The "Deemed to be a License" Provision of the BPCI Act Questions and Answers Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Janice Weiner, 301-796-3475, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

December 2018
Procedural

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Questions and Answers
Guidance for Industry

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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This draft guidance is intended to provide answers to common questions about FDA's interpretation of the "transition" provision of the Biologics Price Competition and Innovation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.

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

Guidance for Industry

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

December 2018
Procedural

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

Guidance for Industry[1]

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

I. INTRODUCTION

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

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

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

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

polypeptide),"[3] and describing procedures for submission of a marketing application for certain biological products.

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

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

II. BACKGROUND

A. BPCI Act

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

[3] FDA has described its interpretation of the statutory terms "protein" and "chemically synthesized polypeptide" in the amended definition of "biological product" in guidance. See draft guidance for industry *New and Revised Draft Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)*. When final, this guidance will represent FDA's current thinking on this topic. FDA's guidances for industry are available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs web guidance page. In addition, in the *Federal Register* of December 12, 2018, FDA also has issued a proposed rule to amend its regulation that defines "biological product" to incorporate changes made by the BPCI Act, and to provide its interpretation of the statutory terms "protein" and "chemically synthesized polypeptide." When final, this regulation will codify FDA's interpretation of these terms.

products are manufactured. Most biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

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

The BPCI Act also includes, among other provisions:

- A 12-year exclusivity period from the date of first licensure of certain reference products, during which approval of a 351(k) application referencing that product may not be made effective (see section 351(k)(7) of the PHS Act)

- A 4-year exclusivity period from the date of first licensure of certain reference products, during which a 351(k) application referencing that product may not be submitted (see section 351(k)(7) of the PHS Act)

- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product (see section 351(k)(6) of the PHS Act)

- Procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act (see section 351(l) of the PHS Act)

B. Transition Period for Certain Biological Products

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

- An application for a biological product ***may*** be submitted under section 505 of the FD&C Act not later than March 23, 2020, if the biological product is in a product 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 the biological product under section 351 of the PHS Act (a "deemed Biologics License Application (BLA)") on March 23, 2020.

III. INTERPRETATION OF THE "DEEMED TO BE A LICENSE" PROVISION

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

Section 7002(e) of the BPCI Act is directed primarily to the submission of an application for a biological product during the transition period ending on March 23, 2020.[6] Though the transition scheme described in section 7002(e) of the BPCI Act culminates with the "deemed to be a license" provision in section 7002(e)(4), the statute is silent regarding the process for

[4] FDA has interpreted the statutory term "product class" for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period (see guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act*, at Q&A II.2).

[5] The term "reference product" means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under section 351(k) (see section 351(i)(4) of the PHS Act).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

or a manufacturing supplement), a supplement for changes being effected (CBE) in 30 days (for certain chemistry, manufacturing, and controls changes), or a supplement for changes being effected upon receipt by the Agency of the supplement (for certain safety-related labeling changes or any other labeling change that FDA specifically requests to be submitted in a CBE supplement).[15] At the time that FDA deems the approved NDA for a biological product to be a BLA on the transition date, FDA intends to also administratively convert any pending supplement to such approved NDA to a pending supplement to the deemed BLA, and to review such supplements under applicable standards for BLAs. For example, a pending "stand-alone" efficacy supplement to a "stand-alone" NDA[16] (e.g., a supplement intended to address a post-approval requirement or post-approval commitment) will be administratively converted to a pending efficacy supplement to the corresponding deemed 351(a) BLA on the transition date and reviewed under applicable standards for 351(a) BLAs. Similarly, a pending CBE supplement to an application submitted under the FD&C Act will be administratively converted to a pending CBE supplement to the deemed BLA on the transition date, irrespective of whether the change described in the CBE supplement has been implemented before or after the transition date. The Agency also intends to maintain the same goal date, where applicable, for completion of its review of such supplements.

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

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

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

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

[15] See generally 21 CFR 314.70.

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

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

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

3. Exclusivity

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

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

- A supplement for the biological product that is the reference product; or

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

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

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

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

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

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

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

1. "Stand-Alone" New Drug Applications

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

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

2. 505(b)(2) Applications

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

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

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

- Modifying the development program to support submission of a 351(k) BLA for a proposed biosimilar product or a proposed interchangeable product at such time as there is a biological product licensed under section 351(a) of the PHS Act that could be a reference product.

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

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

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

- Is "highly similar" to a single reference product licensed under section 351(a) of the PHS Act, and that there are "no clinically meaningful differences" between the proposed product and the reference product in terms of safety, purity, and potency;

- Has the same route of administration, dosage form, and strength as the reference product;

- Utilizes the same mechanism(s) of action as the reference product for the proposed condition(s) of use (but only to the extent that the mechanism(s) of action are known); and

- Seeks licensure for a condition(s) of use (e.g., indication, dosing regimen) previously approved for the reference product.[21]

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

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

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

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

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

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

APPENDIX

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

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

New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-1042 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)

December 2018
Biosimilars

Revision 2

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Guidance for Industry

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U.S. Department of Health and Human Services
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New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) 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.

INTRODUCTION

This draft guidance document provides answers to common questions from prospective applicants and other interested parties regarding the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The question and answer (Q&A) format is intended to inform prospective applicants and facilitate the development of proposed *biosimilars* and *interchangeable biosimilars*,[2] as well as to describe FDA's interpretation of certain statutory requirements added by the BPCI Act.

The BPCI Act amended the Public Health Service Act (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 Patient Protection and Affordable Care Act (Pub. L. 111–148) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA's interpretation of the BPCI Act will enhance transparency and facilitate the development and approval of biosimilar and interchangeable products. In addition, these Q&As respond to questions the Agency has received from prospective applicants regarding

[1] This draft 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 (FDA or the Agency).

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.

[2] In this draft guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) *biosimilar* or *biosimilar product* refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) *interchangeable biosimilar* or *interchangeable product* refers to a biosimilar product that FDA has also determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act). Biosimilarity, interchangeability, and related issues are discussed in more detail in the Background section of this draft guidance.

the appropriate statutory authority under which certain products will be regulated. FDA intends to update this draft guidance document to include additional Q&As as appropriate.

This draft guidance document revises the draft guidance document, *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.*[3] The draft guidance document contains Q&As distributed for comment purposes only and includes new Q&As, as well as revisions to Q&As that appeared in previous versions of the draft or final guidance documents. Additional information about the Q&A format for this draft guidance document is provided in the Background section.

