
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

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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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.

I. INTRODUCTION

This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product (hereinafter *proposed product*²) is biosimilar to a reference product for purposes of the submission of a marketing application under section 351(k) of the Public Health Service Act (PHS Act).³ The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148). Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations for demonstrating biosimilarity. The scientific principles described in this guidance may also apply to other types of proposed biosimilar biological products.

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

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² In Section II (Scope) of this document, the term *proposed product* is also used to describe a product that is the subject of a new drug application (NDA) submitted through the pathway described by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

³ The statutory definition of *biosimilar* and definitions of selected other terms used in this guidance are provided in the glossary at the end of the document.

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- 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
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

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

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

II. SCOPE

This guidance gives an overview of FDA's approach to determining biosimilarity and discusses important scientific considerations in demonstrating biosimilarity, including:

- A stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness
- The *totality-of-the-evidence* approach that FDA will use to review applications for biosimilar products, consistent with a longstanding Agency approach to evaluation of scientific evidence⁴
- General scientific principles in conducting comparative structural analyses, functional assays, animal testing, human PK and PD studies, clinical immunogenicity assessments, and comparative clinical studies (including clinical study design issues)

⁴ The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* provides insight into the concept of the *totality-of-the-evidence* approach in a different context (i.e., considerations of both the quantity and quality of the evidence to support effectiveness for drugs and biological products). Some of the principles discussed in that guidance may also be relevant in the design of a development program to support a demonstration of biosimilarity.

We update guidances periodically. For the most recent version of a guidance, check the FDA guidance Web page at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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Additional topics discussed include the following:

- Considerations of the complexities of therapeutic protein products when designing a biosimilar development program, including manufacturing process considerations
- Use of data derived from studies comparing a proposed product with a non-U.S.-licensed comparator product
- Postmarketing safety monitoring considerations

This guidance applies to applications submitted under section 351(k) of the PHS Act. However, some scientific principles described in this guidance may be informative for the development of certain biological products under section 505(b)(2) of the FD&C Act.⁵ Section 505(b)(2) of the FD&C Act and section 351(k) of the PHS Act are two separate statutory schemes. This guidance is not intended to describe any relationship between the standards for approval under these schemes.

III. 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 demonstrated to be biosimilar to or interchangeable with a reference product. 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.⁶ Section 351(i) of the PHS Act 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.”⁷ The BPCI Act also amended the definition of biological product to include “protein (except any chemically synthesized polypeptide).”⁸

Under section 351(k) of the PHS Act, a proposed biological product that is demonstrated to be biosimilar to a reference product can rely on certain existing scientific knowledge about the

⁵ A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., the Agency’s finding of safety and/or effectiveness for a listed drug or published literature). A 505(b)(2) application that seeks to rely on a listed drug (i.e., the reference product) must contain adequate data and information to demonstrate that the proposed product is sufficiently similar to the listed drug to justify reliance, in part, on FDA’s finding of safety and/or effectiveness for the listed drug. Any aspects of the proposed product that differ from the listed drug must be supported by adequate data and information to support the safety and effectiveness of the proposed product.

⁶ General scientific issues relating to the demonstration of interchangeability will be addressed separately.

⁷ Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

⁸ Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.

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safety, purity, and potency⁹ of the reference product to support licensure. FDA will license a proposed biological product submitted under section 351(k) of the PHS Act if FDA “determines that the information submitted in the application . . . is sufficient to show that the biological product is biosimilar to the reference product . . .” and the 351(k) applicant (or other appropriate person) consents to an inspection of the facility that is the subject of the application (i.e., a facility in which the proposed biological product is manufactured, processed, packed, or held).¹⁰

An application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that “the biological product is biosimilar to a reference product” based upon data derived from:¹¹

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

The Agency has the discretion to determine that an element described above is unnecessary in a 351(k) application.¹² FDA advises sponsors intending to develop biosimilar products to meet with FDA to present their product development plans and establish a schedule of milestones that will serve as landmarks for future discussions with the Agency. FDA anticipates that early discussions with FDA about product development plans and about approaches to providing adequate scientific justifications will facilitate biosimilar development.¹³

IV. COMPLEXITIES OF PROTEIN PRODUCTS

A sponsor should consider the complexities of protein products and related scientific issues when designing a development program to support a demonstration of biosimilarity.

⁹ The standard for licensure of a biological product as *potent* under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). In this guidance, we use the terms *safety and effectiveness* and *safety, purity, and potency* interchangeably in the discussions pertaining to biosimilar products.

¹⁰ Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(3) of the PHS Act.

¹¹ Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(i)(I) of the PHS Act.

¹² Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(ii) of the PHS Act.

¹³ See the draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* for a detailed discussion. When final, this guidance will represent FDA’s current thinking on this topic.

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A. Nature of Protein Products and Related Scientific Considerations

Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in protein structure can arise. Because even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety and/or effectiveness, it is important to evaluate these differences.

