Guidance for Industry

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

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500, or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

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

May 2014
Biosimilars

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance is intended to assist sponsors with the design and use of clinical pharmacology studies to support a decision that a proposed therapeutic biological product is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* to its reference product. This guidance pertains to those products—such as therapeutic biological products—for which pharmacokinetic (PK) and pharmacodynamic (PD) data are required as part of a stepwise approach to developing the data and information necessary 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.

In its final form, this guidance will be one in a series that FDA is developing to implement the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).[2] It 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). Some scientific principles described in this guidance may also be informative for the development of certain biological products under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act),[3] but

[1] This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at FDA.

[2] Sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Affordable Care Act), Public Law 111-148.

[3] A 505(b)(2) application is a new drug application (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 a published study not conducted by or for the applicant). 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.

no particular relationship between the standards for approval under these separate statutory schemes is implied.

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

The BPCI Act, which was enacted as part of the Patient Protection and Affordable Care Act (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. The term *biosimilarity* is defined in section 351(i) 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."[4]

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 (a biological product already licensed under section 351(a) of the PHS Act) based on data derived from analytical studies; animal studies; and a clinical study or clinical studies, including the assessment of immunogenicity and PK and PD; [5]unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application.[6]

Clinical pharmacology studies are normally a critical part of demonstrating biosimilarity by supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar and the reference product. These studies provide the data that describe the degree of similarity in drug exposure between the proposed biosimilar and the reference product. In addition, clinical pharmacology studies often include PD endpoints (both therapeutic and toxic) and pharmacometric analysis to assess whether or not there are clinically meaningful differences between the proposed biosimilar and the reference product. If done well, they can add to the totality of the evidence, reduce residual uncertainty, and thus guide the need for and design of subsequent clinical testing to successfully support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity. Clinical pharmacology data may be an important component of the scientific justification supporting extrapolation of clinical data to one or more additional conditions of use.[7]

[4] Section 351(i)(2) of the PHS Act.

[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 draft guidance for industry *Q & As Regarding Implementation of the BPCI Act of 2009* for more information on this topic. When finalized, the guidance will reflect FDA's current thinking on this issue. The

The types of clinical pharmacology studies to be conducted will depend on the residual uncertainties about biosimilarity that these studies are capable of addressing in the context of the overall program for biosimilar product development.

For a list of definitions of terms specific to development of biosimilar products, see the Definitions section at the end of this draft guidance.

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

Three key concepts, exposure and response assessment, evaluation of residual uncertainty, and assumptions about analytical quality and similarity, are especially relevant to 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. Exposure-response information is important for the determination of safety, purity, and potency of any biological product, as well as for the determination of any potential clinically meaningful difference between two products. Determining the response to exposure to a biological product is particularly challenging, because the active product is not a single chemical and/or its active metabolites; rather, it is a mixture of closely related, complex biological substances that, in aggregate, make up the active component.

For the purposes of 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}), lowest concentration measured following dosing (C_{min}), concentration prior to the next dose during multiple dosing ($C_{trough\ ss}$), and area under the plasma/blood concentration-time curve (AUC). *Response*, referred to here as PD, is a direct measure of the pharmacological or toxicological effect of a drug. Clinical pharmacology similarity may include assessments of PK similarity, and PD similarity.

The PD marker(s) used to measure response may be a single biomarker or a composite of markers that effectively demonstrate the characteristics of the product's target effects. Use of a single, scientifically acceptable, established PD marker or a composite of more than one relevant PD marker, can reduce residual uncertainty with respect to clinically meaningful differences

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guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

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 may be of additional value. When determining which markers should be used to measure response, it is important to consider the following:

- The time of onset of the PD marker relative to dosing
- The dynamic range of the PD marker over the exposure range to the biological product
- The sensitivity of the PD marker to differences between the proposed biosimilar product and the reference product
- The relevance of the PD marker to the mechanism of action of the drug
- The relationship between changes in the PD marker and clinical outcomes

If these criteria are addressed, through the submission of convincing 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. It is important to note that in some instances PD markers with the relevant characteristics listed above have not been identified, but the sponsor is encouraged to incorporate PD biomarkers that correlate well with drug exposure over a wide concentration range as these represent potentially orthogonal tests that may be supportive of clinical pharmacology similarity. When PD markers are not sensitive or specific enough to be used to assess for 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 markers may be used to augment the PK data. A combination of PK and PD similarity representing orthogonal biosimilarity, may be an important assessment in demonstrating no clinically meaningful differences.

