Clinical Pharmacology Data to Support a Demonstration of 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)

December 2016
Biosimilars

C:\Users\CAROLANM\AppData\Local\Microsoft\Windows\Temporary Internet Files\Content.Outlook\NRXMQ6DI\FRDTS 2015-739_FINAL clin pharm biosimilar guidance _111616_for RPMS.docx

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

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or
Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

December 2016
Biosimilars

TABLE OF CONTENTS

Contains Nonbinding Recommendations

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

Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors with the design and use of clinical pharmacology studies to support a decision that a proposed therapeutic biological product is **biosimilar**[2] to its **reference product**. This guidance pertains to those products—such as therapeutic biological products—for which pharmacokinetic (PK) and pharmacodynamic (PD) data are needed to support a demonstration of biosimilarity. Specifically, the guidance discusses some of the overarching concepts related to clinical pharmacology testing for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and the utility of modeling and simulation for designing clinical trials.

This guidance is one in a series that FDA is developing to implement the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).[3] This guidance is intended to assist sponsors in designing clinical pharmacology studies that can support an application submitted under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)) (a 351(k) application) as part of a stepwise approach to support a demonstration of biosimilarity.[4]

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

---

[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.
[2] Terms that appear in bold type are defined in the "Definitions" section at the end of this guidance.
[3] Sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Affordable Care Act), Public Law 111-148.
[4] See FDA's guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. THE ROLE OF CLINICAL PHARMACOLOGY STUDIES IN THE DEMONSTRATION OF BIOSIMILARITY

The BPCI Act, which was enacted as part of the Affordable Care Act, established an abbreviated pathway for FDA licensure of biological products that are demonstrated to be biosimilar to or interchangeable with an FDA-licensed reference product. This pathway is described in section 351(k) of the PHS Act.

Under section 351(k)(2) of the PHS Act, a 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based on data derived from analytical studies, animal studies, and a clinical study or clinical studies, including an assessment of immunogenicity, PK, and PD,[5] unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application.[6]

Biosimilarity is defined at section 351(i)(2) of the PHS Act 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.

Comparative analytical data provide the foundation for a development program for a proposed biosimilar product intended for submission under section 351(k) of the PHS Act. Clinical pharmacology studies build on the comparative analytical studies in the stepwise approach to support a demonstration of biosimilarity, and are normally a critical part of demonstrating biosimilarity by supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product. These studies provide the data that describe the degree of PK similarity between the proposed biosimilar product and the reference product. In addition, clinical pharmacology studies often include PD endpoints (both therapeutic and toxic) and pharmacometric analysis to assess whether there are clinically meaningful differences between the proposed biosimilar product and the reference product. These clinical pharmacology studies may address residual uncertainties that remain after the analytical evaluation, can add to the totality of the evidence supporting a demonstration of biosimilarity, and can guide both the need for and design of subsequent clinical testing to support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity. Clinical pharmacology data can be an important component of the scientific justification supporting extrapolation of data to one or more additional conditions of use.[7]

[5] Section 351(k)(2)(A)(i)(I) of the PHS Act.
[6] Section 351(k)(2)(A)(iii) of the PHS Act.
[7] See FDA's guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* for more information on this topic.

The types of clinical pharmacology studies to be conducted will depend on the residual uncertainties about biosimilarity that these studies can address to add to the totality of evidence for biosimilar product development.

III. CRITICAL CONSIDERATIONS IN THE USE OF CLINICAL PHARMACOLOGY STUDIES TO SUPPORT BIOSIMILARITY

Three key concepts—namely a PK and PD response assessment, an evaluation of residual uncertainty, and assumptions about analytical quality and similarity—are especially relevant to the stepwise development of proposed biosimilar products and are discussed in more detail in this section. Bioanalytical methodology and the use of clinical pharmacology studies to gain safety and immunogenicity information are also examined.