In general, proteins can differ in at least three ways: (1) primary amino acid sequence; (2) modification to amino acids, such as sugar moieties (glycosylation) or other side chains; and (3) higher order structure (protein folding and protein-protein interactions). Modifications to amino acids may lead to heterogeneity and can be difficult to control. Protein modifications and higher order structure can be affected by formulation and environmental conditions, including light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Additionally, process- as well as product-related impurities may increase the likelihood and/or the severity of an immune response to a protein product, and certain excipients may limit the ability to characterize the protein product.

Advances in analytical sciences enable some protein products to be extensively characterized with respect to their physicochemical and biological properties, such as higher order structures and functional characteristics. These analytical methodologies have increasingly improved the ability to identify and characterize not only the drug substance of a protein product but also excipients and product- and process-related impurities.

Despite such significant improvements in analytical techniques, however, current analytical methodology may not be able to detect all relevant structural and functional differences between two protein products. In addition, there may be incomplete understanding of the relationship between a product's structural attributes and its clinical performance. Thus, as set forth in the PHS Act, data derived from analytical studies, animal studies, and a clinical study or studies are required to demonstrate biosimilarity unless FDA determines an element unnecessary.¹⁴

B. Manufacturing Process Considerations

Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. For example, differences in biological systems used to manufacture a protein product may cause different posttranslational modifications, which in turn may affect the safety and/or effectiveness of the product. Thus, when the manufacturing process for a marketed protein product is changed, the application holder must assess the effects of the change and demonstrate—through appropriate analytical testing, functional assays, and/or in some cases animal and/or clinical studies—that the change does not have an adverse effect on the identity, strength, quality, purity, or potency of the product as they relate to the safety or

¹⁴ Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(i)(I) of the PHS Act.

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effectiveness of the product.¹⁵ The International Conference on Harmonisation (ICH) guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (ICH Q5E) describes scientific principles in the comparability assessment for manufacturing changes.

Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer. This is because a manufacturer that modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. By contrast, the manufacturer of a proposed product is likely to have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, FDA anticipates that more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product.

V. U.S.-LICENSED REFERENCE PRODUCT AND OTHER COMPARATORS

To obtain licensure of a proposed product under section 351(k) of the PHS Act, a sponsor must demonstrate that the proposed product is biosimilar to a single reference product that previously has been licensed by FDA.¹⁶ In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product. As a scientific matter, analytical studies and at least one clinical PK study and, if appropriate, at least one PD study, intended to support a demonstration of biosimilarity for purposes of section 351(k) of the PHS Act 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. However, a sponsor may seek to use data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed comparator product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, 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.¹⁷ Sponsors are encouraged to discuss with FDA during the development program their plans to provide an adequate scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of such justification and bridge will be made by FDA during review of the 351(k) application.

¹⁵ See 21 CFR 601.12 and 21 CFR 314.70 for regulatory requirements for changes (including manufacturing changes) made to a licensed biologics license application (BLA) and an approved NDA, respectively.

¹⁶ Sections 7002(a)(2) and (b)(3) of the Affordable Care Act, adding sections 351(k), 351(i)(2), and 351(i)(4) of the PHS Act.

¹⁷ For examples of issues that a sponsor may need to address, see the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

VI. APPROACHES TO DEVELOPING AND ASSESSING EVIDENCE TO DEMONSTRATE BIOSIMILARITY

FDA recommends that sponsors use a stepwise approach to develop the evidence needed to demonstrate biosimilarity. FDA intends to consider the *totality of the evidence* provided by a sponsor when the Agency evaluates the sponsor's demonstration of biosimilarity, consistent with a longstanding Agency approach to evaluating scientific evidence.¹⁸

A. Using a Stepwise Approach to Demonstrate Biosimilarity

The purpose of a biosimilar development program is to support a demonstration of biosimilarity between a proposed product and a reference product, including an assessment of the effects of any observed differences between the products, but not to independently establish the safety and effectiveness of the proposed product. FDA recommends that sponsors use a stepwise approach to developing the data and information needed to support a demonstration of biosimilarity. At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty. Where possible, studies conducted should be designed to maximize their contribution to demonstrating biosimilarity. For example, a clinical immunogenicity study may also provide other useful information about the safety profile of the proposed product.

The stepwise approach should start with extensive structural and functional characterization of both the proposed product and the reference product, which serves as the foundation of a biosimilar development program (sections VII.A and VII.B). The more comprehensive and robust the comparative structural and functional characterization—the extent to which these studies are able to identify (qualitatively or quantitatively) differences in relevant product attributes between the proposed product and the reference product (including the drug substance, excipients, and impurities)—the more useful such characterization will be in determining what additional studies may be needed. For example, rigorous structural and functional comparisons that show minimal or no difference between the proposed product and the reference product will strengthen the scientific justification for a selective and targeted approach to animal and/or clinical testing to support a demonstration of biosimilarity. It may be useful to further quantify the similarity or differences between the two products using a meaningful *fingerprint*-like analyses algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods. Such a strategy may further reduce the possibility of undetected structural differences between the products and lead to a more selective and targeted approach to animal and/or clinical testing. A sufficient understanding of the mechanism of action (MOA) of the drug substance and clinical relevance of any observed structural differences, clinical knowledge of the reference product and its class that indicates low overall safety risks, and the availability of a relevant PD measure(s) may provide further scientific justification for a selective and targeted approach to animal and/or clinical studies.