FDA is also issuing a final guidance document entitled *Questions and Answers on Biosimilar Development and the BPCI Act.* This final guidance document is part of a series of guidance documents that FDA has developed to facilitate development of biosimilar and interchangeable products. The final guidance documents issued to date address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)
- Questions and Answers on Biosimilar Development and the BPCI Act (December 2018)
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (December 2016)
- Labeling for Biosimilar Products (July 2018)

In addition, FDA has published draft guidance documents related to the BPCI Act, which, when finalized, will represent FDA's current thinking. These draft guidance documents include:

- Considerations in Demonstrating Interchangeability With a Reference Product (January 2017)
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018)
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (August 2014)

[3] FDA has adjusted the title of this draft guidance to more clearly communicate that this draft guidance contains *draft* questions and answers.

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.

BACKGROUND

The BPCI Act

The BPCI Act was enacted as part of the ACA on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the ACA). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar or interchangeable product.

Section 351(i) defines the term *biosimilar* or *biosimilarity* "in reference to a biological product that is the subject of an application under [section 351(k)]" to mean "that the biological product is highly similar to the reference product[4] 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" (see section 351(i)(2) of the PHS Act).

Section 351(k)(4) of the PHS Act provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or a supplement to such application) is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient"[5] and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between 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."[6]

[4] *Reference product* means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act).
[5] Section 351(k)(4)(A) of the PHS Act.
[6] Section 351(k)(4)(B) of the PHS Act.

Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

In this draft guidance document, the terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe products that are under development or are the subject of a pending 351(k) biologics license application (BLA).

Certain other provisions of the BPCI Act are discussed in the context of the relevant Q&A.

"Question and Answer" Guidance Format

This draft guidance document is a companion to the final guidance document, *Questions and Answers on Biosimilar Development and the BPCI Act*. In this pair of guidance documents, FDA issues each Q&A in draft form in this draft guidance document, receives comments on the draft Q&A, and, as appropriate, moves the Q&A to the final guidance document, after reviewing comments and incorporating suggested changes to the Q&A, when appropriate. A Q&A that was previously in the final guidance document may be withdrawn and moved to the draft guidance document if FDA determines that the Q&A should be revised in some respect and reissued in a revised draft Q&A for comment. A Q&A also may be withdrawn and removed from the Q&A guidance documents if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance document.

A reference will follow each question in this draft guidance document describing the publication date of the current version of the Q&A, and whether the Q&A has been added to or modified in this draft guidance document. FDA has maintained the original numbering of the guidance Q&As used in the April 2015 final guidance document (*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*) and May 2015 draft guidance document (*Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*). For ease of reference, a Q&A retains the same number when it moves from the draft guidance document to the final guidance document and, where appropriate, when a Q&A is withdrawn from the final guidance document and moved to the draft guidance document.

Where a Q&A has been withdrawn from the final guidance document, this is marked in the final guidance document by several asterisks between nonconsecutively numbered Q&As and, where appropriate, explanatory text.

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

* * * * *

Q. I.12. How can an applicant demonstrate that its proposed injectable biosimilar product or proposed injectable interchangeable product has the same "strength" as the reference product?
[Moved to Draft from Final December 2018]

A. I.12. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the "strength" of the proposed biosimilar product or proposed interchangeable product is the same as that of the reference product. Data and information generated as part of the analytical similarity assessment may inform the determination that a proposed biosimilar product or proposed interchangeable product has the same strength as its reference product. As a scientific matter, there may be a need to take into account different factors and approaches in determining the "strength" of different biological products. Sponsors should discuss their proposed approach with FDA and provide an adequate scientific basis for their approach to demonstrating same strength.

In general, a sponsor of a proposed biosimilar product or proposed interchangeable product with an "injection" dosage form (e.g., a solution) can demonstrate that its product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity) and the same concentration of drug substance (in mass or units of activity per unit volume). In general, for a proposed biosimilar product or proposed interchangeable product that is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, a sponsor can demonstrate that the product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity).

Although not a part of demonstrating same "strength," if the proposed biosimilar product or proposed interchangeable product is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, the 351(k) application generally should contain information that the concentration of the proposed biosimilar product or proposed interchangeable product, when constituted or reconstituted, is the same as that of the reference product, when constituted or reconstituted.

A sponsor should determine the content of drug substance for both the reference product and the proposed biosimilar product or proposed interchangeable product

using the same method. The strength of the proposed product generally should be expressed using the same units of measure as the reference product.

Q. I.16. How can a proposed biosimilar product applicant fulfill the requirement for pediatric assessments or investigations under the Pediatric Research Equity Act (PREA)?
[Updated/Retained in Draft December 2018]

A. I.16. Applicants for proposed biosimilar products should address PREA requirements based upon the nature and extent of pediatric information in the reference product labeling. PREA requirements are applicable to proposed biosimilar products that have not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in: (1) a condition of use that has not been previously approved for the reference product; or (2) a dosage form, strength, or route of administration that differs from that of the reference product.

As a preliminary matter, we note that there are differences in the use of the term "extrapolation" in the context of a proposed biosimilar product under the PHS Act and in the context of PREA.

- An applicant may provide scientific justification for "extrapolation" to support approval of a biosimilar product under section 351(k) of the PHS Act for one or more conditions of use. For more information on extrapolation in this context, see FDA's guidance for industry on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

- "Pediatric extrapolation" refers to establishing the effectiveness of a drug in a pediatric population without requiring a separate study in that population when the course of the disease and the effects of the drug are sufficiently similar in the pediatric population and the adult population (or another pediatric population) in which the drug has been studied and shown to be effective (see section 505B(a)(2)(B) and (a)(3)(B) of the Federal Food Drug and Cosmetic Act (FD&C Act).

In the discussion that follows, the term "extrapolation" generally will be used to refer to extrapolation to support approval of a biosimilar product under section 351(k) of the PHS Act for one or more conditions of use, and not to pediatric extrapolation.

- Adequate pediatric information in reference product labeling

  If the labeling for the reference product contains adequate pediatric information (e.g., information reflecting an adequate pediatric assessment)

with respect to an indication for which a biosimilar applicant seeks licensure in adults, the biosimilar applicant may fulfill PREA requirements for that indication by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification under the BPCI Act for extrapolating the pediatric information from the reference product to the proposed biosimilar product.

If the submitted scientific justification for extrapolation under section 351(k) of the PHS Act is inadequate, a biosimilar applicant must submit appropriate data to fulfill applicable PREA requirements.

- Lack of adequate pediatric information in reference product labeling

  If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and applicable PREA requirements were deferred for the reference product for those pediatric age groups, a biosimilar applicant should request a deferral of PREA requirements for those pediatric age groups. The biosimilar applicant should amend or supplement its 351(k) BLA, as appropriate, to seek approval for updated labeling, supported by biosimilar extrapolation or appropriate data, that includes relevant pediatric information after the reference product labeling is updated with that information.