A. Exposure and Response Assessment to Support a Demonstration of Biosimilarity

The objective of a well-designed clinical PK and PD study in a biosimilar development program is to evaluate the similarities and differences in the PK and PD profiles between the proposed biosimilar product and the reference product. A well-designed clinical PK and PD study should include information about the **exposure** and, when possible, the **exposure-response** to the biological products, which are important for assessing whether there are any potential clinically meaningful differences between two products. Determining the exposure-response to a biological product can be particularly challenging because of the complex nature and heterogeneity of biological products. An evaluation of clinical pharmacology similarity should include assessments of PK similarity, and if applicable, PD similarity.

The PD biomarker(s) used to measure PD response should be a single biomarker or a composite of biomarkers that effectively demonstrate the characteristics of the product's target effects. Use of a single scientifically appropriate PD biomarker or a composite of more than one relevant PD biomarker can reduce residual uncertainty regarding the existence of any clinically meaningful differences between products and can significantly add to the overall demonstration of biosimilarity. Using broader panels of PD biomarkers (e.g., by conducting a protein or mRNA microarray analysis) that capture multiple pharmacological effects of the product can be of additional value. When determining which biomarkers should be used to measure response, it is important to consider the following five characteristics:

- The time of onset of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing
- The dynamic range of the PD biomarker over the exposure range to the biological product
- The sensitivity of the PD biomarker to differences between the proposed biosimilar product and the reference product

- The relevance of the PD biomarker to the mechanism of action of the drug (to the extent that the mechanism of action is known for the reference product)

- The analytical validity of the PD biomarker assay

If these characteristics are addressed, through the submission of PK and PD results, the extent of the clinical development program can be refined in both the design and extent of additional clinical trials necessary to assess whether there are clinically meaningful differences between the proposed biosimilar product and the reference product. In some instances, PD biomarkers with the relevant characteristics listed above are not identified, but the sponsor is still encouraged to incorporate PD biomarkers that achieve a large dynamic range over the concentration range in the PK evaluation because these PD biomarkers represent potential orthogonal tests that can support similarity. When PD biomarkers are not sensitive or specific enough to detect clinically meaningful differences, the derived PK parameters should be used as the primary basis for evaluating similarity from a clinical pharmacology perspective, and the PD biomarkers can be used to augment the PK data. A combination of PK and PD similarity can be an important assessment in demonstrating that there are no clinically meaningful differences between the proposed biosimilar product and the reference product.

B. Evaluation of Residual Uncertainty

In evaluating a sponsor's data to support a demonstration of biosimilarity, FDA will consider the totality of the data and information submitted using a risk-based approach, including data from the structural and functional characterizations, nonclinical evaluations, clinical PK and PD studies, clinical immunogenicity testing and an investigation of clinical safety, and, when appropriate, clinical effectiveness. These data should be collected in a stepwise manner. Especially pertinent to FDA's clinical pharmacology evaluation are the clinical PK and PD data and immunogenicity and other safety data obtained in conjunction with the clinical pharmacology studies. The need for additional studies at each step in this progressive approach will be determined by the degree of residual uncertainty that remains at each step regarding the similarity of the products and whether the study can address these uncertainties.

C. Analytical Quality and Similarity

In a stepwise assessment of biosimilarity, extensive and robust comparative structural and functional studies (e.g., bioassays, binding assays, and studies of enzyme kinetics) should be performed to evaluate whether the proposed biosimilar product and the reference product are highly similar. A meaningful assessment of biosimilarity depends on, among other things, the capabilities of available state-of-the-art analytical assays to evaluate, for example, the molecular weight, the higher-order structure and post-translational modifications, heterogeneity, functional properties, impurity profiles, and degradation profiles denoting stability of the protein. The sponsor should describe the capabilities and limitations of the methods used in the analytical assessment.

