Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-7800.

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)

May 2015
Biosimilarity

Revision 1

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 create 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 provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA's interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). This guidance revises the 2012 draft guidance on *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* to provide new and revised questions and answers. It also includes certain original questions and answers that have not yet been finalized. The questions and answers (Q&As) are grouped below in the following categories:

- Biosimilarity or Interchangeability
- Provisions Related to Requirement to Submit a BLA for a "Biological Product"
- Exclusivity

The BPCI Act amends 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)

[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).

Guidance documents are available on the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and on the CBER guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER or CBER guidance page.

(Affordable Care Act)). On November 2 and 3, 2010, FDA held a public hearing and established a public docket to obtain input on specific issues and challenges associated with the implementation of the BPCI Act (see Docket No. FDA-2010-N-0477). This guidance describes FDA's current interpretation of certain statutory requirements added by the BPCI Act and reflects consideration of the comments concerning those requirements that were submitted to the public docket.

This guidance is one in a series of guidances that FDA is developing to implement the BPCI Act. The guidances address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants

When applicable, references to information in these guidances are included in this Q&A guidance.

The Q&A format is intended to promote transparency and facilitate development programs for proposed biosimilar products by addressing questions that may arise in the early stages of development. In addition, these Q&As respond to questions the Agency has received from prospective BLA and new drug application (NDA) applicants regarding the appropriate statutory authority under which certain products will be regulated. FDA intends to update this guidance to include additional Q&As as appropriate.[2] Table 1 describes the status of the draft guidance Q&As provided in this guidance and final guidance Q&As that are included in the guidance on *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*. FDA has maintained the original numbering of the Q&As used in the February 2012 draft guidance. Q&As that have been finalized appear in the final guidance, and the omission of these Q&As from this revised draft guidance is marked by several asterisks between nonconsecutively numbered Q&As.

[2] The process by which FDA is requesting public comment on proposed Q&As and issuing new Q&As is described in the accompanying FEDERAL REGISTER notice.

Table 1. Status of Draft Guidance Q&As for Comment and Final Guidance Q&As

Q&A Category	Q&A Numbers	Publication Date of Draft Guidance Q&As for Comment	Comment Period	Publication Date of Final Guidance Q&As
Part I. Biosimilarity or Interchangeability	I.1—I.8 I.11—I.12 I.15	2/15/12	2/15/12-4/16/12	April 2015
	I.13—I.14	2/15/12	2/15/12-4/16/12	
	I.9—I.10 (revised)	5/13/15	5/13/15-7/13/15	
	I.16—I.19 (new)	5/13/15	5/13/15-7/13/15	
Part II. Provisions Related To Requirement To Submit A BLA For A "Biological Product"	II.1—II.2	2/15/12	2/15/12-4/16/12	April 2015
	II.3 (new)	5/13/15	5/13/15-7/13/15	
Part III. Exclusivity	III.1 (revised)	5/13/15	5/13/15-7/13/15	
	III.2	2/15/12	2/15/12-4/16/12	April 2015

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 was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the "Hatch-Waxman Act"), which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act).[3] The implementation of an abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger 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 (42 U.S.C. 262(k)), added by the BPCI Act, sets forth 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

[3] See section 505(b)(2) and 505(j) of the FD&C Act (21 U.S.C. 355(b)(2) and 355(j)).

"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" (see section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the additional standard of "interchangeability," an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

The BPCI Act also includes, among other provisions:

- A 12-year exclusivity period from the date of first licensure of the reference product, during which approval of a 351(k) application referencing that product may not be made effective (see section 351(k)(7) of the PHS Act);
- A 4-year exclusivity period from the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted (see section 351(k)(7) of the PHS Act);
- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product (see section 351(k)(6) of the PHS Act);
- An exclusivity period for certain biological products for which pediatric studies are conducted in accordance with a written request (see section 351(m) of the PHS Act);
- A transition provision for biological products that have been or will be approved under section 505 of the FD&C Act (21 U.S.C. 355) before March 23, 2020 (see section 7002(e) of the Affordable Care Act); and
- A provision stating that a 351(k) application for a biosimilar product contains a "new active ingredient" for purposes of the Pediatric Research Equity Act (PREA) (see section 505B(n) of the FD&C Act).

The BPCI Act also establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act.

QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

* * * * *

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? [Revised]

A. I.9. (Revised Proposed Answer): In general, a proposed biosimilar product may rely upon the reference product's clinical evaluation of 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 the proposed biosimilar product. 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 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 biosimilar applicant in appropriate circumstances.

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? [Revised]

A. I.10. (Revised Proposed Answer): 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 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 similarity) that is intended to support a submission under section 351(k) of the PHS Act. For a 3-way PK similarity study, samples of both comparator products should 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, reference product and, if applicable, 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.

- For multi-site studies, 3 or more dosage units each of the proposed biosimilar, reference product, and, if applicable, comparator product, at the site where the highest number of patients enrolled, and 1 or more dosage units from the next highest enrolling sites until the minimum recommended total number of retained samples is met.

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.
- Biologics other than protein therapeutics.
- A product intended for multi-dose administration.

* * * * *

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?

A. I.13. (Proposed Answer): "Publicly-available information" in this context generally includes 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 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 that certain biological products are safe, pure, and potent in order 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 of the 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?