B. Evaluation of Residual Uncertainty

In evaluating a sponsor's data to support a demonstration of biosimilarity, using a risk-based approach, FDA will consider the totality of the data and information submitted, including, for example, data from the structural and functional characterization, nonclinical evaluations, human PK and PD studies, clinical immunogenicity testing, and investigation of clinical safety and when necessary clinical effectiveness. These data should be collected in a stepwise manner. Especially pertinent to FDA's clinical pharmacology evaluation is the clinical PK and PD data and 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 or not the study can address these uncertainties.

C. Assumptions About 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 depends on, among other things, the capabilities of available state-of-the-art analytical assays to assess, for example, the molecular weight of the protein, its higher order structure and post-translational modifications, heterogeneity, functional properties, impurity profiles, and degradation profiles denoting stability. The sponsor should describe the capabilities and limitations of the methods used in the analytical assessment.

An extensive analytical characterization may 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 may demonstrate that the identified difference is within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product. However, certain differences in the results of the analytical characterization may preclude a determination by FDA that the proposed biosimilar product is highly similar to the reference product and, therefore, its further development 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. Such a strategy can further quantify the overall similarity between two products and may provide a basis for a more selective and targeted approach to subsequent animal and/or clinical studies.

The result of the comparative analytical characterization may lead to one of four assessments within a development-phase continuum:

- Not similar: Certain differences in the results of the analytical characterization may lead to an assessment of "not similar" and 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 is likely to lead to a highly similar biological product.

- Similar: Further information is needed to determine if the product is highly similar to the reference product. Additional analytical data or other studies are necessary to determine if observed differences are within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product. As an example, glycosylation plays an important role in the PK of certain protein products. Manufacturing process conditions may impact glycosylation. Comparative PK and PD studies of the proposed biosimilar product and the reference product help resolve that some differences in glycosylation identified in the analytical studies would be within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product.

- Highly similar: The proposed biosimilar product meets the statutory standard for analytical similarity. The results of the comparative analytical characterization permit high confidence in the analytical similarity of the proposed biosimilar and the

reference product, and it would be appropriate for the sponsor to conduct targeted and selective animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity.

- Highly similar with fingerprint-like similarity: The proposed biosimilar product meets the statutory standard for analytical similarity based on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences. The results of these fingerprint-like analyses permit a very high level of confidence in the analytical similarity of the proposed biosimilar 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 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 its reference product. Because of the complex molecular structure of biological products, conventional analytical methods used for chemical drugs may 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 have been described in a separate guidance document.[8]

1. General PK Assay Considerations

A sponsor should design or choose an assay based on a thorough understanding of the mechanism of action and/or structural elements of the proposed biosimilar product and reference product critical for activity. Analytical assays should be able to detect the active and/or free product instead of the total product, particularly if binding to a soluble ligand is a necessary step for activity and clinical effect. The inability to develop such an assay should be supported with justification as to why failure to detect free and/or active forms does not compromise the PK similarity assessment.

2. General PK and PD Assay Considerations

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

[8] FDA guidance for industry *Bioanalytical Method Validation*.

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 in which quantification is based on macromolecular interactions with assay reagents, such as antibodies, receptors or ligands that bind with adequate affinity and selectivity to the biological product. The ligand binding assay reagents chosen for capturing and 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. Some biological products exert pharmacological effects only after multiple molecular interactions. In some cases, monoclonal antibodies, bispecific antibodies, or fusion proteins bind to ligand or receptor proteins through the target antigen binding epitope of the molecule and to FcγR with the crystallizable fragment (Fc) portion of the molecule. 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). Antibody-based assays for biological products that rely on epitopes involved in pharmacological/biochemical interactions with targets are most likely to produce concentration data that are meaningful with respect to target binding activity.

- Concentration and activity assays

  Bioanalytical methods that are not based on ligand binding can be used for quantification of the proposed biosimilar product and 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 may need more than one assay to fully characterize the systemic exposure of the proposed biosimilar product and reference product. In such cases, mass spectrometry and other assays may be useful in distinguishing the structures of product variants.

- PD assays

  Relevant PD markers may 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 provide a

rationale for the selection of the PD endpoints and/or markers, as well as data to demonstrate the quality of the assay, in written communications to FDA. PD assays should be sensitive for a product or product class and designed to quantitatively evaluate the pharmacologic activity of the biologic product. Ideally, the activity measured by the PD assay should be relevant to a clinical outcome; however the PD assay should at least be relevant to a pharmacological effect of the biologic product. If the selected PD endpoint(s) are not closely related to clinical outcome, use of multiple complimentary PD assays may be most useful. 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 may 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. Sponsors should provide supporting data for the choice of assay and the justification of PD markers in submissions to FDA.

