Guidance for Industry

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Biosimilarity

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

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 (Pub. L. 111-148) (Affordable Care Act)). 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.

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

[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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[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 under 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 attachment titled "Terminology."

- 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 guidance.

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.

II. SCOPE

This guidance gives an overview of FDA's approach to determining biosimilarity, consistent with a longstanding Agency approach to evaluation of scientific evidence.[4] FDA intends to consider the *totality of the evidence* provided by a sponsor to support a demonstration of biosimilarity, and recommends that sponsors use a stepwise approach in their development of biosimilar products. This guidance 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
- General scientific principles in conducting comparative structural and functional analysis, animal testing, human PK and PD studies, clinical immunogenicity assessment, and clinical safety and effectiveness studies (including clinical study design issues)

Additional topics discussed include the following:

[4] The guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) provides insight to 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.

- 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 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. 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."[6] The BPCI Act also amended the definition of biological product to include "protein (except any chemically synthesized polypeptide)."[7]

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 safety, purity, and potency[8] 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

[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 show that the differences do not affect the safety and effectiveness of the proposed product.

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

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

[8] 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 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.

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).[9]

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:[10]

- 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.[11] 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 the appropriate scientific justifications will facilitate biosimilar development.

IV. COMPLEXITIES OF PROTEIN PRODUCTS

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

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, purity, and/or potency, it is important to evaluate these differences.

[9] Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(3) of the PHS Act; section 351(a)(2)(C) of the PHS Act.

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

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

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 environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Additionally, process-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 drug substance.

Advances in analytical sciences enable some protein products to be extensively characterized with respect to their physico-chemical 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 proteins. 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.[12]

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 post-translational modifications, which in turn may affect the safety 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 effectiveness of the product.[13] The International Conference on Harmonisation (ICH) guidance Q5E *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* 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 who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. In contrast, the manufacturer of a proposed product will likely have a different manufacturing process (e.g.,

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

[13] 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.

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, 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.[14] In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product. For example, analytical studies and at least one human PK and/or PD study intended to support a demonstration of biosimilarity for purposes of section 351(k) of the PHS Act must, as a scientific matter, include an adequate comparison to the reference product licensed under section 351(a). However, under certain circumstances, a sponsor may seek to use data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed 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 this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.[15] 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 such adequacy will be made by FDA during review of the 351(k) application.

For additional scientific considerations relating to bridging studies, please refer to ICH guidance E5 *Ethnic Factors in the Acceptability of Foreign Clinical Data*.

VI. APPROACHES TO DEVELOPING AND ASSESSING EVIDENCE TO DEMONSTRATE BIOSIMILARITY

As described in detail below, FDA recommends that sponsors use a stepwise approach to develop the evidence needed to demonstrate biosimilarity. This approach may also be applicable to biosimilar applications for other types of biological products. 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.[16]

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[14] 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.

[15] For examples of issues that a sponsor may need to address, see draft guidance entitled *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

[16] See footnote 4.

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 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, if rigorous structural and functional comparisons show minimal or no difference between the proposed product and the reference product, the stronger 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 analysis 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 indicating that the overall safety risks are low, and the availability of a clinically relevant PD measure may provide further scientific justification for a selective and targeted approach to animal and/or clinical studies.

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 studies, and PD studies if there is a clinically relevant PD measure, in an appropriate study population (section VII.D.1). Sponsors should then compare the clinical immunogenicity of the two products (section VII.D.2). If there are residual uncertainties about the biosimilarity of the two products after conducting structural and functional studies, animal toxicity studies, human PK and PD studies, and clinical immunogenicity assessment, the sponsor should then consider what comparative clinical safety and effectiveness data may be adequate (section VII.D.3). FDA encourages sponsors to consult extensively with the Agency after completion of

comparative structural and functional analysis (before finalizing the clinical program), and throughout development as needed.

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 clinical safety and effectiveness data. FDA intends to use a risk-based, *totality-of-the-evidence* approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.

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 post-translational 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.[17] Clinically meaningful differences could include a difference in the expected range of safety, purity, and potency of the proposed and reference products. By contrast, slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful differences.

VII. DEMONSTRATING BIOSIMILARITY

This section discusses scientific considerations in the stepwise approach to developing data and information needed to support a demonstration of biosimilarity. Although this guidance focuses on proposed biosimilar therapeutic protein products, the scientific principles discussed may also apply to other types of proposed biosimilar biological products. 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.[18] 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 Analysis

[17] 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.