  If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and PREA requirements were waived for, or inapplicable to, the reference product for those pediatric age groups, a biosimilar applicant should note this information in its initial pediatric study plan (iPSP), if any, but does not need to request a waiver of PREA requirements for those age groups. For proposed biosimilars, obligations under PREA are circumscribed by the BPCI Act to require an assessment only for indications and age groups or other conditions of use in which the reference product has been or will be assessed. In other words, the Agency has determined that PREA requirements are applicable to a proposed biosimilar product that has not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in: (1) a condition of use that has not been previously approved for the reference product, or (2) a dosage form, strength, or route of administration that differs from that of the reference product.

FDA's recommendations to biosimilar applicants with respect to the PREA requirements reflect a clarification based on the Agency's interpretation of the

interaction between section 505B of the FD&C Act (PREA) and section 351(k) of the PHS Act. Biosimilar applicants previously requested, and the Agency granted, waivers in instances where PREA requirements were waived for or determined to be inapplicable to the reference product. However, upon further consideration, waivers for biosimilars applicants under those circumstances were not necessary, and the practice is more accurately described in terms of the Agency's interpretation of the BPCI Act and PREA. The BPCI Act added section 351(k) of the PHS Act and amended section 505B of the FD&C Act to specify that PREA is applicable to a biosimilar product that has not been determined to be interchangeable with a reference product (see section 7002(a), (d)(2) of the BPCI Act). FDA reads section 351(k) of the PHS Act and PREA together with respect to the need to conduct assessments of and seek licensure for certain pediatric uses and pediatric formulations. An application submitted under section 351(k) of the PHS Act must include, among other things, information demonstrating that "the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product" and "the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product" (section 351(k)(2)(A)(i)(III)-(IV) of the PHS Act). FDA has determined that, when the reference product does not have adequate pediatric use information in its labeling or an age-appropriate formulation for a relevant pediatric population, the obligations for the biosimilar applicant under PREA are circumscribed by section 351(k) of the PHS Act insofar as the biosimilar applicant would not be expected to obtain licensure for a pediatric use (or describe that use in product labeling) that has not been licensed for the reference product and would not be expected to obtain licensure of a product that would result in a dosage form, strength, or route of administration that differs from that of the reference product.

By establishing an abbreviated licensure pathway for biosimilar and interchangeable products, the BPCI Act reflects the strong public health interest in the licensure and availability of those products. Such licensure could result in increased competition, as well as greater access to biological products. The Agency's interpretation of section 351(k) and PREA assures that biosimilar applicants are not subject to greater regulatory burdens than those faced by reference product sponsors with respect to the study of pediatric uses.

This approach preserves the intent and availability of an abbreviated licensure pathway for biosimilars, while helping to ensure that a biosimilar product is labeled and formulated for relevant pediatric conditions of use that have been approved for the reference product. FDA also recognizes the important interests furthered by PREA and appreciates the need to study pediatric uses of biological products and to include pediatric use information in product labeling. Consequently, in appropriate cases, FDA may take additional steps within its authority to assure that pediatric use information is included in biological product

labeling.[7] Such actions may include invoking the "marketed drugs" provision under PREA, in certain circumstances, to require sponsors to conduct pediatric assessments, or take other appropriate steps, to support pediatric labeling for both the biosimilar product and the reference product.[8]

If a biosimilar applicant believes that none of the situations described above applies to its proposed product, the applicant should contact FDA for further information.

Q. I.20. What is the nature and type of information that a sponsor should provide to support a post-approval manufacturing change for a licensed biosimilar product?
[New December 2018]

A. I.20 In general, a sponsor who intends to make a manufacturing change to a licensed biosimilar product should follow the principles outlined in the International Council for Harmonisation (ICH) guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (June 2005).* Accordingly, the sponsor should provide sufficient data and information to demonstrate the comparability of the biosimilar product before and after the manufacturing change. The comparability assessment should include: a) side-by-side analytical comparison of a sufficient number of lots of pre-change and post-change material, including an assessment of stability; and b) a comparison of analytical data from the post-change material to historical analytical data from lots used in the analytical similarity assessment, including data from lots used in clinical studies that supported licensure of the biosimilar product. A well-qualified, in-house reference standard should also be included in the comparability exercise. In certain cases, additional reference materials may be included in the comparability study. The extent of data and information necessary to establish comparability would be commensurate with the type of manufacturing change and its potential impact on product quality, safety, and efficacy.

In addition, FDA continues to consider the nature and type of information a sponsor should provide to support a post-approval manufacturing change to a biological product determined by FDA to be interchangeable with the reference product under section 351(k)(4) of the PHS Act. FDA intends to provide specific recommendations for post-approval manufacturing changes to interchangeable biological products in future guidance.

[7] For instance, if the Agency determines that the basis for the reference product's waiver under PREA no longer applies to a particular age group (e.g., because it is now feasible to study a younger pediatric age group), FDA may, as appropriate, contact the 351(k) biosimilar product sponsor, as well as the reference product sponsor, and require further action by both parties to comply with PREA. *See* § 505B(a)(5) of the FD&C Act.
[8] *See* § 505B(b) of the FD&C Act.

A sponsor may seek approval, in a supplement to an approved 351(k) BLA, of a route of administration, a dosage form, or a strength that is the same as that of the reference product, but that has not previously been licensed under the 351(k) BLA.[9] FDA intends to provide specific recommendations on this topic in future guidance.

Q. I.21. May a sponsor seek approval, in a 351(k) application or a supplement to an approved 351(k) application, of a route of administration, a dosage form, or a strength that is not the same as that of the reference product?
[New December 2018]

A. I.21. No. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, a 351(k) application must include information demonstrating that "the route of administration, the dosage form, and the strength" of the proposed biosimilar or interchangeable product "are the same as those of the reference product." An applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, for a route of administration, a dosage form, or a strength that is not the same as that of the reference product.

Q. I.22. May a sponsor seek approval, in a 351(k) application or a supplement to an approved 351(k) application, for a condition of use that has not previously been approved for the reference product?
[New December 2018]

A. I.22 No. Under section 351(k)(2)(A)(i)(III) of the PHS Act, the 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the proposed biosimilar or interchangeable product have been previously approved for the reference product. A 351(k) applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, of a condition of use (e.g., indication, dosing regimen) that has not been previously approved for the reference product.

Q.I.23 May a prospective 351(k) BLA applicant request a letter from FDA stating that study protocols intended to support a 351(k) application contain safety protections comparable to an applicable Risk Evaluation and Mitigation Strategy (REMS) for the reference product?
[New December 2018]

[9] As described elsewhere in this draft guidance (Q&A I.21), a 351(k) applicant may not seek approval of a route of administration, a dosage form, or a strength that is not the same as the reference product, including in a supplement to an approved 351(k) application. This draft guidance, when finalized, will represent FDA's current thinking on this topic. See Q&A I.21 for additional information.