¹⁸ See footnote 4.

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The sponsor should then consider the role of animal data in assessing toxicity and, in some cases, in providing additional support for demonstrating biosimilarity and in contributing to the immunogenicity assessment (section VII.C). The sponsor should then conduct comparative human PK and PD studies (if there is a relevant PD measure(s)) (section VII.D.1) and compare the clinical immunogenicity of the two products in an appropriate study population (section VII.D.2). If there is residual uncertainty about biosimilarity after conducting structural analyses, functional assays, animal testing, human PK and PD studies, and the clinical immunogenicity assessment, the sponsor should then consider what additional clinical data may be needed to adequately address that uncertainty (section VII.D.3). FDA encourages sponsors to consult extensively with the Agency after completion of comparative structural and functional analyses (before finalizing the clinical program) and throughout development as needed.

FDA recognizes that some of the aforementioned investigations could be performed in parallel; however, the Agency recommends that sponsors use a stepwise approach to better address residual uncertainty about biosimilarity that might remain at each step and incorporate FDA's advice provided after FDA review of data and information collected at certain milestones.

B. Using a *Totality-of-the-Evidence* Approach to Assess a Demonstration of Biosimilarity

In evaluating a sponsor's demonstration of biosimilarity, FDA will consider the totality of the data and information submitted in the application, including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical study(ies) data. FDA intends to use a risk-based approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.

Thus, a sponsor may be able to demonstrate biosimilarity even though there are formulation or minor structural differences, provided that the sponsor provides sufficient data and information demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity. For example, differences in certain posttranslational modifications or differences in certain excipients (e.g., human serum albumin) might not preclude a finding of biosimilarity if data and information provided by the sponsor show that the proposed 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 products in terms of safety, purity, and potency.¹⁹ Clinically meaningful differences could include a difference in the expected range of safety, purity, or potency of the proposed product and the reference product. By contrast, slight differences in rates of occurrence of certain adverse events between the two products ordinarily would not be considered clinically meaningful differences.

¹⁹ In this example, because some excipients may affect the ability to characterize products, a sponsor should provide evidence that the excipients used in the reference product will not affect the ability to characterize and compare the products.

VII. DEMONSTRATING BIOSIMILARITY

This section discusses scientific considerations in the stepwise approach to developing data and information needed to support a demonstration of biosimilarity. To demonstrate biosimilarity, a sponsor must provide sufficient data and information to show that the proposed product and the reference product are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency.²⁰ The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

A. Structural Analyses

The PHS Act requires that a 351(k) application include information demonstrating biosimilarity based on data derived from, among other things, analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, unless FDA determines that an element is unnecessary in a 351(k) application.²¹ FDA expects that first, a sponsor will extensively characterize the proposed product and the reference product with state-of-the-art technology, because extensive characterization of both products serves as the foundation for a demonstration of biosimilarity. It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product. However, minor modifications such as N- or C-terminal truncations that are not expected to change the product performance may be justified and should be explained by the sponsor. Additionally, sponsors should consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structure; posttranslational modifications; and biological activities) to demonstrate that the proposed product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. The more comprehensive and robust the comparative structural and functional characterization is, the stronger the scientific justification for a selective and targeted approach to animal and/or clinical testing.

Sponsors should use appropriate analytical methodologies with adequate sensitivity and specificity for structural characterization of the proteins. Generally, such tests include the following comparisons of the proposed product and the reference product:

- Primary structures, such as amino acid sequence
- Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation)
- Enzymatic posttranslational modifications, such as glycosylation and phosphorylation

²⁰ Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

²¹ Section 7002(a)(2) of the Affordable Care Act, adding sections 351(k)(2)(A)(i)(I)(aa) and 351(k)(2)(A)(ii) of the PHS Act.

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- Other potential variations, such as protein deamidation and oxidation
- Intentional chemical modifications, such as PEGylation sites and characteristics

Sponsors should conduct extensive structural characterization of both the proposed product and the reference product in multiple representative lots to understand the lot-to-lot variability of both products in the manufacturing processes. Lots used for the analyses should support the biosimilarity of both the clinical material used in the clinical study(ies) intended to support a demonstration of biosimilarity, and the to-be-marketed proposed product, to the reference product. Characterization of lots manufactured during process development for the proposed product may also be useful. Sponsors should justify the selection of the representative lots, including the number of lots.

In addition, FDA recommends that sponsors analyze the finished dosage form of multiple lots of the proposed product and the reference product, assessing excipients and any formulation effect on purity, product- and process-related impurities, and stability.²² Differences in formulation between the proposed product and the reference product are among the factors that may affect the extent and nature of subsequent animal or clinical testing.²³ A sponsor considering manufacturing changes after completing the initial analytical similarity assessment or after completing clinical testing intended to support a 351(k) application should perform an additional analytical similarity assessment with lots manufactured by the new process and the reference product and establish comparability of the proposed product manufactured by the old and new manufacturing processes. The nature and extent of the changes may determine the extent of the analytical similarity and comparability studies and any necessary additional studies.