An extensive analytical characterization can reveal differences between the proposed biosimilar product and the reference product. The type, nature, and extent of any differences between the

two products should be clearly identified, and the potential effect of these differences should be addressed and supported by appropriate data. In some cases, additional studies can demonstrate that the identified difference is within an appropriate range to consider the proposed biosimilar product to be highly similar to the reference product.[8] However, certain differences in the results of the analytical characterization can preclude a determination by FDA that the proposed biosimilar product is highly similar to the reference product and, therefore, the further development of the proposed biosimilar product through the 351(k) regulatory pathway is not recommended.

It may be useful to compare the quality attributes of the proposed biosimilar product with those of the reference product using a meaningful **fingerprint-like** analysis algorithm that covers a large number of product attributes and their combinations with high sensitivity using orthogonal methods. Comparison of quality attributes in this manner can further quantify the overall similarity between two products and might provide a basis for a more selective and targeted approach to subsequent animal and/or clinical studies.

The result of the comparative analytical characterization during product development can lead to one of the following four assessments within a *development-phase* continuum, with the understanding that FDA does not make the ultimate determination that the proposed biosimilar product is highly similar to the U.S.-licensed reference product until the time of licensure.

- Insufficient analytical similarity: Certain differences in the results of the analytical characterization are sufficiently significant such that further development through the 351(k) regulatory pathway is not recommended unless, for example, modifications are made to the manufacturing process for the proposed biosimilar product that are likely to lead to the minimization or elimination of such differences.

- Analytical similarity with residual uncertainty: Further information, additional analytical data, or other studies are needed to determine if observed analytical differences are likely to fall within an appropriate range when the 351(k) application for the proposed biosimilar product is submitted. As an example, glycosylation plays an important role in the PK of certain protein products. Manufacturing process conditions can affect glycosylation and in some cases PK. Comparative PK and PD studies of the proposed biosimilar product and the reference product, in addition to supporting a demonstration of no clinically meaningful differences, may address residual uncertainties regarding certain glycosylation differences and the impact on PK. Thus PK and PD studies could support that some differences in glycosylation identified in the analytical studies might fall within an appropriate range.

- Tentative analytical similarity: At this stage of development, the results of the comparative analytical characterization permit high confidence in the analytical similarity of the proposed biosimilar product and the reference product, and it can be

[8] See FDA's guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*.

appropriate for the sponsor to conduct targeted and selective animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity.

- Fingerprint-like analytical similarity: The results of integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences (i.e., fingerprint-like analyses) permit a very high level of confidence in the analytical similarity of the proposed biosimilar product and the reference product, and it would be appropriate for the sponsor to use a more targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and to support a demonstration of biosimilarity.

The outcome of the comparative analytical characterization should inform the next steps in the demonstration of biosimilarity.

D. Integrity of the Bioanalytical Methods Used in PK and PD Studies

When performing an evaluation of clinical pharmacology similarity, it is critical to use the appropriate bioanalytical methods to evaluate the PK and PD properties of a proposed biosimilar product and the reference product. Because of the generally complex molecular structure of biological products, conventional analytical methods might not be suitable for biological products. The bioanalytical methods used for PK and PD evaluations should be accurate, precise, specific, sensitive, and reproducible. The scientific requirements of bioanalytical methods are described in a separate FDA guidance document.[9]

1. General PK Assay Considerations

A sponsor should design or choose an assay based on a thorough understanding of the mechanism of action (to the extent that the mechanism of action is known for the reference product) and/or structural elements of the proposed biosimilar product and reference product that are critical for activity. An assay producing concentration data that correlate to the pharmacological/PD activity is preferred. The same assay should be used for measuring concentrations of the proposed biosimilar product and the reference product and validated for use with both products. Analytical assays should have design and performance parameters that are consistent with current industry best practices.

2. General PD Assay Considerations

Sponsors should make every effort to employ the most suitable assays and methodologies to obtain data that are meaningful and reflective of PK, the biological activity, and/or the PD effect of the proposed biosimilar product and the reference product. Furthermore, in submissions to the FDA, the sponsor should provide a rationale for the choice of assay and the relevance of the assay to drug activity.