A.I.23 Yes. There have been reports of instances in which a reference product holder has refused to sell product to a prospective applicant for a competing product that is seeking to conduct studies to support approval, and the reference product holder cites the risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) for the reference product as justification.

In the interest of facilitating a prospective biosimilar applicant's access to supplies of the reference product to conduct the testing necessary to support 351(k) BLA approval, FDA will, on request, review (one or more) study protocols submitted by a prospective 351(k) BLA applicant to assess whether they provide safety protections comparable to those in the applicable REMS with ETASU. If the Agency determines that comparable protections exist, FDA will notify the prospective 351(k) BLA applicant. If requested to do so by the prospective 351(k) BLA applicant, FDA will then issue a separate letter to the reference product holder stating that comparable protections exist and indicating that FDA will not consider it to be a violation of the REMS for the reference product holder to provide the prospective 351(k) BLA applicant with a sufficient quantity of the reference product to allow it to perform testing necessary to support its 351(k) BLA.

Requesting such a protocol review or letter is not a legal requirement. If a prospective 351(k) BLA applicant wishes to request such a letter or protocol review, however, it should (1) confirm that the product at issue is subject to a REMS with ETASU by checking the Agency's online listing of approved REMS[10], and (2) contact FDA for more information. For contact information, see FDA's website, "Biosimilars," available at https://www.fda.gov/biosimilars and click on the link, "Industry Information and Guidance" listed in the left column.

Q.I.24 May an applicant submit data and information to support approval of a proposed biosimilar or interchangeable product for an indication for which the reference product has unexpired orphan exclusivity?
[New December 2018]

A.I.24 Yes. An applicant may submit data and information to support approval of a proposed biosimilar or interchangeable product for one or more indications for which the reference product has unexpired orphan exclusivity. For example, an applicant may submit data and information intended to provide sufficient scientific justification for extrapolation to support approval of a proposed biosimilar or interchangeable product for one or more indications for which the reference product has unexpired orphan exclusivity. However, FDA will not be able to approve the proposed biosimilar or interchangeable product for the protected indication(s) until the orphan exclusivity expires.

[10] See Approved Risk Evaluation and Mitigation Strategies (REMS): https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

II. PROVISIONS RELATED TO REQUIREMENTS TO SUBMIT A BLA FOR A "BIOLOGICAL PRODUCT"

Q. II.1. How does FDA interpret the category of "protein (except any chemically synthesized polypeptide)" in the amended definition of "biological product" in section 351(i)(1) of the PHS Act?
[Moved to Draft from Final December 2018]

A. II.1. The BPCI Act amends the definition of "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)" and provides that an application for a biological product must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period ending on March 23, 2020, described in section 7002(e) of the Affordable Care Act.

FDA has developed the following interpretations of the statutory terms "protein" and "chemically synthesized polypeptide" to implement the amended definition of "biological product" and provide clarity to prospective applicants regarding the statutory authority under which such products are regulated.

Protein — 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.

Where a single amino acid polymer is greater than 40 amino acids in size and is related to a naturally occurring peptide, such polymer would be reviewed to determine whether the additional amino acids that cause the peptide to exceed 40 amino acids in size raise any concerns about the risk/benefit profile of the product.

Some amino acid polymers are composed of multiple amino acid chains that are associated with each other. When two or more amino acid chains are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of our interpretation of the statutory terms "protein" and "chemically synthesized polypeptide" is based on the total number of amino acids in those chains, and is not limited to the number of amino acids in a contiguous sequence. In other words, the amino acids in each such amino acid chain will be added together to determine whether the product meets the numerical threshold in FDA's interpretation of the terms "protein" and "chemically synthesized polypeptide." However, for products with amino acid chains that are associated with each other in a manner that is not found in nature (i.e., amino acid chains that

are associated with each other in a novel manner that is not found in naturally occurring proteins), FDA intends to conduct a fact-specific, case-by-case analysis to determine whether the size of the amino acid polymer, for purposes of our interpretation of the statutory terms "protein" and "chemically synthesized polypeptide," should be based on adding each of the amino acids in the amino acid chains together or should be based on separate consideration of the amino acid chains (e.g., the number of amino acids in the largest chain). In such cases, FDA may consider in its analysis, among other things, any structural or functional characteristics of the product.

Chemically synthesized polypeptide — The term "chemically synthesized polypeptide" means 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, as described, 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."

Where a single amino acid polymer is greater than 99 amino acids in size and is related to a naturally occurring peptide or polypeptide of shorter length, such polymer would be reviewed to determine whether the additional amino acids that cause the polymer to exceed 99 amino acids in size raise any concerns about the risk/benefit profile of the product.

FDA's interpretation of these statutory terms is informed by several factors. The scientific literature describes a "protein" as a defined sequence of alpha amino acid polymers linked by peptide bonds, and generally excludes "peptides" from the category of "protein." A "peptide" generally refers to polymers that are smaller, perform fewer functions, contain less three-dimensional structure, are less likely to be post-translationally modified, and thus are generally characterized more easily than proteins. Consistent with the scientific literature, FDA interprets the term "protein" in the statutory definition of biological product in a manner that does not include peptides. To enhance regulatory clarity and minimize administrative complexity, FDA has decided to distinguish proteins from peptides based solely on size (i.e., number of amino acids).

In the absence of clear scientific consensus on the criteria that distinguish proteins from peptides, including the exact size at which a chain(s) of amino acids becomes a protein, FDA reviewed the pertinent literature and concluded that a threshold of 40 amino acids is appropriate for defining the upper size boundary of a peptide. Accordingly, FDA interprets the BPCI Act such that any polymer composed of 40 or fewer amino acids is a peptide and not a protein. Therefore,

unless a peptide otherwise meets the statutory definition of a "biological product" (e.g., a peptide vaccine), it will be regulated as a drug under the FD&C Act.

The statutory category of "protein" parenthetically excludes "any chemically synthesized polypeptide." There are several definitions of "polypeptide" in the scientific literature. Some are broad (e.g., polypeptide means any amino acid polymer), while others are more narrow (e.g., polypeptide means any amino acid polymer composed of fewer than 100 amino acids). FDA believes that a narrow interpretation of polypeptide is most appropriate in this context because, among other reasons, this avoids describing an exception to the category of "protein" that includes a broader category of molecules. Therefore, FDA interprets the statutory exclusion for "chemically synthesized polypeptide" to mean any molecule that is made entirely by chemical synthesis and that is composed of greater than 40 amino acids but less than 100 amino acids in size. Such molecules will be regulated as drugs under the FD&C Act, unless the chemically synthesized polypeptide otherwise meets the statutory definition of a "biological product."

There may be additional considerations for proposed products that are combination products or meet the statutory definition of both a "device" and a "biological product." We encourage prospective sponsors to contact FDA for further information on a product-specific basis.

