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

Guidance for Industry

DRAFT GUIDANCE

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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)

December 2018
Biosimilars

Revision 2

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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This draft guidance document provides answers to common questions from prospective applicants and other interested parties regarding the Biologics Price Competition and Innovation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[1] This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug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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