---

[9] See FDA's revised draft guidance for industry, *Bioanalytical Method Validation*, for more information on this topic. When final, this guidance will represent FDA's current thinking on this issue.

3. Specific Assays

Three types of assays are of particular importance for biosimilar product development: ligand binding assays, concentration and activity assays, and PD assays.

- Ligand binding assays

  Currently, the concentration of most biological products in circulation is measured using ligand binding assays. These assays are analytical methods for quantifying high affinity and selective macromolecular interactions between assay reagents (e.g. antibodies, receptors or ligands) and the biological product. The ligand binding assay reagents chosen for detecting the biological product should be carefully evaluated with the goal of producing product concentration data that are meaningful to, and reflective of, the pharmacological activity and/or PD effect of the biological product of interest. Assays that rely upon antibody reagents and epitopes involved in pharmacological/biochemical interactions with targets are most likely to produce concentration data that are meaningful for target binding activity.

  Some biological products exert pharmacological effects only after multiple molecular interactions. For example, in some cases, the in vivo mechanism of action of monoclonal antibodies, bispecific antibodies, or fusion proteins involves binding mediated by different regions of the protein product (e.g. binding to both a ligand or receptor through a target antigen binding epitope of the protein and to Fc gamma receptors with the fragment crystallizable (Fc) region of the protein. A sponsor should choose the most appropriate interactions to measure. Generally, assays for monoclonal antibody product concentrations rely on molecular interactions involving the antigen binding (Fab) region, in particular epitopes in the complementarity determining regions (CDRs).

- Concentration and activity assays

  Bioanalytical methods that are not based on ligand binding can be used for quantification of the proposed biosimilar product and the reference product concentrations. For some biological products, such as those that are used to achieve enzyme replacement, the drug availability measurements may rely on activity and should be captured through an appropriate activity assay. Depending on the complexity of the structural features, some biological products should have more than one assay to characterize the systemic exposure of the proposed biosimilar product and the reference product. If more than one assay is used, mass spectrometry and other assays can be useful for distinguishing the structures of product variants, if relevant.

- PD assays

Relevant PD biomarkers might not always be available to support a proposed biosimilar product's development through clinical pharmacology studies. However, when PD assessment is a component of the biosimilarity evaluation, sponsors should submit (1) a rationale for the selection of the PD endpoints and/or biomarkers and (2) data to demonstrate the quality of the assay. PD assays should be sensitive for a product or product class and designed to quantitatively evaluate the pharmacological effects of the biologic product. The use of multiple complementary PD assays that reflect different aspects of pharmacologic activity of the product might be particularly useful to reduce residual uncertainty regarding clinically meaningful differences between the products. Because the PD assay is highly dependent on the pharmacological activity of the product, the approach for assay validation and the characteristics of the assay performance might differ depending on the specific PD assay. However, the general guiding principles for choosing PK assays (i.e., demonstration of specificity, reliability, and robustness) also apply to PD assays.

E. Safety and Immunogenicity

When **immunogenicity** results in, for example, either loss of PD effect or efficacy (e.g., neutralizing antibodies) or immune-mediated toxicity, the incidence and severity of the response should be assessed.[10] Safety and immunogenicity data from the clinical pharmacology studies should be collected and evaluated. FDA recognizes that safety and immunogenicity data derived from these studies may need to be supplemented by additional evaluations. The overall immunogenicity assessment should include relevant patient populations that are not immunocompromised and thus are able to mount an immune response. However, as part of their role in the overall assessment of biosimilarity, clinical pharmacology studies can sometimes suggest that there are clinically meaningful differences between the products that can inform the design and the details of additional investigations and/or clinical studies conducted to investigate these potential differences. The extent of such potential differences will determine whether or not further development of the proposed biosimilar product should continue, and if so, what studies should be conducted.