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III. EXCLUSIVITY

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Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

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

December 2018
Biosimilars

Revision 1

Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

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

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Biosimilars

Revision 1

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Questions and Answers on Biosimilar Development and the BPCI Act Guidance for Industry[1]

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

INTRODUCTION

This guidance document provides answers to common questions from prospective applicants and other interested parties regarding the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The question and answer (Q&A) format is intended to inform prospective applicants and facilitate the development of proposed *biosimilars* and *interchangeable biosimilars*,[2] as well as to describe FDA's interpretation of certain statutory requirements added by the BPCI Act.

The BPCI Act amended the Public Health Service Act (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 Patient Protection and Affordable Care Act (Pub. L. 111–148) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA's interpretation of the BPCI Act will enhance transparency and facilitate the development and approval of biosimilar and interchangeable products. In addition, these Q&As respond to questions the Agency has received from prospective applicants regarding the appropriate statutory authority under which certain products will be regulated. FDA intends to update this guidance document to include additional Q&As as appropriate.

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[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 (FDA or the Agency).

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.

[2] In this guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) *biosimilar* or *biosimilar product* refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) *interchangeable biosimilar* or *interchangeable product* refers to a biosimilar product that FDA has determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act). Biosimilarity, interchangeability, and related issues are discussed in more detail in the Background section of this guidance.

This guidance document revises the final guidance document entitled *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,* to clarify and update certain Q&As and to add new Q&As. For certain Q&As, FDA has updated the Q&A by abbreviating the answer and, where appropriate, referring the reader to a separate guidance document that provides additional information on the topic. Alternatively, FDA may have withdrawn a Q&A if the topic is addressed in a separate guidance document or if FDA determined that the Q&A should be revised in some respect and reissued. Additional information about the Q&A format for this guidance document is provided in the Background section.

FDA is also issuing a draft guidance document entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).* When finalized, this draft guidance document will be part of a series of guidance documents that FDA has developed to facilitate development of biosimilar and interchangeable products. The final guidance documents issued to date address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (December 2016)
- Labeling for Biosimilar Products (July 2018)

In addition, FDA has published draft guidance documents related to the BPCI Act, which, when finalized, will represent FDA's current thinking. These draft guidance documents include:

- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018)
- Considerations in Demonstrating Interchangeability With a Reference Product (January 2017)
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018)
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (August 2014)

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.

BACKGROUND

The BPCI Act

The BPCI Act was enacted as part of the ACA on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the ACA). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar or interchangeable product.

Section 351(i) defines the term *biosimilar* or *biosimilarity* "in reference to a biological product that is the subject of an application under [section 351(k)]" to mean "that the biological product is highly similar to the reference product[3] 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" (see section 351(i)(2) of the PHS Act).

Section 351(k)(4) of the PHS Act provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or a supplement to such application) is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient"[4] and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between 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."[5]

Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

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[3] *Reference product* means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act).
[4] Section 351(k)(4)(A) of the PHS Act.
[5] Section 351(k)(4)(B) of the PHS Act.

In this guidance document, the terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe products that are under development or are the subject of a pending 351(k) biologics license application (BLA).

Certain other provisions of the BPCI Act are discussed in the context of the relevant Q&A.

"Question and Answer" Guidance Format

This final guidance document is a companion to the draft guidance document entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).* In this pair of guidance documents, FDA issues each Q&A in draft form in the draft guidance document, receives comments on the draft Q&A, and, as appropriate, moves the Q&A to this final guidance document after reviewing comments and incorporating suggested changes to the Q&A, when appropriate. A Q&A that was previously in the final guidance document may be withdrawn and moved to the draft guidance document if FDA determines that the Q&A should be revised in some respect and reissued in the draft Q&A guidance document. A Q&A also may be withdrawn and removed from the Q&A guidance documents if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance document.

A reference will follow each question in this final guidance document describing the publication date of the current version of the Q&A, and whether the Q&A has been added to or modified in this final guidance document. FDA has maintained the original numbering of the Q&As used in the April 2015 final guidance document (*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*) and May 2015 draft guidance document (*Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*). For ease of reference, a Q&A retains the same number when it moves from the draft guidance document to the final guidance document and, where appropriate, when a Q&A is withdrawn from the final guidance document and moved to the draft guidance document.

Where a Q&A has been withdrawn from the final guidance document, this is marked in the final guidance document by several asterisks between nonconsecutively numbered Q&As and, where appropriate, explanatory text.

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q. I.1. Whom should a sponsor contact with questions about its proposed development program for a proposed biosimilar product or a proposed interchangeable product?
[Updated/Retained in Final December 2018]

A. I.1. FDA provides current contact information on its website. See FDA's website, "Biosimilars," available at https://www.fda.gov/biosimilars and click on the link, "Industry Information and Guidance" listed in the left column.

Q. I.2. When should a sponsor request a meeting with FDA to discuss its development program for a proposed biosimilar product or a proposed interchangeable product, and what data and information should a sponsor provide to FDA as background for this meeting?
[Updated/Retained in Final December 2018]

A. I.2. See FDA's draft guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*[6] for a description of the different meeting types intended to facilitate biosimilar development programs in accordance with the Biosimilar User Fee Act of 2012 (BsUFA), as reauthorized by the Biosimilar User Fee Amendments of 2017 (BsUFA II) and the criteria/data needed to support the request. The type of meeting granted will depend on the stage of product development and whether the information submitted in the meeting package meets the criteria for the type of meeting.

Q. I.3. Can a proposed biosimilar product have a formulation that is different from the reference product?
[Updated/Retained in Final December 2018]

A. I.3. Differences between the formulation of a proposed biosimilar product and the reference product may be acceptable. A 351(k) application must contain information demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. In addition, an applicant would need to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. It may be possible, for example, for a proposed biosimilar product formulated without human serum albumin to demonstrate biosimilarity to a reference product formulated with human serum albumin. For more information about FDA's current thinking on

[6] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

the interpretation of the statutory standard for biosimilarity, see FDA's guidances for industry on *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* and *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*

Q. I.4. Can a proposed biosimilar product have a delivery device or container closure system that is different from its reference product? [Updated/Retained in Final December 2018]

A. I.4. Some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable. It may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a pre-filled syringe or in an auto-injector device (which are considered the same dosage form), even if the reference product is licensed in a vial presentation, provided that the proposed biosimilar product meets the statutory standard for biosimilarity and adequate performance data for the delivery device or container closure system are provided. For a proposed biosimilar product in a different delivery device or container closure system, the delivery device or container closure system must be shown to be compatible for use with the final formulation of the biological product through appropriate studies, including, for example, extractable/leachable studies and stability studies. Also, for design differences in the delivery device or container closure system, performance testing and a human factors study may be needed.