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

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.[19] FDA expects that a sponsor first will extensively characterize the proposed product and reference product with state-of-the-art technology, because extensive characterization of both products serves as the foundation for a demonstration of biosimilarity. In general, FDA expects that the expression construct for a proposed product will encode the same primary amino acid sequence as the reference product. However, minor modifications such as N- or C-terminal truncations that will not affect safety and effectiveness may be justified and should be explained by the sponsor. Additionally, sponsors should consider all relevant characteristics of the proposed product (e.g., the primary, secondary, tertiary, and quaternary structure; post-translational 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 are, the stronger the scientific justification for a selective and targeted approach to animal and/or clinical testing.

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

- Primary structures, such as amino acid sequence
- Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation)
- Enzymatic post-translational modifications, such as glycosylation and phosphorylation
- Other potential variants, such as protein deamidation and oxidation
- Intentional chemical modifications, such as PEGylation sites and characteristics

Sponsors should conduct extensive structural characterization in multiple representative lots of the proposed product and the reference product to understand the lot-to-lot variability of both drug substances in the manufacturing processes. Lots used for the analysis should support the biosimilarity of both the clinical material used in confirmatory clinical trials and the to-be-marketed proposed product. 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. Differences in formulation

[19] 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.

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.[20]

If the reference product cannot be adequately characterized with state-of-the-art technology, the sponsor should consult FDA for guidance on whether an application for such a protein product is appropriate for submission under section 351(k) of the PHS Act.

B. Functional Assays

The pharmacologic activity of protein products can be evaluated by in vitro and/or in vivo functional assays. These assays may include, but are not limited to, bioassays, biological assays, binding assays, and enzyme kinetics. 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.

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 demonstrate 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 analysis, investigate the consequences of observed structural differences, and explore structure-activity relationships.[21] To be useful, these assays should 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 structural variations 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 the FDA.

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 reference product. For example, cell-based bioactivity assays can 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 for the structural evaluation, appropriate lots should be used in the analysis.

C. Animal Data

[20] See also draft guidance entitled *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*.

[21] See also draft guidance entitled *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*.

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.[22]

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. Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the protein product (i.e., no species in which the biologic activity of the protein product mimics the human response). However, there may be some instances when animal data from a pharmacologically non-responsive 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. For a more detailed discussion about demonstrating species relevance, see the criteria described in the ICH S6 guidance addendum *ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

The scope and extent of any animal toxicity studies will depend on the body of information available on the reference product, the proposed product, and the extent of known similarities or differences between the two. If animal toxicity studies are not warranted, additional comparative in vitro testing, using human cells or tissues when appropriate, may be warranted. 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 the scope and extent of such a study.

When animal toxicity studies are conducted, it will generally be useful to perform a comparative animal toxicology study with the proposed product and 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. A sponsor may be able to provide a scientific justification for a stand-alone toxicology study using only the proposed product instead of a comparative toxicology study. For a more detailed discussion on the design of animal toxicology studies, see *ICH S6/S6(R1)*.

In general, nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not warranted when the proposed product and reference product have been demonstrated to be highly similar through extensive structural and functional characterization and animal toxicity studies. If there are specific safety

[22] 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.

concerns based on the clinical use of the reference product, some of or all such additional animal studies with the proposed product may be warranted.

2. Inclusion of Animal PK and PD Measures

Under certain circumstances, a single-dose study in animals comparing the proposed product and 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 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. Animal Immunogenicity Studies

Animal immunogenicity assessments generally do not predict potential immunogenic 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-protein antibody responses in animals may provide useful information relevant to patient safety. Additionally, significant differences in the immune response profile in inbred strains of mice, for example, may indicate that the proposed product and the reference product differ in one or more product attributes not captured by other analytical methods. If available, this information is of value in the design of clinical immunogenicity assessment.

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."[23]

In general, the clinical program for a 351(k) application must include a clinical study or studies (including an 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, as set forth in the PHS Act.[24] The scope and magnitude of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional characterization and possible animal studies. The frequency and severity of safety risks and other safety and effectiveness concerns for the reference product may also affect the design of the clinical program. Lessening the number or narrowing the scope of any of these types of clinical studies (i.e., human PK, PD, clinical immunogenicity, or clinical safety and effectiveness) should be scientifically justified by the sponsor.

[23] Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2)(B) of the PHS Act.

