Biosimilars: Questions and Answers Regarding Implementation 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)

April 2015
Biosimilarity

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Contains Nonbinding Recommendations

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Biosimilars: Questions and Answers Regarding Implementation 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 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). 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) (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.

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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).

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.

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 that will be provided in Revision 1 to the draft guidance on *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* and final guidance Q&As that are included in this guidance. FDA has maintained the original numbering of the Q&As used in the February 2012 draft guidance. Q&As that have not yet been finalized will appear in Revision 1 to the draft guidance, and the omission of these Q&As from the final 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)	(forthcoming)	(forthcoming)	
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
Part III. Exclusivity	III.1 (revised)	(forthcoming)	(forthcoming)	
	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 "that the biological product is highly similar to the reference product notwithstanding minor

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

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.1. Whom should a sponsor contact with questions about its proposed biosimilar development program?

A. I.1. If the reference product for a proposed biosimilar product is regulated by the Center for Drug Evaluation and Research (CDER), contact the Therapeutic Biologics and Biosimilars Team (TBBT) in CDER's Office of New Drugs at 301-796-0700.

If the reference product for a proposed biosimilar product is regulated by the Center for Biologics Evaluation and Research (CBER), contact the Office of Communication, Outreach and Development (OCOD) at 800-835-4709 or 240-402-7800 or by email to ocod@fda.hhs.gov.

For general questions related to FDA's implementation of the BPCI Act, contact Sandra Benton in CDER's Office of Medical Policy at 301-796-2500.

Q. I.2. When should a sponsor request a meeting with FDA to discuss their proposed biosimilar development program, and what data and information should a sponsor provide to FDA as background for this meeting?

A. I.2. Sponsors can request meetings at any time point in their development program. FDA recommends that sponsors refer to the draft guidance for industry titled *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* to determine the most appropriate meeting type to request. This draft guidance describes the different meeting types intended to facilitate biosimilar development programs in accordance with the Biosimilar User Fee Act of 2012 (BsUFA) 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.

See FDA's draft guidance for industry on *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf

See FDA's BsUFA website
http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm

Q. I.3. Can a proposed biosimilar product have a different formulation than the reference product?

A. I.3. Yes, differences between the formulation of a proposed 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 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 the interpretation of the statutory standard for biosimilarity, see FDA's draft 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?

A. I.4. Yes, 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 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 presentation 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, a prospective biosimilar applicant will not be able to obtain licensure under section 351(k) for its 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 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.

Additional considerations apply for a proposed interchangeable product. For example, in reviewing an application for a proposed interchangeable product, FDA may consider whether the differences from the reference product significantly alter critical design attributes, product performance, or operating principles, or would require additional instruction to healthcare providers or patients, for patients to be safely alternated or switched between the reference product and one or more interchangeable products without the intervention of the prescribing healthcare provider. Additional performance data about the delivery device may also be necessary.

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.

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?

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?

A. I.6. Yes, an applicant is not required to obtain licensure 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?

A. I.7. Yes, a biosimilar applicant generally may obtain licensure 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).

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?

A. I.8. Yes, 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 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;

- 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 also should 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 impact 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.

At this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.

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Q. I.11. Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed?

A. I.11. Yes. If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use for which licensure is sought; this may include:
  - the target/receptor(s) for each relevant activity/function of the product;
  - the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptor(s);
  - the relationships between product structure and target/receptor interactions;
  - the location and expression of the target/receptor(s);
- The PK and bio-distribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to "off-target" activities); and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.

In choosing which condition of use to study that would permit subsequent extrapolation of clinical data to other conditions of use, FDA recommends that a sponsor consider choosing a condition of use that would be adequately sensitive to detect clinically meaningful differences between the two products.

The sponsor of a proposed product may obtain licensure only for a condition of use that has been previously licensed for the reference product. If a reference product has a condition of use that was licensed under section 506(c) of the FD&C Act and 21 CFR part 601, subpart E (accelerated approval), and the reference product's clinical benefit in this condition of use has not yet been verified in postmarketing trials, the proposed product sponsor should consider studying another condition of use for which the reference product is licensed to avoid potential complications in the event that postmarketing trials fail to verify the clinical benefit of the reference product for the condition of use.

Q. I.12. How can an applicant demonstrate that its proposed injectable biosimilar product has the same "strength" as the reference product?

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 is the same as that of the 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 types of biological products.

In general, we expect injectable biological products to have both the same total content of drug substance (in mass or units of activity in a container closure) and the same concentration of drug substance (in mass or units of activity per unit volume) as the reference product to have the same "strength" under section 351(k)(2)(A)(i)(IV) of the PHS Act. We note, however, that for certain complex biological products, a modified approach may be needed.

The total content of drug substance generally should be expressed using the same measure as the reference product. For example, if the strength of the reference product is expressed as milligrams (mg) per total volume in a container closure, for example mg/5 milliliters (mL), the proposed biosimilar product generally should also describe its strength in mg/5 mL, rather than units per 5 mL. If the total content of drug substance is expressed in units of activity (e.g., international units (IU) or units per total volume in a container closure), the units of the proposed biosimilar product should be the same as the reference product.

The concentration of the drug substance (in mass or units of activity per unit volume) generally should be expressed using the same measure as the reference product. The extinction coefficient used to calculate the concentration of a protein drug substance should be determined experimentally, and a justification for the experimental method should be provided. If the proposed biosimilar product is a dry solid (e.g., lyophilized) from which a constituted or reconstituted solution is prepared, then the 351(k) application should contain information demonstrating that the concentration of the proposed biosimilar product, when constituted or reconstituted, is the same as that of the reference product.

The requirement for a 351(k) application to contain information demonstrating that the proposed product and the reference product have the same "strength" applies to both biosimilar products and interchangeable products.

* * * * *

Q. I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?

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

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

Section 505B(n) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, 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 required unless waived or deferred. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA. Therefore, if a biological product is determined to be interchangeable with the reference product, PREA would not be triggered and a pediatric assessment of the interchangeable product would not be required. However, if an applicant first seeks licensure of its proposed product as a non-interchangeable biosimilar product and intends to subsequently seek licensure of the product as interchangeable, the applicant still must address PREA requirements when it seeks initial licensure as a non-interchangeable biosimilar product.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies as early as practicable during product development. If there is no active IND for the proposed 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 draft question and answer I.17 in FDA's draft guidance for industry (revision 1) on *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, which, when finalized, will represent the Agency's current thinking on this topic. 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* (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf)

II. PROVISIONS RELATED TO REQUIREMENT 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?

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 regulatory definitions of "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 products will be regulated.

Protein — The term "protein" means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

For purposes of this definition, the size of the molecule is based on the total number of amino acids and is not limited to the number of amino acids in a contiguous sequence. However, compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile 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 less than 100 amino acids in size.

A chemically synthesized polypeptide, as defined, is not a "biological product" and will be regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory definition of a "biological product."

For purposes of this definition, the size of the molecule is based on the total number of amino acids and is not limited to the number of amino acids in a contiguous sequence. However, chemically synthesized compounds greater than 99 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.

FDA's interpretation of these statutory terms is informed by several factors, including the following. 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 has decided that the term "protein" in the statutory definition of biological product 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 considers any polymer composed of 40 or fewer amino acids to be 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 definition of polypeptide is most appropriate in this context because, among other reasons, this avoids describing an exception to the category of protein using a term that relates to a larger 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 up to 99 amino acids. 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.

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?

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.

III. EXCLUSIVITY

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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?

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 http://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.