Publicly available information on the safety and immunogenicity profile of the reference product should be considered when incorporating safety and immunogenicity measurements in the clinical pharmacology studies.[11] For example, when the reference product is known to have the potential for immune-mediated toxicity, assays capable of detecting binding antibodies (and their neutralizing potential) should be developed in advance to analyze samples obtained from PK and PD studies, so that immunogenicity can be evaluated in real time. Generally, samples can be stored for future analysis if such assays are not yet developed.[12] In all cases, sponsors should carefully consider assay confounders such as the systemic presence of the proposed biosimilar

[10] See FDA's guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products.*
[11] See footnote 4 for more information on this topic.
[12] FDA has issued the draft guidance for industry *Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products*.

product or the reference product. Recommendations for immunogenicity assay development are described in a separate FDA guidance document.[13]

When evaluating data (e.g., safety or immunogenicity) collected during the PK and PD studies, sponsors should have an understanding of the time course of the appearance and resolution of safety signals or immune responses. The PK profile of the proposed biosimilar product and/or the publicly available PK data for the reference product can be used to inform the duration of follow-up for safety signals or immunogenicity.

IV. DEVELOPING CLINICAL PHARMACOLOGY DATA FOR SUPPORTING A DEMONSTRATION OF BIOSIMILARITY

Sponsors are encouraged to discuss their clinical pharmacology development plan with FDA in the early stages of the biosimilar product development program. Critical topics that should be discussed with FDA are set forth below.

A. Study Design

To evaluate clinical PK and PD similarity for the development of proposed biosimilar products, two study designs are of particular relevance: crossover designs and parallel study designs. All clinical pharmacology studies of the proposed biosimilar product should be performed using materials from the final manufacturing process expected to be used for the marketed product if approval is granted. The relevance of data submitted from studies using materials from different manufacturing processes may need to be adequately justified, for example, by establishing an analytical and PK bridge to the to-be-marketed product.

- Crossover design

  For PK similarity assessments, a single-dose, randomized, crossover study is generally preferred. A crossover study is recommended for a product with a short half-life (e.g., shorter than 5 days), a rapid PD response (e.g., the time of onset, maximal effect, and disappearance in conjunction with drug exposure), and a low anticipated incidence of immunogenicity. This design is considered the most sensitive to assess PK similarity, and can provide reliable estimates of differences in exposure with a minimum number of subjects. For PD similarity assessments, a multiple-dose design may be appropriate when the PD effect is delayed or otherwise not parallel to the single-dose drug PK profile. The time course of appearance and disappearance of immunogenicity and its relation to the washout period should be considered for studies using a crossover design.

- Parallel design

[13] See footnote 10.

Many biological products have a long half-life and elicit immunogenic responses. A parallel group design is appropriate for products that have a long half-life or for products where repeated exposures can lead to an increased immune response that can affect the PK and/or PD similarity assessments. This design is also appropriate for diseases that exhibit time-related changes associated with exposure to the drug.

B. Reference Product

Analytical studies, clinical PK and, if appropriate, PD studies that are intended to support a demonstration of biosimilarity should include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. However, a sponsor could use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. If a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed comparator product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the scientific relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product. [14]

C. Study Population

Healthy Subject vs. Patient: The study population selected should be the most informative for detecting and evaluating differences in PK and PD profiles between the proposed biosimilar product and the reference product. Clinical PK and PD studies should be conducted in healthy subjects if the product can be safely administered to them. A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with a study in patients with potential confounding factors such as underlying and/or concomitant disease and concomitant medications. If safety or ethical considerations preclude the participation of healthy subjects in human PK and PD studies for certain products (e.g., immunogenicity or known toxicity from the reference product), or if PD biomarkers can only be relevant in patients with the relevant condition or disease, the clinical pharmacology studies should be conducted in such patients. A population that is representative of the patient population to which the drug is targeted will be appropriate unless a study in a different population would be more sensitive to detect potential differences between the proposed biosimilar product and the reference product.