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

1. Human Pharmacology Data

Human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity. We have determined that both PK and PD studies (where there is a relevant PD measure) generally will be expected to establish biosimilarity, unless a sponsor can scientifically justify that an element is unnecessary.[25]

Human PK and PD profiles of a protein product often cannot be adequately predicted from functional assays and/or animal studies alone. Therefore, comparative human PK studies and, if clinically relevant PD measures are available, comparative human PD studies would be expected, unless a sponsor can provide a scientific justification that such studies are unnecessary. In addition, a human PK study that demonstrates similar exposure (e.g., serum concentration over time) with the proposed product and reference product can provide support for a biosimilarity demonstration. For example, a human PK study can be particularly useful when the exposure correlates to clinical safety and effectiveness. A human PD study that demonstrates a similar effect on a clinically relevant PD measure or measures related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) can also provide strong support for a biosimilarity determination.

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 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, FDA recommends that, to the extent possible, the sponsor select PD measures that (1) are relevant to clinical outcomes (e.g., on mechanistic path of MOA or disease process related to effectiveness or safety); (2) can be assessed after a sufficient period of time after dosing, and with appropriate precision; and (3) have the sensitivity to detect clinically meaningful differences between the proposed product and reference product. Sponsors should predefine and justify the criteria for PK and PD parameters for studies included in the application to demonstrate biosimilarity. Establishing a similar human PK and PD profile contributes to the demonstration of biosimilarity and may provide a scientific basis for a selective and targeted approach to subsequent clinical testing. Demonstrating that the proposed product and reference product have similar effects on a PD measure that is known to be clinically related to

[25] 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 or measures 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) generally will be expected.

safety or effectiveness can provide further support for a selective and targeted approach to clinical safety/effectiveness studies. In certain circumstances, human PK and PD data may provide sufficient clinical data to support a demonstration of biosimilarity.

The list provided below in section VII.D.3 (Clinical Safety and Effectiveness Data) includes some of the factors that can affect the ability of the human PK and PD studies to support a selective and targeted approach to the clinical program, and contribute to a demonstration of biosimilarity. Such factors also include whether the human PK and PD studies have used (1) clinically relevant PK and PD parameters (multiple PD measures that assess different domains of activities may be of value); (2) populations, dose(s), and route of administration that are the most sensitive to detect differences in PK and PD profiles; and (3) sensitive and relevant assays.

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 data[26] 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 generally be expected.

The extent and timing (e.g., premarket testing versus pre- and postmarket testing) of a clinical immunogenicity program 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, non-redundant biological function or is known to provoke anaphylaxis), more extensive immunogenicity assessments will likely be needed. If the immune response to the reference product is rare, two separate studies may be sufficient to evaluate immunogenicity: (1) a premarket study powered to detect major differences in immune responses between the two products and (2) a postmarket study designed to detect more subtle differences in immunogenicity.

The overall design of immunogenicity studies will consider both the severity of consequences and the incidence of immune responses. FDA recommends use of a comparative parallel design (i.e., a head-to-head study) to assess potential differences in the risk of immunogenicity and support appropriate labeling. As discussed in section

[26] Section VII.C.3 contains a discussion concerning animal immunogenicity studies.

VII.D.4, it is generally only important to demonstrate that the immunogenicity of the proposed product is not increased, so a one-sided design will ordinarily be adequate to compare clinical immunogenicity of the proposed product and reference product. Acceptable differences in incidence and other immune response parameters should be discussed with the FDA in advance of 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 to assess whether there are clinically meaningful differences between the proposed product and the reference product.

The study population used to compare immunogenicity should be justified and agreed to by the Agency. If a sponsor is seeking to extrapolate immunogenicity findings for one indication to other indications, the sponsor should consider using the study population and treatment regimen that are the most sensitive for detecting a difference in immune responses. Most often, 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 with autoimmune diseases would be more likely to develop immune responses than patients with malignancies).

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), using established criteria where available, for each type of potential immune response and obtain agreement from FDA on these criteria before initiating the study.

The follow-up period 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, the minimal follow-up period for chronically administered agents should be one year, unless a shorter duration can be justified by the sponsor.

As a scientific matter, it is expected that the following will be assessed in clinical immunogenicity studies:

- Binding antibody: titer, specificity, relevant isotype distribution, time course of development, persistence, disappearance, and association with clinical sequelae

- Neutralizing antibody: all of the above, plus neutralizing capacity to all relevant functions (e.g., uptake and catalytic activity, neutralization for replacement enzyme therapeutics)

The sponsor should develop assays capable of sensitively detecting immune responses, even in the presence of circulating drug product (proposed product and reference product).[27] The proposed product and 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 with respect to both the proposed product and reference product early in development. Sponsors should consult with FDA on the sufficiency of assays before initiating any clinical immunogenicity study.