E. Safety and Immunogenicity

In the context of this guidance, immunogenicity refers to an immune response to the biological product that may result in immune-mediated toxicity and/or lack of effectiveness. 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 either preapproval or postapproval. However, as part of their role in the overall assessment of biosimilarity, clinical pharmacology studies may sometimes suggest that there are clinically meaningful differences between the products that may inform the design and details of additional investigations and/or clinical studies conducted to further investigate these potential differences. It is important to note that depending on the extent of such potential differences, it may not be appropriate for additional studies to be conducted in the context of a biosimilar development program.

Publicly available information on the safety and immunogenicity profile of a reference product should be considered when incorporating safety and immunogenicity measurements in the clinical pharmacology studies.[9] For example, when a 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 may be evaluated in real time. Generally, samples can be stored for future analysis if such assays are not yet developed.[10] In either approach, sponsors should carefully consider assay confounders, such as the systemic presence of the proposed biosimilar or reference product. Recommendations for immunogenicity assay development have been described in a separate guidance document.[8]

[9] See FDA's draft guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* for more information on this topic. When finalized, the guidance will reflect FDA's current thinking on this issue.

[10] FDA has issued the draft guidance for industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins*. Once finalized, it will represent FDA's perspective on this topic.

When evaluating data (e.g., safety, immunogenicity) collected during the PK and PD studies, sponsors should have an understanding of the time course for 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 the crucial aspects of their clinical pharmacology development plan with FDA in the early stages of the biosimilar development program. Some critical study design issues 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.

- Crossover design

  For PK similarity assessments, a single-dose, randomized, crossover study is generally the preferred design. 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., onset, maximal effect, and disappearance in conjunction with drug exposure), and a low incidence of immunogenicity. This design is considered the most sensitive to assess PK similarity, and it can provide reliable estimates of differences in exposure with a minimum number of subjects. For PD similarity assessments, multiple doses 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 is an issue for consideration for studies using a crossover design.

- Parallel design

  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 which 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

The BPCI Act defines the *reference product* for a proposed biosimilar product as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application.[11] As a scientific matter, analytical studies and at least one clinical PK and, if appropriate, PD study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. However, a sponsor may use a non-U.S. licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. If a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compares all three products (i.e., (the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed product) and is likely to also include PK and, if appropriate, PD study data for all three products .

C. Study Population

Healthy Volunteer 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. Human PK and PD studies should be conducted in healthy volunteers if the product can be safely administered to this population. A study in healthy volunteers is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK variability compared with that in patients with potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. If safety or ethical considerations preclude the participation of healthy volunteers in human PK and PD studies for certain products (e.g., immunogenicity or known toxicity from the reference product), or if PD markers would only be relevant in patients with the condition or disease, the clinical pharmacology studies should be conducted in patients. In cases where PK and/or PD will be the full assessment for clinically meaningful differences, a population that is representative of the patient population to which the drug is targeted will be appropriate for the study.

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 provide justification for why the subject or patient group chosen for clinical pharmacology studies will provide the most sensitive measure of difference between the proposed biosimilar and reference products. The total number of subjects should provide adequate power for similarity assessment. Analysis of the data from all subjects as one group represents the primary study endpoint, and a statistical analysis of the data from the subgroups would be exploratory only.

D. Dose Selection

[11] See sections 351(i)(4) of the PHS Act.

As in the selection of study population, the dose selected should be the most sensitive to detect and 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 may be the appropriate choice, because this may best demonstrate the pharmacological effects in a clinical setting. However, a lower dose in the steep part of the exposure-response curve may be 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 may 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 acceptable if the approved dose results in nonlinear PK or exceeds the dose required for maximal PD effect, and therefore will not allow for the detection of differences. However, the appropriateness of an alternative dosing regimen will depend on certain factors, e.g., the lower dose is known to have the same effect as the approved dose or if it is ethically acceptable to give lower doses notwithstanding differences in effect. Adequate justification for the selection of an alternative dosing regimen should be provided in written communication to FDA.