Demographic Group: Clinical pharmacology studies should be conducted in the subject or patient demographic group most likely to provide a sensitive measure of differences between the proposed biosimilar product and the reference product. The sponsor should justify why the subject or patient group chosen for clinical pharmacology studies will provide an adequately sensitive measure of difference between the proposed biosimilar product and the reference product. The total number of subjects studied should provide adequate statistical power for PK, and, when relevant, PD similarity assessment. Analysis of the data should be conducted

[14] See footnote 4 and footnote 7 for more information on the bridging data needed and examples of issues that a sponsor may need to address.

according to the pre-specified analysis plan, and any post hoc statistical analysis is exploratory only.

D. Dose Selection

As in the selection of study population, the most sensitive dose should be selected to detect and to evaluate differences in the PK and PD profiles between the proposed biosimilar product and the reference product. The dose selected should be one most likely to provide clinically meaningful and interpretable data. If a study is conducted in a patient population, the approved dose for the reference product can be the appropriate choice, because this approved dose can best demonstrate the pharmacological effects in a clinical setting. However, a lower dose on the steep part of the exposure-response curve is generally appropriate when PD is being measured or when healthy subjects are selected for evaluation (See section V, "Utility of Simulation Tools in Study Design and Data Analysis").

In certain cases, a dose selected from a range of doses can be useful for a clinical PK and PD similarity assessment. For example, if the concentration-effect relationship of the reference product is known to be highly variable or nonlinear, a range of doses can be used to assess dose-response (See Section V, "Utility of Simulation Tools in Study Design and Data Analysis").

If the product can only be administered to patients, an alternative dosing regimen such as a single dose for a chronic indication or a lower dose than the approved dose may be preferable to increase the sensitivity for detecting differences if the approved dose either results in nonlinear PK or exceeds the dose required for maximal PD effect. The appropriateness of an alternative dosing regimen will depend on certain factors, e.g., whether the lower dose is known to have the same effect as the approved dose and whether it is ethically appropriate to give lower doses notwithstanding differences in effect. An adequate justification for the selection of an alternative dosing regimen should be provided.

When appropriate, PD biomarkers should be used to assess PK/PD similarity between the proposed biosimilar product and the reference product. Development of an exposure-response profile that includes the steep part of the exposure-response curve is a sensitive test for PK/PD similarity between products; if clinical pharmacology similarity between products is demonstrated, in some instances, the exposure-response profile might support an adequate assessment of whether there are clinically meaningful differences between the products, and in others, the exposure-response profile might support a more targeted clinical development program to address residual uncertainty regarding whether there are any such clinically meaningful differences.

E. Route of Administration

Clinical PK and PD studies should be conducted using the same route of administration for the proposed biological product and the reference product. If more than one route of administration (e.g., both intravenous and subcutaneous) is approved for the reference product, the route selected for the assessment of PK and PD similarity should be the one most sensitive for detecting clinically meaningful differences. In most cases, the most sensitive route is likely to be

the subcutaneous or other extravascular routes of administration, because extravascular routes can provide insight into potential PK differences during the absorption phase in addition to the distribution and elimination phases. In addition, extravascular routes of administration may provide a more sensitive assessment for differences in immunogenicity.

F. Pharmacokinetic Measures

All PK measures should be obtained for both the proposed biosimilar product and the reference product. The sponsor should obtain measures of peak concentration (C_{max}) and total area under the curve (AUC) in a relevant biological fluid. For single-dose studies, AUC should be calculated as the area under the biological product concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$ (or C_t (concentration at the last measurable timepoint) divided by k_{el} (elimination rate constant)) is calculated based on an appropriate method. C_{max} should be determined from the data without interpolation. For intravenous studies, $AUC_{0-\infty}$ will be considered the primary endpoint. For subcutaneous studies, C_{max} and AUC will be considered coprimary study endpoints. For multiple dose studies, the measurement of total exposure should be the area under the concentration-time profile from time zero to the end of the dosing interval at steady-state (AUC_{0-tau}), and is considered the primary endpoint. Both the concentration prior to the next dose during multiple dosing ($C_{trough\ ss}$) and C_{max} are considered secondary endpoints. Population PK data will not provide an adequate assessment for PK similarity.

