or interchangeability under section 351(k) of the PHS Act to another biological product licensed under section 351(a) of the PHS Act?

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

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

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

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

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);

- The name and address of the manufacturer of the biological product (provided that the current labeling includes the name and place of business of the manufacturer, packer, or distributor as required by 21 CFR 201.1);

- The applicable license number; or

- For biological products with approved labeling in the format described by 21 CFR 201.56(d) and 201.57 (PLR format), the year of Initial U.S. Approval of the new biological product (provided that the current labeling includes the year of Initial U.S. Approval of the new molecular entity).

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

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