If the reference product or the proposed product cannot be adequately characterized with state-of-the-art technology, the application for the proposed product may not be appropriate for submission under section 351(k) of the PHS Act; and the sponsor should consult FDA for guidance on the appropriate submission pathway.

B. Functional Assays

The pharmacologic activity of protein products should be evaluated by in vitro and/or in vivo functional assays. In vitro assays may include, but are not limited to, biological assays, binding assays, and enzyme kinetics. In vivo assays may include the use of animal models of disease (e.g., models that exhibit a disease state or symptom) to evaluate functional effects on pharmacodynamic markers or efficacy measures. A functional evaluation comparing a proposed product to the reference product using these types of assays is also an important part of the foundation that supports a demonstration of biosimilarity and may be used to scientifically justify a selective and targeted approach to animal and/or clinical testing.

²² See also the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*.

²³ See also the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*.

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Sponsors can use functional assays to provide additional evidence that the biologic activity and potency of the proposed product are highly similar to those of the reference product and/or to support a conclusion that there are no clinically meaningful differences between the proposed product and the reference product. Such assays also may be used to provide additional evidence that the MOA of the two products is the same to the extent the MOA of the reference product is known. Functional assays can be used to provide additional data to support results from structural analyses, investigate the consequences of observed structural differences, and explore structure-activity relationships.²⁴ These assays are expected to be comparative so they can provide evidence of similarity or reveal differences in the performance of the proposed product compared to the reference product, especially differences resulting from variations in structure that cannot be detected using current analytical methods. FDA also recommends that sponsors discuss limitations of the assays they used when interpreting results in their submissions to FDA. Such discussions would be useful for the evaluation of analytical data and may guide whether additional analytical testing would be necessary to support a demonstration of biosimilarity.

Functional assays can also provide information that complements the animal and clinical data in assessing the potential clinical effects of minor differences in structure between the proposed product and the reference product. For example, cell-based bioactivity assays may be used to detect the potential for inducing cytokine release syndrome in vivo. The available information about these assays, including sensitivity, specificity, and extent of validation, can affect the amount and type of additional animal or clinical data that may be needed to establish biosimilarity. As is the case for the structural evaluation, sponsors should justify the selection of the representative lots, including the number of lots.

C. Animal Data

The PHS Act also requires that a 351(k) application include information demonstrating biosimilarity based on data derived from animal studies (including the assessment of toxicity), unless FDA determines that such studies are not necessary in a 351(k) application.²⁵ Results from animal studies may be used to support the safety evaluation of the proposed product and more generally to support the demonstration of biosimilarity between the proposed product and the reference product.

1. Animal Toxicity Studies

As a scientific matter, animal toxicity data are considered useful when, based on the results of extensive structural and functional characterization, uncertainties remain about the safety of the proposed product that need to be addressed before initiation of clinical studies in humans (assuming results from animal studies can meaningfully address the remaining uncertainties).

²⁴ See also the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*.

²⁵ Section 7002(a)(2) of the Affordable Care Act, adding sections 351(k)(2)(A)(i)(I)(bb) and 351(k)(2)(A)(ii) of the PHS Act.

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The scope and extent of any animal toxicity studies will depend on information about the reference product, information about the proposed product, and the extent of known similarities or differences between the two. As described further in section IX, FDA encourages sponsors to initiate early discussions with the Agency with regard to their biosimilar development plans, including identifying appropriate scientific justifications for not conducting an animal toxicity study or for the scope and extent of such a study.

If comparative structural and functional data using the proposed product provide strong support for analytical similarity to a reference product, then limited animal toxicity data may be sufficient to support initial clinical use of the proposed product. Such a study may be non-sacrificial and include endpoints that measure in-life parameters, PD, and PK (with an assessment of immunogenicity).

If the structural and functional data are limited in scope or there are concerns about the proposed product quality, a general toxicology study may be needed that includes full animal pathology, histopathology, PD, PK, and immunogenicity assessments. When animal toxicology studies are conducted, it will be useful to perform a comparative study with the proposed product and the reference product (i.e., comparative bridging toxicology studies). The selection of dose, regimen, duration, and test species for these studies should provide a meaningful toxicological comparison between the two products. It is important to understand the limitations of such animal studies (e.g., small sample size, intra-species variations) when interpreting results comparing the proposed product and the reference product. For a detailed discussion on the design of animal toxicology studies relevant to biological products, see the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (ICH S6(R1)).

Safety data derived from animal toxicity studies generally are not expected if clinical data (e.g., from studies or marketing experience outside the United States) using the proposed product are available (with the same proposed route of administration and formulation) that provide sufficient evidence for its safe use, unless animal toxicity studies are otherwise needed to address a specific product quality concern.

Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the product (i.e., no species in which the biologic activity of the product mimics the human response). For a detailed discussion about demonstrating species relevance, see the criteria described in ICH S6(R1). However, there may be some instances when animal data from a pharmacologically nonresponsive species (including rodents) may be useful to support clinical studies with a proposed product that has not been previously tested in human subjects, for example, comparative PK and systemic tolerability studies. If animal toxicity studies are not warranted based on an acceptable scientific justification, additional comparative in vitro testing (using human cells or tissues when appropriate) is encouraged. Data derived using human cells can provide important comparative information between the proposed product and the reference product regarding potential clinical effects (section VII.B), particularly in situations where there are no animal species available for safety testing.