G. Pharmacodynamic Measures

In certain circumstances, clinical PK and PD data that demonstrate similar exposure and response between a proposed biosimilar product and the reference product can be sufficient to completely assess whether there are clinically meaningful differences between products, notwithstanding the need for an adequate assessment of immunogenicity. The biosimilarity assessment should be based on similarity in PD using a biomarker that reflects the mechanism of drug action when the PD measure has a wide dynamic range over the range of drug concentrations achieved during the PK study. In such instances, a full evaluation of safety and immunogenicity should still be conducted. When human PD data in a PK/PD study are insufficient to fully assess whether there are clinically meaningful differences between the proposed biosimilar and the reference product, human PD data can nonetheless be helpful to support a more targeted approach for the collection of subsequent clinical safety and effectiveness data. Selection of appropriate time points and durations for the measure of PD biomarkers will depend on the characteristics of the PD biomarkers (e.g., the timing of the PD response after administration of the product based on the half-life of the product and the anticipated duration of the product's effect). When a PD response lags after initiation of product administration, a study of multiple-dose and steady state conditions can be important, especially if the proposed therapy is intended for long-term use. The PD biomarker(s) evaluated for the proposed biosimilar product and the reference product should be compared by determining the area under the effect curve (AUEC). If only one PD measurement is available because of the characteristics of the PD biomarker, the measurement should be linked to a simultaneous drug concentration measurement. The relationship of drug concentration and the PD biomarker should then be used as a basis for comparison between products.

Use of a single, scientifically appropriate PD biomarker as described above, or a composite of more than one relevant PD biomarkers, can reduce any residual uncertainty about whether there are clinically meaningful differences between products and add significantly to the overall demonstration of biosimilarity. Using broader panels of biomarkers (e.g., by conducting a protein or mRNA microarray analysis) that capture multiple pharmacological effects of the product can also add value.

When available and appropriate, clinical endpoints in clinical pharmacology studies can also provide useful information about the presence of clinically meaningful differences between two products.

H. Defining the Appropriate Pharmacodynamic Time Profile

The optimal sampling strategy for determining PD measures can differ from the strategy used for PK measures. For PK sampling, frequent sampling at early time points following product administration with decreased frequency later is generally most effective to characterize the concentration-time profile. However, the PD-time profile might not mirror the PK-time profile. In such cases, the PD sampling should be well justified. When both PK and PD data are to be obtained during a clinical pharmacology study, the sampling strategy should be optimized for both PK and PD measures.

I. Statistical Comparison of PK and PD Results

The assessment of the clinical pharmacology similarity of a proposed biosimilar product and the reference product in PK and PD studies is based on statistical evaluation. The recommended clinical pharmacology similarity assessment relies on: (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) an acceptable limit for the biosimilarity assessment. FDA recommends that log-transformation of the exposure measures be performed before the statistical analysis. Sponsors should use an **average equivalence** statistical approach[15] to compare PK and PD parameters for both replicate and nonreplicate design studies. This average equivalence approach involves a calculation of a 90% confidence interval for the ratio between the geometric means of the parameters of the proposed biosimilar product and the reference product. To establish PK and/or PD similarity, the calculated confidence interval should fall within an acceptable limit. Selection of the confidence interval and the acceptable limits can vary among products. An appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80–125%; if other limits are proposed, the sponsor should justify the limits selected for the proposed biosimilar product. There can be situations in which the results of the PK and/or PD study fall outside the pre-defined limits. Because such results can suggest existence of underlying differences between the proposed biosimilar product and the reference product that can preclude development under the 351(k) pathway, FDA encourages sponsors to analyze and explain such findings and discuss them with the FDA before proceeding to the next step in the development program.