A. I.14. (Proposed Answer): Yes. Under the BPCI Act, FDA can make a determination of interchangeability in a 351(k) application or any supplement to a 351(k) application. An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4) of

the PHS Act. At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.

Q. I.16. How can a proposed biosimilar product applicant fulfill the requirement for pediatric assessments under the Pediatric Research Equity Act (PREA)? [New]

A. I.16. (Proposed Answer): Applicants for proposed biosimilar products should address PREA requirements based upon the nature and extent of pediatric information in the reference product labeling.

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 BPCI Act and in the context of PREA. Under the BPCI Act, if a biosimilar applicant fulfills the requirements for demonstrating its product is biosimilar to a reference product in one condition of use for which the reference product is licensed (e.g., an indication for an adult population), information regarding the safety, purity, and potency of the reference product in one or more additional conditions of use for which the reference product is licensed (e.g., the same indication in the pediatric population) may be extrapolated to the proposed biosimilar product if sufficient scientific justification for extrapolation is provided by the applicant (see question and answer I.11 in FDA's guidance for industry on *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*). In this context, extrapolation occurs across drug products (i.e., from the reference product to the proposed biosimilar product).

Under PREA, a single sponsor with a single drug or biological product or drug or biological product line may conduct studies in an indication in one population (e.g., adults or older pediatric populations) and extrapolate efficacy findings to satisfy, in part, PREA requirements regarding use of that same product or product line in additional populations (e.g., younger pediatric populations). In this context, "extrapolation" occurs in a single product or product line without relying on studies comparing the product to an approved product and without conducting a full complement of additional studies in those additional populations. Under PREA, extrapolation of efficacy (but not safety or dosing) from adult populations to pediatric populations in a single drug or biological product or drug or biological product line may be permitted if the adult and pediatric indications are the same indication and the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients. Extrapolation from one pediatric age group to another pediatric age group for a single drug or biological

product or drug or biological product line also may be appropriate to fulfill a PREA requirement under these circumstances. However, under PREA, extrapolation of dosing or safety from adult populations to pediatric populations in a single drug or biological product or drug or biological product line generally is not permitted and will not satisfy a PREA requirement.

In the discussion that follows, the term "extrapolation" generally refers to extrapolation from the reference product to the proposed biosimilar product under the BPCI Act, not to extrapolation from adults or older pediatric populations to younger pediatric populations within a single product or product line under PREA.

- Adequate pediatric information in reference product labeling

  If the labeling for the reference product contains adequate pediatric information (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 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. See question and answer I.11 in FDA's guidance for industry on *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* for additional information on extrapolation under the BPCI Act.

  If the submitted scientific justification for extrapolation under the BPCI 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 indications for which a biosimilar applicant seeks licensure in adults, and applicable PREA requirements were deferred for the reference product for those indications, a biosimilar applicant should request a deferral of PREA requirements for those indications.

  If PREA requirements were waived for the reference product sponsor for those indications, and if the biosimilar applicant believes that its proposed product meets the requirements for a full or partial waiver of PREA requirements under section 505B(a)(4) of the FD&C Act, the biosimilar applicant should request a full or partial waiver for those indications.

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.17. When should a proposed biosimilar product applicant submit an initial pediatric study plan (PSP)? [New]

A. I.17. (Proposed Answer): Section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by Section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA), 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. This provision of FDASIA has an effective date of January 5, 2013. FDA has issued draft guidance on the PSP process, including the timing of PSP submission, as required by section 505B(e)(7) of the FD&C Act.

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 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.

The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or full waiver, if applicable, along with any supporting documentation; and should also include any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://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? [New]

A. I.18. (Proposed Answer): 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 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 reference product is an "injection," an applicant could not obtain licensure of a proposed biosimilar "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 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. For more information about the prescription drug user fee *bundling policy*, see FDA's guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf.

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 a proposed biosimilar development program (e.g., a bridging clinical PK and/or PD study), is a separate IND required for the non-U.S.-licensed product? [New]

A. I.19. (Proposed Answer): No, a sponsor may submit a single IND for its proposed biosimilar development program, and may submit information supporting the proposed clinical investigation with the non-U.S.-licensed comparator product under the same 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 to the U.S.-licensed reference product and scientific justification for the relevance of these comparative data to an assessment of biosimilarity.

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 that FDA waive the requirement for complete CMC information on the non-U.S.-licensed comparator product (21 CFR 312.10). The IND must include, as part of the waiver request, at least one of the following:

- A sufficient explanation why compliance with the complete 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.

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 trial.

As 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 Public Health Service Act against which the proposed biosimilar 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 biosimilar 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," "highly similar") that have not been made.

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

* * * * *

Q. II.3. What type of marketing application should be submitted for a proposed antibody-drug conjugate? [New[

A. II.3. (Proposed Answer): As described in further detail below, 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 (see section 503(g) of the FD&C Act; see, e.g., Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research (June 30, 2003), available at http://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 http://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 should 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?

A. III.1. (Proposed Answer): Yes. FDA is continuing to review the reference product exclusivity provisions of section 351(k)(7) of the PHS Act and has published a draft guidance addressing certain exclusivity issues (see FDA's draft guidance for industry on *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf). 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. 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.