However, an applicant will not be able to obtain licensure of a proposed biosimilar product when a design difference in the delivery device or container closure system results in any of the following:

- A clinically meaningful difference between the proposed biosimilar product and the reference product in terms of safety, purity, and potency;
- A different route of administration or dosage form; or
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved;

or otherwise does not meet the standard for biosimilarity.

A proposed biosimilar product in a delivery device will be considered a combination product and may, in some instances, require a separate application for the device.

For information about a delivery device or container closure system for a proposed interchangeable product, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product*.[7]

[7] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Q. I.5. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?
[Issued April 2015]

A. I.5. Yes, an applicant may obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed. An applicant must demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of safety, purity, and potency. In a limited number of circumstances, this may include providing information from one or more studies using a route of administration for which licensure is not requested (e.g., a study using subcutaneous administration may provide a more sensitive comparative assessment of immunogenicity of the reference product and a proposed biosimilar product, even though licensure of the proposed biosimilar product is requested only for the intravenous route of administration).

Q. I.6. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?
[Updated/Retained in Final December 2018]

A. I.6. An applicant is not required to obtain licensure of a proposed biosimilar product for all presentations for which the reference product is licensed. However, if an applicant seeks licensure for a particular indication or other condition of use for which the reference product is licensed and that indication or condition of use corresponds to a certain presentation of the reference product, the applicant may need to seek licensure for that particular presentation (see also questions and answers I.4 and I.5).

Q. I.7. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?
[Updated/Retained in Final December 2018]

A. I.7. An applicant generally may obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed. The 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling submitted for the proposed biosimilar product have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act).

For information about the licensure of a proposed interchangeable product, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product*.[8]

Q. I.8. Can a sponsor use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?
[Updated/Retained in Final December 2018]

A. I.8. A sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is *biosimilar* to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed.

If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity. The acceptability of such an approach will be evaluated on a case-by-case basis, and should be discussed in advance with the Agency. For certain complex biological products, a modified approach may be needed. A final determination about the adequacy of the scientific justification and bridge will be made during the review of the application.

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include, but are not limited to, the following:

- The relevance of the design of the clinical program to support a demonstration of biosimilarity to the U.S.-licensed reference product for the condition(s) of use and patient population(s) for which licensure is sought;

[8] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

- The relationship between the license holder for the non-U.S.-licensed comparator product and BLA holder for the U.S.-licensed reference product;

- Whether the non-U.S.-licensed comparator product was manufactured in a facility(ies) licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries);

- Whether the non-U.S.-licensed comparator product was licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., ICH countries) and the duration and extent to which the product has been marketed; and

- The scientific bridge between the non-U.S.-licensed comparator product and the U.S.-licensed reference product, including comparative physicochemical characterization, biological assays/functional assays, degradation profiles under stressed conditions, and comparative clinical PK and, when appropriate, PD data, to address the impact of any differences in formulation or primary packaging on product performance.

A sponsor should also address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed comparator product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed comparator product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. The complexity of the products, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation), and the degree of heterogeneity associated with the product may affect the considerations for the scientific justification regarding the extent of bridging data. Additional factors that FDA may consider regarding the extent of bridging data include, but are not limited to, the following:

- Whether the formulation, dosage form, and strength of the U.S.-licensed reference product and non-U.S.-licensed comparator products are the same;

- The route of administration of the U.S.-licensed reference product and non-U.S.-licensed comparator products;

- The design of the physicochemical and biological/functional assessments and the use of multiple orthogonal methods with adequate sensitivity to detect differences among the products;

- The scientific justification for the selection of the non-U.S.-licensed comparator lots used to establish the scientific bridge and how the selected lots relate to the material used in the nonclinical and clinical studies. The scientific bridge should include a sufficient number of lots of non-U.S.-licensed comparator product to adequately capture the variability in product quality attributes. When possible, the non-U.S.-licensed comparator lots used in the nonclinical or clinical studies should be included in the assessment performed to establish the analytical bridge.

Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by FDA during review of the 351(k) application.

For more information about whether a non-U.S.-licensed comparator can be used in studies intended to support the additional criteria required for a determination of interchangeability with the reference product, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product*.[9]

Q. I.9. Is a clinical study to assess the potential of the biological product to delay cardiac repolarization (a QT/QTc study) or a drug-drug interaction study generally needed for licensure of a proposed biosimilar product? [Moved to Final from Draft December 2018]

A. I.9. In general, a 351(k) application for a proposed biosimilar product may rely upon the Agency's previous determination of safety, purity, and potency for the reference product, including any clinical QT/QTc interval prolongation and proarrhythmic potential and drug-drug interactions. If such studies were not required for the reference product, then these data generally would not be needed for licensure of a proposed biosimilar product under section 351(k) of the PHS Act. However, if the BLA holder for the reference product has been required to conduct postmarket studies or clinical trials under section 505(o)(3) of the Federal Food, Drug and Cosmetic Act (FD&C Act) to assess or identify a certain risk related to a QT/QTc study or a drug-drug interaction study and those studies have not yet been completed, then FDA may impose similar postmarket requirements on the 351(k) applicant in appropriate circumstances.

[9] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

Q. I.10. How long and in what manner should sponsors retain reserve samples of the biological products used in comparative clinical PK and/or PD studies intended to support a 351(k) application?
[Moved to Final from Draft December 2018]

A. I.10. Reserve samples establish the identity of the products tested in the actual study, allow for confirmation of the validity and reliability of the results of the study, and facilitate investigation of further follow-up questions that arise after the studies are completed. FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples for at least 5 years following the date on which the 351(k) application is licensed, or, if such application is not licensed, at least 5 years following the date of completion of a comparative clinical PK and/or PD study of the reference product and the proposed biosimilar product (or other clinical study in which PK or PD samples are collected with the primary objective of assessing PK or PD similarity) that is intended to support a submission under section 351(k) of the PHS Act. Contact the FDA for specific advice if an alternative approach is being considered. For a 3-way PK similarity study, FDA recommends that samples of both comparator products be retained, in addition to samples of the proposed biosimilar product.

For most protein therapeutics, FDA recommends that a sponsor retain the following quantities of product and dosage units, which are expected to be sufficient for evaluation by state of the art analytical methods:

- A minimum of 10 dosage units each of the proposed biosimilar product, reference product and, if applicable, non-U.S.-licensed comparator product, depending on the amount of product within each unit. In general, this should provide for a total product mass of equal to or greater than 200 mg in a volume equal to or greater than 10 mL.

FDA recommends that the sponsor contact the review division to discuss the appropriate quantities of reserve samples in the following situations:

- A product mass of equal to or greater than 200 mg in a volume equal to or greater than 10 mL requires a large number of dosage units.
- Biological products other than protein therapeutics.