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In general, nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not warranted when the proposed product and the reference product have been demonstrated to be highly similar through extensive structural and functional characterization and animal toxicity studies (if such studies were conducted).

2. Inclusion of Animal PK and PD Measures

Under certain circumstances, a single-dose study in animals comparing the proposed product and the reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity. Specifically, sponsors can use results from animal studies to support the degree of similarity based on the PK and PD profiles of the proposed product and the reference product. PK and PD measures also can be incorporated into a single animal toxicity study, where appropriate. Animal PK and PD assessment will not negate the need for human PK and PD studies.

3. Interpreting Animal Immunogenicity Results

Animal immunogenicity assessments are conducted to assist in the interpretation of the animal study results and generally do not predict potential immune responses to protein products in humans. However, when differences in manufacturing (e.g., impurities or excipients) between the proposed product and the reference product may result in differences in immunogenicity, measurement of anti-therapeutic protein antibody responses in animals may provide useful information. Additionally, differences observed in animal immunogenicity assessments may reflect potential structural or functional differences between the two products not captured by other analytical methods.

D. Clinical Studies – General Considerations

The sponsor of a proposed product must include in its submission to FDA information demonstrating 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.”²⁶

The nature and scope of the clinical study or studies will depend on the nature and extent of residual uncertainty about biosimilarity after conducting structural and functional characterization and, where relevant, animal studies. The frequency and severity of safety risks

²⁶ Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2)(B) of the PHS Act. To support a demonstration of biosimilarity, the statute also requires a clinical study or studies (including the assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product, unless FDA determines an element unnecessary (section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(i)(I)(cc) of the PHS Act). As a general matter, FDA anticipates that the recommendations described in this guidance designed to demonstrate that the proposed product is highly similar to its reference product notwithstanding minor differences in clinically inactive components and to demonstrate that no clinically meaningful differences exist between the two products will provide data sufficient to demonstrate the safety, purity, and potency of the proposed product. FDA recommends that sponsors identify which study or studies will provide data regarding no clinically meaningful differences prior to starting clinical studies.

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and other safety and effectiveness considerations (e.g., poor relationship between pharmacologic effects and effectiveness) for the reference product may also affect the design of the clinical program. The scope of the clinical program and the type of clinical studies (i.e., comparative human PK, PD, clinical immunogenicity, or clinical safety and effectiveness) should be scientifically justified by the sponsor.

As a scientific matter, FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s))²⁷ and a clinical immunogenicity assessment. In certain cases, the results of these studies may provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between the proposed biosimilar product and the reference product. However, if residual uncertainty about biosimilarity remains after conducting these studies, an additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products.

1. Human Pharmacology Data²⁸

Human PK and PD profiles of a protein product often cannot be adequately predicted from functional assays and/or animal studies alone. Therefore, human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity. Both PK and PD studies (where there is a relevant PD measure(s)) generally will be expected to establish biosimilarity, unless a sponsor can scientifically justify that such a study is not needed.²⁹ Even if relevant PD measures are not available, sensitive PD endpoints may be assessed if such assessment may help reduce residual uncertainty about biosimilarity.

Sponsors should provide a scientific justification for the selection of the human PK and PD study population (e.g., patients versus healthy subjects) and parameters, taking into consideration the relevance and sensitivity of such population and parameters, the population and parameters studied for the licensure for the reference product, as well as the current knowledge of the intra-subject and inter-subject variability of human PK and PD for the reference product. For example, comparative human PK and PD studies should use a population, dose(s), and route of administration that are adequately sensitive to allow for the detection of differences in PK and PD profiles. FDA recommends that, to the extent possible, the sponsor select PD measures that (1) are relevant to clinical

²⁷ A PD study may also incorporate PK measures (i.e., a combined PK/PD study).

²⁸ See the draft guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* for a more detailed discussion on the design and use of clinical pharmacology studies to support a demonstration of biosimilarity. When final, this guidance will represent FDA's current thinking on this topic.

²⁹ PK and PD studies provide quite different types of information. In simple terms, a PK study measures how the body acts on a drug (how the drug is absorbed, distributed, metabolized, and eliminated), and a PD study measures how the drug acts on the body (typically assessing a measure(s) related to the drug's biochemical and physiologic effects on the body). Therefore, one type of study does not duplicate or substitute for the information provided by the other. Both PK studies and PD studies provide important information for assessing biosimilarity; and therefore, as a scientific matter, comparative human PK studies and PD studies (where there is a relevant PD measure(s)) generally will be expected.

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outcomes (e.g., on mechanistic path of MOA or disease process related to effectiveness or safety); (2) are measurable for a sufficient period of time after dosing to ascertain the full PD response and with appropriate precision; and (3) have the sensitivity to detect clinically meaningful differences between the proposed product and the reference product. Use of multiple PD measures that assess different domains of activities may also be of value.