When appropriate, PD markers should be used to assess PK/PD similarity between a proposed biosimilar product and the reference product. Development of a dose-response profile that includes the steep part of the dose-response curve is a sensitive test for similarity between products, and if clinical pharmacology similarity between products is demonstrated, in some instances this may complete the clinical evaluation, and in others it may support a more targeted clinical development program.

E. Route of Administration

Human 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, this 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.

F. Pharmacokinetic Measures

All PK measures should be obtained for the proposed biosimilar product and the reference product. The sponsor should obtain measures of C_{max} and total exposure (AUC) in a relevant

biological fluid. For single-dose studies, total exposure should be calculated as the area under the biological product concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$ (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 time tau over a dosing interval at steady-state (AUC_{0-tau}), where tau is the length of the dosing interval and this is considered the primary endpoint. The steady state trough concentration ($C_{trough\ ss}$) should be measured at the end of a dosing interval before initiating the next dose and C_{max} the maximum measured concentration following the dose and these are considered secondary endpoints. Population PK data will not provide an adequate assessment for PK similarity.

G. Pharmacodynamic Measures

In certain circumstances, human PK and PD data that demonstrate similar exposure and response between a proposed biosimilar product and the reference product may be sufficient to completely assess clinically meaningful differences between products. This would be based on similar pharmacodynamics using a PD measure that reflects the mechanism of drug action in cases where 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 would still be necessary, either before or after approval. When human PD data in a PK/PD study are insufficient to completely assess for clinically meaningful differences, obtaining such data may 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 markers will depend on the characteristics of the PD markers (e.g., timing of PD response with respect to product administration based on the half life of the product and anticipated duration of effect). When a PD response lags after initiation of product administration, it may be important to study multiple-dose and steady state conditions, especially if the proposed therapy is intended for long-term use. Comparison of the PD marker(s) between proposed biosimilar product and the reference product should be by determination of the area under the effect curve (AUEC). If only one PD measurement is available due to the characteristics of the PD marker, it should be linked to a simultaneous drug concentration measurement and this should be used as a basis for comparison between products.

Use of a single, scientifically acceptable, established PD marker as described above, or a composite of more than one relevant PD markers, can reduce residual uncertainty with respect to 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 may be of additional value.

When available and appropriate, clinical endpoints in clinical pharmacology studies may 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 may 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 may 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 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. FDA recommends that log-transformation of the exposure measures be performed before the statistical analysis. Sponsors should use an average equivalence statistical approach[12] to compare PK and PD parameters for both replicate and nonreplicate design studies. This approach involves a calculation of a 90% confidence interval for the ratio between the 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 may vary among products. An appropriate starting point for an acceptable limit for the confidence interval of the ratio may be 80–125%; however, this is not a default range, and the sponsor should justify the limits selected for the proposed biosimilar product. There may be situations in which the results of the PK and/or PD study fall outside the pre-defined limits. Although such results may suggest existence of underlying differences between the proposed biosimilar product and the reference product that may preclude development under the 351(k) pathway, FDA encourages sponsors to analyze and explain such findings. If such differences do not translate into clinically meaningful differences and the safety, purity and potency of the product are not affected, it may be possible to continue development under the 351(k) pathway.

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, such 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 result in observed differences between two products. Publicly available data for the dose (or

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

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.

If the exposure-response data for the reference product are not available, the sponsor may decide to generate this information using a small study to determine an optimally informative dose (e.g., representing the ED_{50} of the reference product). Such a study may involve evaluating PK/PD at multiple dose levels (e.g., low, intermediate, and the highest approved dose) to obtain dose-response and/or exposure-response data.[13] Alternatively, when possible, sponsors can conduct a similarity study between the reference product and the proposed biosimilar product with low, intermediate, and the highest approved dose where a clear dose-response is observed. If multiple doses are studied, PK/PD parameters such as EC_{50}, Emax, and slope of the concentration effect relationship should be evaluated for similarity. Such studies would 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 acceptable 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 and add to the *totality of the evidence* to support an overall demonstration of biosimilarity between the proposed biosimilar product and the reference product through the demonstration of no clinically meaningful differences. Data gathered from clinical pharmacology studies may also support a selective and targeted approach to the design of any necessary subsequent clinical studies to support a demonstration of biosimilarity.

[13] For more, 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."[14]

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."[15]

Fingerprint-like: a term to describe integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.

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.[16]

Average equivalence: an approach to statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (Cmax). 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.

[14] Section 351(i)(1) of the PHS Act.
[15] Section 351(i)(2) of the PHS Act.
[16] Section 351(i)(4) of the PHS Act.