[15] See FDA's guidance for industry *Statistical Approaches to Establishing Bioequivalence*.

V. UTILITY OF SIMULATION TOOLS IN STUDY DESIGN AND DATA ANALYSIS

Modeling and simulation tools can be useful when designing a PK and/or PD study. For instance, these tools can contribute to the selection of an optimally informative dose or doses for evaluating PD similarity. When a biomarker-based comparison is used, it is preferable that the selected dose be on the steep portion of the dose-response curve of the reference product. Sponsors should provide data to support the claim that the selected dose is on the steep part of the dose-response curve and not on the plateau of the dose-response curve where it is not likely to detect differences between the two products. Publicly available data for the dose (or exposure)-response relationship of the reference product can be analyzed using model-based simulations to justify the dose selected for the PK and/or PD study or studies.

If the exposure-response data for the reference product are not available, the sponsor can decide to generate this information using a small study to determine an optimally informative dose (e.g., a dose representing the effective dose to achieve the 50% maximal response [ED_{50}] of the reference product). This small study can involve evaluating the PK/PD relationship at multiple dose levels (e.g., the low, intermediate, and highest approved dose) to obtain dose-response and/or exposure-response data.[16] Alternatively, when possible, sponsors can conduct a PK/PD similarity study between the reference product and the proposed biosimilar product with low, intermediate, and the highest approved doses where a clear dose-response is observed. If multiple doses are studied, PK/PD parameters such as EC_{50}, the maximum PD response (E_{max}), and the slope of the concentration-effect relationship should be evaluated for similarity. Such studies should be useful for the demonstration of PK, PK/PD, and PD similarity when the clinical pharmacology evaluation is likely to be the major source of information to assess clinically meaningful differences. Publicly available information on biomarker-clinical endpoint relationships accompanied with modeling and simulation can also be used to define the appropriate limits for PD similarity.

VI. CONCLUSION

Clinical pharmacology studies play a critical role in the development of biosimilar products. These studies are part of a stepwise process for demonstrating biosimilarity between a proposed biosimilar product and the reference product. These studies may support a demonstration that there are no clinically meaningful differences between the products. These studies may address residual uncertainties that remain after the analytical evaluation, may add to the totality of the evidence supporting a demonstration of biosimilarity, and may also support a selective and targeted approach to the design of any recommended subsequent clinical studies to support a demonstration of biosimilarity.

[16] For more information, see FDA's guidance for industry *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*.

DEFINITIONS

Biological product: "[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."[17]

Biosimilar or biosimilarity: In reference to a biological product that is the subject of an application under subsection 351(k) of the PHS Act, the term '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."[18]

Exposure: In this guidance, we use the broad term *exposure* to refer to PK variables, including input of all active components of the biological product as measured by dose (drug input to the body) and various measures of single or integrated drug concentrations in plasma and other biological fluid, e.g., peak concentration (C_{max}), concentration prior to the next dose during multiple dosing ($C_{trough\ ss}$), and area under the plasma/blood concentration-time curve (AUC).

Fingerprint-like: Integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.

Immunogenicity: In this guidance immunogenicity refers to an immune response that a biological product elicits through formation of antibodies to the administered biological product.

Reference product: 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.[19]

Exposure-Response: Pharmacodynamic response, referred to here as PD (a direct measure of the pharmacological or toxicological effect of a drug) in relationship to drug exposure (PK) variables.

Average equivalence: An approach to statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (C_{max}). It is based on the *two one-sided tests procedure* to determine whether the average values for the pharmacokinetic measures determined after administration of the Test (T) and Reference (R) products are comparable. This approach involves the calculation of a 90% confidence interval for the ratio of the log-transformed averages of the measures for the T and R products.

[17] Section 351(i)(1) of the PHS Act.
[18] Section 351(i)(2) of the PHS Act.
[19] Section 351(i)(4) of the PHS Act.