Guidance for Industry

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

DRAFT GUIDANCE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 301-827-1800.

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)

February 2012
Biosimilarity

Guidance for Industry

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Guidance[1]
Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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).

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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 to a Reference Protein 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

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]

FDA's guidance documents, including this guidance, 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.

[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.

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

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 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 higher 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 biosimilar development program?

A. I.1. (Proposed Answer): If the reference product for a proposed biosimilar product is regulated by the Center for Drug Evaluation and Research (CDER), contact the Biosimilars Program Staff 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 301-827-1800 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 an initial meeting with FDA and what data and information should a sponsor provide to FDA as background for a proposed biosimilar development program?

A. I.2. (Proposed Answer): FDA recommends that sponsors of proposed biosimilar products request an initial meeting with FDA at such time as the sponsor can provide a proposed plan for its biosimilar development program, manufacturing process information (including planned methodology and assay validation), and preliminary comparative analytical data with the reference product.

Comparative analytical data provide the foundation for a biosimilar development program and can influence decisions about the type and amount of animal and clinical data needed. Such data should be available early in development and allow for a more detailed discussion with the Agency. FDA will best be able to provide meaningful input on the extent and scope of animal and clinical studies for a proposed biosimilar development program once the Agency has considered the comparative analytical data.

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

A. I.3. (Proposed Answer): 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 to a Reference Protein 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. (Proposed Answer): 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 "injectable" 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 certain 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:

- 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 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. (Proposed Answer): 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. 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. (Proposed Answer): 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 responses to Q. I.4 and Q. 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. (Proposed Answer): 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. (Proposed Answer): 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. We note, however, that for certain complex biological products, a modified approach may be 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 to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed likely would include a clinical PK and/or PD study conducted with the U.S.-licensed reference product.

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 product and BLA holder for the U.S.-licensed reference product, including whether the non-U.S.-licensed product, and/or any components thereof, are manufactured in the same facility(ies) as the U.S.-licensed reference product during the relevant time period;

- whether the non-U.S.-licensed 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 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 product and the U.S.-licensed reference product, including comparative physico-chemical characterization, bioassays/functional assays, and comparative clinical and/or nonclinical PK and/or PD data, as appropriate, and data to address any differences in formulation or primary packaging.

A sponsor also should address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed 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 product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. 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.

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?

A. I.9. (Proposed Answer): No. 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.

Q. I.10. How long 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?

A. I.10. (Proposed Answer): The requirements in 21 CFR 320.38 and 320.63 for retention of reserve samples of the products used in bioavailability and bioequivalence studies apply to applications submitted under section 505 of the FD&C Act. However, FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples in the same manner and for the same time period (at least 5

years) as described in 21 CFR 320.38 and 320.63 following a comparative clinical PK or PD study of the reference product and the proposed biosimilar product (or other clinical study in which PK or PD samples are collected) that is intended to support a submission under section 351(k) of the PHS Act. Retention of samples used in a comparative clinical PK or PD study or other clinical study in which PK or PD samples are collected would serve the same purpose described in the Final Rule for the cited regulations (58 FR 25918, April 28, 1993). Specifically, 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.

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. (Proposed Answer): 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 sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the biosimilar product to be licensed 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/receptors;
  - 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);
- 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.

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

A. I.15. (Proposed Answer): 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. An interchangeable product is not considered to have a "new active ingredient" for purposes of PREA. If a biological product is determined to be interchangeable with the reference product, a pediatric assessment of the interchangeable product is not required.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies during the investigational new drug (IND) stage of product development. See also the guidance for industry, *How to Comply with the Pediatric Research Equity Act* (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.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. (Proposed Answer): 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.

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."

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).

Although scientific references do not agree on the criteria that distinguish proteins from peptides, including the exact size at which a chain of amino acids becomes a protein, several references support a threshold of 40 amino acids as 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. (Proposed Answer): 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

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 requested public comment on factors to consider in FDA's interpretation of certain statutory provisions (see Docket No. FDA-2010-N-0477). 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. At this time, FDA suggests that an applicant's request for reference product exclusivity specifically describe how the proposed product meets the statutory requirements in section 351(k)(7) of the PHS Act, and include adequate data and information to support the request.

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. (Proposed Answer): 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.