When there are established dose-response or systemic exposure-response relationships (response may be PD measures or clinical endpoints), it is important to select, whenever possible, a dose(s) for study on the steep part of the dose-response curve for the proposed product. Studying doses that are on the plateau of the dose-response curve is unlikely to detect clinically meaningful differences between the two products. Sponsors should predefine and justify the criteria for PK and PD parameters for studies included in the application to demonstrate biosimilarity.

A human PK study that demonstrates similar exposure (e.g., serum concentration over time) for the proposed product and the reference product may provide support for a demonstration of biosimilarity. A human PK study may be particularly useful when the exposure correlates with clinical safety and effectiveness. A human PD study that demonstrates a similar effect on a relevant PD measure(s) related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) represents even stronger support for a biosimilarity determination.

In certain cases, establishing a similar clinical PK, PD, and immunogenicity profile may provide sufficient clinical data to support a conclusion that there are no clinically meaningful differences between the two products. PK and PD parameters are generally more sensitive than clinical efficacy endpoints in assessing the similarity of two products. For example, an effect on thyroid stimulating hormone (TSH) levels would provide a more sensitive comparison of two thyroxine products than an effect on clinical symptoms of euthyroidism.

In cases where there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary. For example, similar dose-response curves of the proposed product and the reference product on a relevant PD measure, combined with a similar human PK profile and clinical immunogenicity profile, could provide sufficient evidence to support a conclusion of no clinically meaningful differences. Even if there is still residual uncertainty about biosimilarity based on PK and PD results, establishing a similar human PK and PD profile may provide a scientific basis for a selective and targeted approach to subsequent clinical testing.

For PD studies using products with a short half-life (e.g., shorter than 5 days), a rapid PD response, and a low incidence of immunogenicity, a crossover design is appropriate, when feasible. For products with a longer half-life (e.g., more than 5 days), a parallel design will usually be needed. Sponsors should provide a scientific justification for the selection of study dose (e.g., one dose or multiple doses) and route of administration.

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FDA recommends that sponsors consider the duration of time it takes for a PD measure to change and the possibility of nonlinear PK. FDA also encourages consideration of the role of modeling and simulation in designing comparative human PK and PD studies.

2. Clinical Immunogenicity Assessment

The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses. Immune responses may affect both the safety and effectiveness of the product by, for example, altering PK, inducing anaphylaxis, or promoting development of neutralizing antibodies that neutralize the product as well as its endogenous protein counterpart. Thus, establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key element in the demonstration of biosimilarity. Structural, functional, and animal data³⁰ are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will be expected. FDA encourages that, where feasible, sponsors collect immunogenicity data in any clinical study, including human PK or PD studies.

The extent and timing of the clinical immunogenicity assessment will vary depending on a range of factors, including the extent of analytical similarity between the proposed product and the reference product, and the incidence and clinical consequences of immune responses for the reference product. For example, if the clinical consequence is severe (e.g., when the reference product is a therapeutic counterpart of an endogenous protein with a critical, nonredundant biological function or is known to provoke anaphylaxis), a more extensive immunogenicity assessment will likely be needed to support a demonstration of biosimilarity. If the immune response to the reference product is rare, a premarketing evaluation to assess apparent differences in immune responses between the two products may be adequate to support biosimilarity. In addition, in some cases certain safety risks may need to be evaluated through postmarketing surveillance or studies.

The overall immunogenicity assessment should consider the nature of the immune response (e.g., anaphylaxis, neutralizing antibody), the clinical relevance and severity of consequences (e.g., loss of efficacy of life-saving therapeutic and other adverse effects), the incidence of immune responses, and the population being studied. FDA recommends use of a comparative parallel design (i.e., a head-to-head study) in treatment-naïve patients as the most sensitive design for a premarketing study to assess potential differences in the risk of immunogenicity. However, depending on the clinical experience of the reference and proposed products (taking into consideration the conditions of use and patient population), a sponsor may need to evaluate a subset of patients to provide a substantive descriptive assessment of whether a single cross-over

³⁰ Section VII.C.3 of this guidance contains a discussion concerning the interpretation of animal immunogenicity results.

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from the reference product to the proposed biosimilar would result in a major risk in terms of hypersensitivity, immunogenicity, or other reactions. The design of any study to assess immunogenicity and acceptable differences in the incidence and other parameters of immune response should be discussed with FDA before initiating the study. Differences in immune responses between a proposed product and the reference product in the absence of observed clinical sequelae may be of concern and may warrant further evaluation (e.g., extended period of follow-up evaluation).

The study population used to compare immunogenicity should be justified by the sponsor and agreed to by the Agency. If a sponsor is seeking to extrapolate immunogenicity findings for one condition of use to other conditions of use, the sponsor should consider using a study population and treatment regimen that are adequately sensitive for predicting a difference in immune responses between the proposed product and the reference product across the conditions of use. Usually, this will be the population and regimen for the reference product for which development of immune responses with adverse outcomes is most likely to occur (e.g., patients on background immunosuppressants would be less likely to develop immune responses than patients who are not immunosuppressed).