3. Clinical Safety and Effectiveness Data

As a scientific matter, comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. A sponsor may provide a scientific justification if it believes that some or all of these comparisons on clinical safety and effectiveness are not necessary.

The following are examples of factors that may influence the type and extent of the comparative clinical safety and effectiveness data needed.

1. 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

2. The extent to which differences in structure, function and nonclinical pharmacology and toxicology predict differences in clinical outcomes, as well as the degree of understanding of the MOA of the reference product and disease pathology

3. The extent to which human PK or PD predicts clinical outcomes (e.g., PD measures known to be clinically relevant to effectiveness)

4. 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)

5. The extent of any clinical experience with the proposed product

Sponsors should provide a scientific justification for how it intends to integrate these factors to determine whether and what types of clinical trials are needed and the design of any necessary trials. For example, if comparative clinical trials (using an equivalence or a non-inferiority design) are needed, these factors are also relevant to determining the equivalence or non-inferiority margin.

[27] See draft guidance entitled *Assay Development for Immunogenicity Testing of Therapeutic Proteins* for more detailed discussion.

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 safety and effectiveness data. Alternatively, if the reference product has a long, relatively safe marketing history and there have been multiple versions of the reference product on the market with no apparent differences in clinical safety and effectiveness profiles, there may be a basis for a selective and targeted approach to the clinical program.

4. Clinical Study Design Issues

Clinical studies should be designed such that they can demonstrate that the proposed product has neither decreased nor increased activity compared to the reference product. Decreased activity ordinarily would preclude licensure of a proposed product. Increased activity might be associated with more adverse effects, or might suggest that the proposed product should be treated as an entirely different product with superior efficacy, in which case the appropriate licensure pathway would be section 351(a) of the PHS Act. A study employing a two-sided test in which the null hypothesis is that either (1) the proposed product is inferior to the reference product or (2) the proposed product is superior to the reference product based on a pre-specified equivalence margin is the most straightforward study design for accomplishing this objective. The margins should be scientifically justified and adequate to enable the detection of clinically meaningful differences in effectiveness and safety between the proposed product and the reference product. A sponsor should use clinical knowledge about the reference product and its therapeutic class to establish an appropriate equivalence margin. Although the upper (superiority) and lower (inferiority) bounds of the margin will usually be the same, there may be cases in which a different upper and lower bound may be appropriate.

In some cases, a one-sided test – non-inferiority design – may be appropriate for comparing safety and effectiveness and also advantageous as it would generally allow for a smaller sample size than an equivalence (two-sided) design. For example, if it is well-established that doses of the reference product higher than are recommended in its labeling do not create safety concerns, a one-sided test may be sufficient for comparing the efficacy of certain protein products (e.g., those products that pharmacodynamically saturate the target at some level and are used at or near the maximal level of clinical effect). Because it is generally important to demonstrate that a proposed product has no more risk in terms of safety and immunogenicity compared to a reference product, a one-sided test may also be adequate in a clinical study evaluating immunogenicity or other safety endpoints as long as it is clear that lower immunogenic or other adverse events would not have implications for the effectiveness of a protein product. A non-inferiority margin should also be scientifically based and pre-specified.[28]

FDA recommends that sponsors provide a scientific justification for the proposed size and length of their clinical trials to allow for: (1) sufficient exposure to the proposed

[28] A draft guidance entitled *Non-inferiority Clinical Trials* contains a discussion on choosing the non-inferiority margin.

product and reference product; (2) the detection of relevant safety signals (including immunogenic responses), except for rare events or those that require prolonged exposure; and (3) the detection of clinically meaningful differences in effectiveness and safety between the two products. The size of the clinical trials also may be influenced by the specific treatment effect(s) and the effect size of the reference product, as well as the size of the disease population.

FDA recommends that sponsors consider the use of population pharmacokinetics (PPK) to explain observed differences in safety and effectiveness that may occur due to variability in PK. PPK methods are described in the guidance for industry on *Population Pharmacokinetics* and involve the collection of only a few blood samples per patient. PPK methods are an efficient way to quantitate the influence of covariates (e.g., age or renal function) on PK and, in some cases, PD. Sponsors should consult the PPK guidance, in particular the discussion concerning the design of PPK studies to ensure the validity of the study results.