Q. I.11. This question and answer have been withdrawn. For information on extrapolation, see FDA's guidance for industry on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

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Q.I.12. This question and answer have been withdrawn and moved to FDA's draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).*

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Q. I.13. What constitutes "publicly-available information" regarding FDA's previous determination that the reference product is safe, pure, and potent to include in a 351(k) application?
[Moved to Final from Draft December 2018]

A. I.13. "Publicly-available information" in this context generally includes the current FDA-approved labeling for the reference product and the types of information found in the "action package" for a BLA (see section 505(l)(2)(C) of the FD&C Act). However, FDA notes that submission of publicly available information composed of less than the current FDA-approved labeling for the reference product and the action package for the reference product BLA will generally not be considered a bar to submission or approval of an acceptable 351(k) application.

FDA intends to post on the Agency's Web site publicly available information regarding FDA's previous determination of safety, purity, and potency for certain biological products to facilitate biosimilar development programs and submission of 351(k) applications. We note, however, that the publicly available information posted by FDA in this context does not necessarily include all information that would otherwise be disclosable in response to a Freedom of Information Act request.

Q. I.14. Can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) application?
[Moved to Final from Draft December 2018]

A. I.14. Yes. For more information, see FDA's draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product.*[10]

Q. I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?
[Updated/Retained in Final December 2018]

A. I.15. Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the

[10] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

product for the claimed indication unless this requirement is waived, deferred, or inapplicable. [11]

Section 505B(l) of the FD&C Act[12] provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA. However, if an applicant first seeks licensure of its proposed product as a biosimilar product, the applicant must address applicable PREA requirements for its non-interchangeable biosimilar product even if it ultimately intends to subsequently seek licensure of the product as an interchangeable product.

See question and answer I.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2),* for information on how a proposed biosimilar product applicant may fulfill the requirement for pediatric assessments under PREA.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies as early as practicable during product development. If there is no active investigational new drug application (IND) for the proposed biosimilar product and the sponsor intends to conduct a comparative clinical study as part of its development program, the initial pediatric study plan (PSP) should be submitted as a pre-IND submission. In this scenario, FDA encourages the sponsor to meet with FDA before submission of the initial PSP to discuss the details of the planned development program. It is expected that the sponsor will submit the initial PSP before initiating any comparative clinical study in its biosimilar development program. For more information see question and answer I.17 of this guidance. See also the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (March 2016).*[13]

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[11] Section 505B(a)(1) was amended in 2017 by section 504 of the Food and Drug Administration Reauthorization Act (FDARA) (**Public Law 115-52**) (August 18, 2017) to include requirements for the submission of molecularly targeted pediatric cancer investigations for certain applications submitted on or after August 18, 2020, under section 505 of the FD&C Act or section 351 of the PHS Act. These requirements are not specifically addressed in this guidance.

[12] The statutory provision that appears in section 505(l) of the FD&C Act was originally enacted as section 505(n) of the FD&C Act (as amended by the BPCI Act on March 23, 2010). The provision was subsequently redesignated as 505(m) of the FD&C Act. See section 501(b) of the Food and Drug Administration Safety and Innovation Act (**Public Law 112-144**) (July 9, 2012). The provision was redesignated again as section 505(l). See section 3102(3) of the 21st Century Cures Act (**Public Law 114-255**) (December 13, 2016).

[13] This guidance, when finalized, will provide FDA's current thinking on issues related to pediatric study plans.

Q. I.17. When should a proposed biosimilar product applicant submit an initial pediatric study plan (PSP)?
[Moved to Final from Draft December 2018]

A. I.17. Section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires applicants subject to the Pediatric Research Equity Act (PREA) to submit an initial pediatric study plan (PSP) no later than 60 calendar days after the date of an end-of-Phase 2 (EOP2) meeting, or at another time agreed upon by FDA and the applicant. FDA has issued draft guidance on the PSP process, including the timing of PSP submission.[14]

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process for reaching agreement between an applicant and FDA on an initial PSP that generally lasts up to 210 days. Given the potential length of this process, and in the absence of an EOP2 meeting for a proposed biosimilar product, FDA recommends that if a sponsor has not already initiated a comparative clinical study intended to address the requirements under section 351(k)(2)(A)(i)(I)(cc) of the Public Health Service (PHS) Act, the sponsor should submit an initial PSP as soon as feasible, but no later than 210 days before initiating such a study. This is intended to provide adequate time to reach agreement with FDA on the initial PSP before the study is initiated. Depending on the details of the clinical program, it may be appropriate to submit an initial PSP earlier in development. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP.

For additional guidance on submission of the PSP, including a PSP Template, please refer to: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

Q. I.18 For biological products intended to be injected, how can an applicant demonstrate that its proposed biosimilar product has the same "dosage form" as the reference product?
[Moved to Final from Draft December 2018]

A. I.18. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the *dosage form* of the proposed biosimilar or interchangeable product is the same as that of the reference product. For purposes of implementing this statutory

[14] See the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (March 2016)*. This draft guidance, when finalized, will provide FDA's current thinking on this topic.

provision, FDA considers the *dosage form* to be the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. In the context of proposed biosimilar products intended to be injected, FDA considers, for example, "injection" (e.g., a solution) to be a different dosage form from "for injection" (e.g., a lyophilized powder). Thus, if the dosage form of the reference product is "injection," an applicant could not obtain licensure of a proposed biosimilar product with a dosage form of "for injection" even if the applicant demonstrated that the proposed biosimilar product, when constituted or reconstituted, could meet the other requirements for an application for a proposed biosimilar product.

For purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act, FDA also considers emulsions and suspensions of products intended to be injected to be distinct dosage forms. Liposomes, lipid complexes, and products with extended-release characteristics present special scenarios due to their unique composition, and prospective applicants seeking further information should contact FDA.

It should be noted, however, that this interpretation regarding the same dosage form is for purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act only. For example, this interpretation should not be cited by applicants seeking approval of a new drug application under section 505(c) of the FD&C Act, approval of an abbreviated new drug application under section 505(j) of the FD&C Act, or licensure of a BLA under section 351(a) of the PHS Act for purposes of determining whether separate applications should be submitted and assessed separate fees for different dosage forms.

Q. I.19. If a non-U.S.-licensed product is proposed for importation and use in the U.S. in a clinical investigation intended to support licensure of a proposed product under section 351(k) (e.g., a bridging clinical PK and/or PD study), is a separate IND required for the non-U.S.-licensed product?
[Moved to Final from Draft December 2018]

A. I.19. A sponsor may submit a single IND for a development program that is intended to support licensure of a proposed product under section 351(k) of the PHS Act and includes use of a non-U.S.-licensed product. The sponsor should submit information supporting the proposed clinical investigation with the non-U.S.-licensed comparator product under the IND. This scenario may occur, for example, if a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, and proposes to conduct a clinical PK and/or PD study in the U.S. with all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed product) to support establishment of a bridge between all three products and scientific justification for the relevance of these comparative data to an assessment of biosimilarity to the U.S.-licensed reference product.