The selection of clinical immunogenicity endpoints or PD measures associated with immune responses to therapeutic protein products (e.g., antibody formation and cytokine levels) should take into consideration the immunogenicity issues that have emerged during the use of the reference product. Sponsors should prospectively define the clinical immune response criteria (e.g., definitions of significant clinical events such as anaphylaxis), using established criteria where available, for each type of potential immune response and should obtain agreement from FDA on these criteria before initiating the study.

The duration of follow-up evaluation should be determined based on (1) the time course for the generation of immune responses (such as the development of neutralizing antibodies, cell-mediated immune responses) and expected clinical sequelae (informed by experience with the reference product), (2) the time course of disappearance of the immune responses and clinical sequelae following cessation of therapy, and (3) the length of administration of the product. For example, for chronically administered agents, the follow-up period is recommended to be 1 year unless a shorter duration can be scientifically justified based on the *totality of the evidence* to support biosimilarity.

As a scientific matter, a sponsor should evaluate the following antibody parameters in the clinical immunogenicity assessment:

- Titer, specificity, relevant isotype distribution, time course of development, persistence, disappearance, impact on PK, and association with clinical sequelae
- Neutralization of product activity: neutralizing capacity to all relevant functions (e.g., uptake and catalytic activity, neutralization for replacement enzyme therapeutics)

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The sponsor should develop assays capable of sensitively detecting immune responses, even in the presence of the circulating drug product (proposed product and reference product).³¹ The proposed product and the reference product should be assessed in the same assay with the same patient sera whenever possible. FDA recommends that immunogenicity assays be developed and validated early in development, and the validation should consider both the proposed product and the reference product. Sponsors should consult with FDA on the sufficiency of assays before initiating any clinical immunogenicity assessment.

3. Comparative Clinical Studies

As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there is residual uncertainty about whether there are clinically meaningful differences between the proposed product and the reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. A sponsor should provide a scientific justification if it believes that a comparative clinical study is not necessary.

The following are examples of factors that may influence the type and extent of the comparative clinical study data needed:

- a. The nature and complexity of the reference product, the extensiveness of structural and functional characterization, and the findings and limitations of comparative structural, functional, and nonclinical testing, including the extent of observed differences
- b. The extent to which differences in structure, function, and nonclinical pharmacology and toxicology predict differences in clinical outcomes, in conjunction with the degree of understanding of the MOA of the reference product and disease pathology
- c. The extent to which human PK or PD is known to predict clinical outcomes (e.g., PD measures known to be relevant to effectiveness or safety)
- d. The extent of clinical experience with the reference product and its therapeutic class, including the safety and risk-benefit profile (e.g., whether there is a low potential for off-target adverse events), and appropriate endpoints and biomarkers for safety and effectiveness (e.g., availability of established, sensitive clinical endpoints)
- e. The extent of any other clinical experience with the proposed product (e.g., if the proposed product has been marketed outside the United States)

³¹ See the draft guidance for industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins* for a detailed discussion. When final, this guidance will represent FDA's current thinking on this topic.

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A sponsor should provide a scientific justification for how it intends to use these factors to determine what type(s) of clinical study(ies) are needed and the design of any necessary study(ies). For example, if a comparative clinical study is needed, a sponsor should explain how these factors were considered in determining the design of such a study, including the endpoint(s), population, similarity margin, and statistical analyses.

Additionally, specific safety or effectiveness concerns regarding the reference product and its class (including history of manufacturing- or source-related adverse events) may warrant more comparative clinical data. Alternatively, if there is information regarding other biological products that could support a biosimilarity determination (with marketing histories that demonstrate no apparent differences in clinical safety and effectiveness profiles), such information may be an additional factor supporting a selective and targeted approach to the clinical program.

Endpoints

A sponsor should use endpoints that can assess clinically meaningful differences between the proposed product and the reference product in a comparative clinical study. The endpoints may be different from those used as primary endpoints in the reference product's clinical studies if they are scientifically supported. As discussed in section VII.D.1, certain endpoints (such as PD measures) are more sensitive than clinical endpoints and, therefore, may enable more precise comparisons of relevant therapeutic effects. There may be situations when the assessment of multiple PD measures in a comparative clinical study will enhance the sensitivity of the study. The adequacy of the endpoints depends on the extent to which PD measures correlate with clinical outcome, the extent of structural and functional data support for biosimilarity, the understanding of MOA, and the nature or seriousness of outcome affected.

Study Population

The choice of study population should allow for an assessment of clinically meaningful differences between the proposed product and the reference product. Often the study population will have characteristics consistent with those of the population studied for the licensure of the reference product for the same indication. However, there are cases where a study population could be different from that in the clinical studies that supported the licensure of the reference product. For example, if a genetic predictor of response was developed following licensure of the reference product, it may be possible to use patients with the response marker as the study population.

Sample Size and Duration of Study

The sample size for and duration of the comparative clinical study should be adequate to allow for the detection of clinically meaningful differences between the two products. As discussed in section VII.D.1, certain endpoints, such as PD measures, may be more sensitive than clinical endpoints and facilitate the conduct of a smaller study of limited duration. In such cases where the size and duration of the comparative clinical study may

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not be adequate for the detection of relevant safety signals, a separate assessment of safety and immunogenicity may be needed.