FDA recommends that a sponsor use endpoints and study populations that will be clinically relevant and sensitive in detecting clinically meaningful differences in safety and effectiveness between the proposed product and reference product. A sponsor can use endpoints that are different from those in the reference product's clinical trials if they are scientifically justified. For example, certain endpoints (such as PD measures) are more sensitive than clinical endpoints and, therefore, may enable more precise comparisons of relevant therapeutic effects (e.g., international normalized ratio, or INR, is more sensitive to anticoagulant comparisons than the incidence of cerebral bleeds or stroke). There may be situations when multiple PD measures enhance the sensitivity of a study. The adequacy of the endpoints also 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 effected (risk of difference).

When selecting the study population for a comparative safety and effectiveness study, a sponsor should consider, for example, whether its study population has characteristics consistent with those of the population studied for the licensure of the reference product for the same indication and whether patients have different co-morbidities and disease states (e.g., immuno-competent or immuno-suppressed) and receive different concomitant medications. In general, using similar study populations is essential for supporting the constancy assumption that is critical to interpreting the non-inferiority finding in a one- or two-sided comparative test.[29]

For human PK and PD studies, FDA recommends use of a crossover design for products with a short half-life (e.g., shorter than five days) and low incidence of immunogenicity. For products with a longer half-life (e.g., more than five days), a parallel study will usually be needed. In addition, sponsors should provide a scientific justification for the selection of study subjects (e.g., healthy volunteers or patients), study dose (e.g., one dose

[29] A draft guidance entitled *Non-inferiority Clinical Trials* contains a discussion on the constancy assumption.

or multiple doses), route of administration, and sample size. FDA recommends that sponsors consider the duration of time it takes for a PD measure or biomarker to change, and the possibility of nonlinear PK caused by dose or PD. FDA also recommends consideration of the role of modeling and simulation in designing clinical studies on human PK or PD. When there are established dose-response or systemic exposure-response relationships (response may be PD measures or clinical endpoints), comparative exposure-response data can support a selective and targeted approach to clinical safety/effectiveness studies. It is important to select, whenever possible, doses for study on the steepest part (as opposed to the plateau) of the dose-response curve for the proposed product (see below), because even drugs with quite different potency will appear similar if the doses are studied on or near the plateau of a dose-response curve.

Sponsors should consider the limitations of the clinical trial design and results. As noted, when the administered dose is on the plateau of a dose-response curve, the clinical trial will not be sensitive in detecting PD differences between the two products. In such a case, a sponsor should use lower doses if available and appropriate (e.g., known to have the same effect or ethically acceptable to give lower doses notwithstanding differences in effect), or a sponsor could use a study subgroup whose response is not on the plateau of the dose-response curve. A low efficacy rate (e.g., ≤ 25%) also may reduce the sensitivity of detecting product differences in patients in a clinical trial.

5. 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 sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the proposed product to be licensed for one or more additional conditions of use for which the reference product is licensed. However, the sponsor will 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 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 following
  - 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 relationship 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; PD measures may provide important information on the MOA

- 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 effectiveness of the product in each condition of use and patient population for which licensure is sought

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 whether the tested condition of use is the most sensitive one in detecting clinically meaningful differences in safety (including immunogenicity) and effectiveness. A sponsor should be cautious with respect to the extrapolation of safety risk profiles across indications, because patient populations for different indications may have different co-morbidities and receive different concomitant medications. The sponsor of a proposed product may seek licensure only for a condition of use that has been previously licensed for the reference product.

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

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, as well as the proposed product in its development and clinical use (if marketed outside the United States). 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, like any other biological products, FDA may take any appropriate action to ensure the safety and effectiveness of a proposed product, including, for example, requiring a postmarketing study to evaluate certain safety risks.[30]

[30] See, e.g., sections 505(o)(3) and 505(p)(1)(A)(ii) of the FD&C Act.

Labeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that:

- This product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s).

- This product (has or has not) been determined to be interchangeable with the reference product.

IX. CONSULTATION WITH FDA

As discussed above, 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 analysis) at one step can influence decisions about the type and amount of subsequent data for the next step. For these reasons, as indicated above, FDA recommends that sponsors use a stepwise procedure 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 appropriate scientific justifications will facilitate biosimilar development.

ATTACHMENT: TERMINOLOGY

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."[31]

- *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."[32]

- *Chemically synthesized polypeptide* means any alpha amino acid polymer that is a) 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.[33]

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

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

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