A non-U.S.-licensed comparator product is considered an investigational new drug in the United States, and thus would require an IND for importation and use in the United States (see 21 CFR 312.110(a)). If a sponsor intends to conduct a clinical investigation in the United States using a non-U.S.-licensed comparator product, the IND requirements in 21 CFR part 312 also would apply to this product (see, e.g., 21 CFR 312.2).

With respect to chemistry, manufacturing, and controls (CMC) information, a sponsor should submit to the IND as much of the CMC information required by 21 CFR 312.23(a)(7) as is available. However, FDA recognizes that a sponsor may not be able to obtain all of the CMC information required by 21 CFR 312.23(a)(7) for a non-U.S.-licensed comparator product for which it is not the manufacturer. In these circumstances, the sponsor can request in an IND submission that FDA waive the regulatory requirements related to CMC information on the non-U.S.-licensed comparator product (21 CFR 312.10). The waiver request must include at least one of the following:

- An explanation why compliance with the requirements of 21 CFR 312.23(a)(7) is unnecessary or cannot be achieved;
- Information that will satisfy the purpose of the requirement by helping to ensure that the investigational drug will have the proper identity, strength, quality, and purity; or
- Other information justifying a waiver.[15]

Information that is relevant to whether the investigational drug will have the proper identity, strength, quality, and purity may include, for example, information indicating whether the investigational drug has been licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries). This should include, to the extent possible, summary approval information and current product labeling made public by the foreign regulatory authority. In addition, a sponsor should also provide information on the conditions and containers that will be used to transport the drug product to the US clinical site(s) and information on the relabeling and repackaging operations that will be used to relabel the drug product vials for investigational use. This should include information on how exposure of the product to light and temperature conditions outside of the recommended storage conditions will be prevented. A risk assessment on the impact the relabeling operations may have on drug product stability should also be included.

The sponsor should consult with the appropriate FDA review division regarding the CMC information necessary to support the proposed clinical study.

[15] See 21 CFR 312.10(a).

As would be applicable to all investigational drugs, FDA reminds sponsors that the investigator brochure (IB) for studies to be conducted under the IND should be carefully prepared to ensure that it is not misleading, erroneous, or materially incomplete, which can be a basis for a clinical hold (see 21 CFR 312.42(b)(1)(iii) and (b)(2)(i)). For example, the term *reference product* should be used in the IB only to refer to the single biological product licensed under section 351(a) of the PHS Act against which the proposed product is evaluated for purposes of submitting a 351(k) application. The IB and study protocol(s) should use consistent nomenclature that clearly differentiates the proposed product from the reference product. The IB and study protocol(s) also should clearly describe whether the comparator used in each study is the US-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature that clearly differentiates these products. If a non-U.S.-licensed comparator product is being used in a study conducted in the United States, the IB and study protocol(s) should clearly convey that the product is not FDA-approved and is considered an investigational new drug in the United States. The IB and study protocol(s) also should avoid conclusory statements regarding regulatory determinations (e.g., "comparable," "biosimilar," "interchangeable," "highly similar") that have not been made.

II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A "BIOLOGICAL PRODUCT"

Q.II.1. [This question and answer have been withdrawn and moved to FDA's draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).*]

Q. II.2. How is "product class" defined 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?
[Issued April 2015]

A. II.2. For purposes of section 7002(e)(2) of the Affordable Care Act, a proposed biological product will be considered to be in the same "product class" as a protein product previously approved under section 505 of the FD&C Act on or before March 23, 2010, if both products are homologous to the same gene-coded sequence (e.g., the INS gene for insulin and insulin glargine) with allowance for additional novel flanking sequences (including sequences from other genes). Products with discrete changes in gene-coded sequence or discrete changes in post-translational modifications may be in the same product class as the previously approved product even if the result may be a change in product pharmacokinetics.

For naturally derived protein products that do not have identified sequences linked to specific genes and that were approved under section 505 of the FD&C Act on or before March 23, 2010, a proposed biological product is in the same product class as the naturally derived protein product if both products share a primary biological activity (e.g., the 4-number Enzyme Commission code for enzyme activity).

However, for any protein product (whether naturally derived or otherwise), if the difference between the proposed product and the protein product previously approved under section 505 of the FD&C Act alters a biological target or effect, the products are not in the same product class for purposes of section 7002(e)(2) of the Affordable Care Act.

Q. II.3. What type of marketing application should be submitted for a proposed antibody-drug conjugate?
[Moved to Final from Draft December 2018]

A. II.3. A BLA should be submitted for a proposed monoclonal antibody that is linked to a drug (antibody-drug conjugate). FDA considers an antibody-drug conjugate to be a combination product composed of a biological product constituent part and a drug constituent part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857-49858 (August 25, 2005)).

CDER is the FDA center assigned to regulate antibody-drug conjugates, irrespective of whether the biological product constituent part or the drug constituent part is determined to have the primary mode of action. For more information see section 503(g) of the FD&C Act; see also, e.g., Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research (June 30, 2003), available at https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm; Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (October 31, 1991), available at https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm.

To enhance regulatory clarity and promote consistency, CDER considered several factors to determine the appropriate marketing application type for antibody-drug conjugates, including the relative significance of the safety and effectiveness questions raised by the constituent parts, particularly the highly specific molecular targeting by the antibody to a cell type, cellular compartment, or other marker at the site of action (as distinguished from mere alteration of systemic pharmacokinetics).

In light of such factors, CDER considers submission of a BLA under section 351 of the PHS Act to provide the more appropriate application type for antibody-drug conjugates.

Sponsors seeking to submit a BLA for a proposed antibody-drug conjugate may contact CDER's Office of New Drugs at 301-796-0700 for further information.

III. EXCLUSIVITY

Q. III.1. Can an applicant include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act?
[Moved to Final from Draft December 2018]

A. III.1. Yes. An applicant may include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act, and FDA will consider the applicant's assertions regarding the eligibility of its proposed product for exclusivity. For more information, see FDA's draft guidance for industry on *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act.*[16] The draft guidance describes the types of information that reference product sponsors should provide to facilitate FDA's determination of the date of first licensure for their products.

Q. III.2. How can a prospective biosimilar applicant determine whether there is unexpired orphan exclusivity for an indication for which the reference product is licensed?
[Issued April 2015]

A. III.2. A searchable database for Orphan Designated and/or Approved Products and indications is available on FDA's Web site, and is updated on a monthly basis (see https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm). FDA will not approve a subsequent application for the "same drug" for the same indication during the 7-year period of orphan exclusivity, except as otherwise provided in the FD&C Act and 21 CFR part 316.

[16] This draft guidance, when finalized, will provide FDA's current thinking on this topic.