Study Design and Analyses

A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences between the proposed product and the reference product. The design should take into consideration the nature and extent of residual uncertainty that remains about biosimilarity based on data generated from comparative structural and functional characterization, animal testing, human PK and PD studies, and clinical immunogenicity assessment.

Generally, FDA expects a clinical study or studies designed to establish statistical evidence that the proposed product is neither inferior to the reference product by more than a specified margin nor superior to the reference product by more than a (possibly different) specified margin. Typically, an equivalence design with symmetric inferiority and superiority margins would be used. Symmetric margins would be reasonable when, for example, there are dose-related toxicities.

In some cases, it would be appropriate to use an asymmetric interval with a larger upper bound to rule out superiority than lower bound to rule out inferiority. An asymmetric interval could be reasonable, for example, if the dose used in the clinical study is near the plateau of the dose-response curve and there is little likelihood of dose-related effects (e.g., toxicity). In most cases, use of an asymmetric interval would generally allow for a smaller sample size than would be needed with symmetric margins. However, if there is a demonstration of clear superiority, then further consideration should be given as to whether the proposed product can be considered biosimilar to the reference product.

In some cases, depending on the study population and endpoint(s), ruling out only inferiority may be adequate to establish that there are no clinically meaningful differences between the proposed product and the reference product. For example, if it is well established that doses of a reference product pharmacodynamically saturate the target at the clinical dose level and it would be unethical to use lower than clinically approved doses, a non-inferiority (NI) design may be sufficient.³²

A sponsor should provide adequate scientific justification for the choice of study design, study population, study endpoint(s), estimated effect size for the reference product, and margin(s) (how much difference to rule out). Sponsors should discuss their study proposal(s) and overall clinical development plan with FDA before initiating the comparative clinical study(ies).

³² If an NI design is considered appropriate, sponsors are encouraged to refer to the draft guidance for industry *Non-inferiority Clinical Trials*. When final, this guidance will represent FDA's current thinking on this topic.

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4. Extrapolation of Clinical Data Across Indications

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 of the proposed product 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 MOA(s) 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 may also provide important information on the MOA.)
- 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)
- 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.

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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 studies, 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 studies fail to verify the clinical benefit of the reference product for the condition of use.

VIII. POSTMARKETING SAFETY MONITORING CONSIDERATIONS

Robust postmarketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar therapeutic protein products.

Postmarketing safety monitoring should first take into consideration any particular safety or effectiveness concerns associated with the use of the reference product and its class, the proposed product in its development and clinical use (if marketed outside the United States), the specific condition of use and patient population, and patient exposure in the biosimilar development program. Postmarketing safety monitoring for a proposed product should also have adequate mechanisms in place to differentiate between the adverse events associated with the proposed product and those associated with the reference product, including the identification of adverse events associated with the proposed product that have not been previously associated with the reference product. Rare, but potentially serious, safety risks (e.g., immunogenicity) may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events. In particular cases, such risks may need to be evaluated through postmarketing surveillance or studies. In addition, as with any other biological product, FDA may take any appropriate action to ensure the safety and effectiveness of a proposed product, including, for example, requiring a postmarketing study or clinical trial to evaluate certain safety risks.³³

Because some aspects of postmarketing safety monitoring are product-specific, FDA encourages sponsors to consult with appropriate FDA divisions to discuss the sponsor's proposed approach to postmarketing safety monitoring.

IX. CONSULTATION WITH FDA

Many product-specific factors can influence the components of a product development program intended to establish that a proposed product is biosimilar to a reference product. Therefore, FDA will ordinarily provide feedback on a case-by-case basis on the components of a development program for a proposed product. In addition, it may not be possible to identify in advance all the necessary components of a development program; and the assessment of one element (e.g., structural analyses) at one step can influence decisions about the type and amount

³³ See, for example, sections 505(o)(3) and 505(p)(1)(A)(ii) of the FD&C Act.

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of subsequent data for the next step. For these reasons, FDA recommends that sponsors use a stepwise approach to establish the *totality of the evidence* that supports a demonstration of biosimilarity.

FDA also advises sponsors intending to develop biosimilar products to meet with FDA to present their product development plans and establish a schedule of milestones that will serve as landmarks for future discussions with the Agency. FDA anticipates that early discussions with FDA about product development plans and about the approaches to providing adequate scientific justifications will facilitate biosimilar development.

GLOSSARY

As used in this guidance, the following terms are defined below:

- *Biological product* means “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”³⁴
- *Biosimilar* or *biosimilarity* means 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.”³⁵
- *Chemically synthesized polypeptide* means any alpha amino acid polymer that (a) is made entirely by chemical synthesis and (b) is less than 100 amino acids in size.
- *Product*, when used without modifiers in this guidance, is intended to refer to the intermediates, drug substance, and/or drug product, as appropriate. The use of the term *product* is consistent with the use of the term in ICH Q5E.
- *Protein* means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.
- *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.³⁶

³⁴ Section 7002(b)(2) of the Affordable Care Act, amending section 351(i)(1) of the PHS Act.

³⁵ Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

³⁶ Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(4) of the PHS Act.