Considerations in Demonstrating Interchangeability With 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)

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Considerations in Demonstrating Interchangeability With 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 in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)). The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar[2] to or interchangeable with an FDA-licensed biological reference product[3] (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148)). Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations in demonstrating interchangeability of a proposed therapeutic protein product (*proposed interchangeable biosimilar*[4] or *proposed interchangeable product*) with a reference product.

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

[2] Section 351(i)(2) of the PHS Act defines *biosimilar* or *biosimilarity* to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" (highly similar provision) 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" (no clinically meaningful differences provision).

[3] Section 351(i)(4) defines *reference product* to mean "the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)."

[4] In this guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) "biosimilar" or "biosimilar product" refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) "interchangeable biosimilar" or "interchangeable product" refers to a biosimilar product that FDA has determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act).

This guidance is one in a series of guidances that FDA is developing to implement the BPCI Act and includes references to information from other FDA guidances, where appropriate.

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

II. BACKGROUND

Section 351(k) of the PHS Act, as amended by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(k)(4) of the PHS Act further provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application or the supplement is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient"[5] and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[6]

Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[7]

III. SCOPE

This guidance provides an overview of important scientific considerations in demonstrating interchangeability with a reference product, including the following:

- Data and information needed to support a demonstration of interchangeability

[5] Section 351(k)(4)(A) of the PHS Act.

[6] Section 351(k)(4)(B) of the PHS Act.

[7] The terms *interchangeable* or *interchangeability* in this guidance have the same meaning as defined in section 351(i)(3) of the PHS Act.

- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability
- Considerations regarding the comparator product in a switching study or studies
- Abbreviated considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products[8,9]

IV. GENERAL PRINCIPLES

FDA intends to consider the totality of the evidence provided by a sponsor when the Agency evaluates the sponsor's demonstration of interchangeability according to the criteria set forth in section 351(k).

To support a demonstration of interchangeability, section 351(k)(4)(A) of the PHS Act provides, among other things, that a sponsor must show that the proposed interchangeable product "is biosimilar to the reference product." Where a product is first licensed as a biosimilar, that licensure may be referenced to support a showing for this statutory criterion for demonstrating interchangeability.

In addition, section 351(k)(4)(A) of the PHS Act provides that an application for an interchangeable product must include information sufficient to show that the proposed interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient." FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use.

[8] Products that include both a biological product and a device constituent part to deliver the biological product are combination products (see 21 CFR parts 3 and 4). For example, the delivery device constituent part and the biological product constituent part may be a single entity (e.g., a prefilled syringe) or the two constituent parts may be co-packaged (e.g., a biologic in a vial packaged in the same box with a syringe). The primary mode of action of these combination products is provided by the biological product constituent part, which is regulated by CDER or CBER. CDER or CBER, therefore, will have primary jurisdiction for these combination products; and these Centers and the Center for Devices and Radiological Health (CDRH) will coordinate as appropriate.

[9] Considerations specific to demonstrating interchangeability under section 351(k)(4) of the PHS Act with respect to container closure systems and delivery device constituent parts are addressed in section VIII of this guidance. This guidance does not address other information generally necessary to support the proposed container closure system and/or the delivery device constituent part of a proposed interchangeable product. Sponsors should also refer to relevant FDA guidance documents and resources from CBER, CDRH, CDER, and the Office of Combination Products (OCP) to assess what other data and information should be included to support the proposed container closure system(s) and/or delivery device constituent part(s). (Some of the FDA guidances and other resources that address these topics are referenced at appropriate places in section VIII of this guidance.)

The data and information necessary to meet the section 351(k)(4)(A) standard may vary depending on the nature of the proposed interchangeable product[10] and may include the following:

- The identification and analysis of the critical quality attributes[11]
- The identification of analytical differences between the reference product and the proposed interchangeable product, and, in addition, an analysis of the potential clinical impact of the differences
- An analysis of mechanism or mechanisms of action in each condition of use for which the reference product is licensed, which may include the following:
  - The target receptor or receptors for each relevant activity/function of the product
  - The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target receptor or receptors
  - The relationship between product structure and target/receptor interactions
  - The location and expression of target receptor or receptors
- An analysis of any differences in the expected pharmacokinetics and biodistribution of the product in different patient populations for which the reference product is licensed
- An analysis of any differences in the expected immunogenicity risk of the product in different patient populations for which the reference product is licensed
- An analysis of any differences in expected toxicities of the product in each condition of use and patient population (including whether the expected toxicities are related to the pharmacological activity of the product or to off-target activities) for which the reference product is licensed
- Information on any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which the reference product is licensed

Where applicable, the data and information should include a scientific justification as to why any differences that exist between the reference product and the proposed interchangeable product, with respect to the factors described, do not preclude a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in any given patient. As previously noted, the data and information may vary depending

[10] Some of this data and information may have been generated previously by the sponsor to support a demonstration that the biological product is biosimilar to the reference product. If the applicant has previously submitted this data or information to FDA, (e.g., in an application for a biosimilar product) the applicant should consult with FDA as to how to reference or submit these data for purposes of seeking licensure as an interchangeable product.

[11] Critical quality attributes include those attributes that define a product's identity, quantity, safety, purity and potency. See the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

on the nature of the proposed interchangeable product, and not all factors will necessarily be relevant to a given scientific justification. The data and information may also include a scientific rationale for extrapolation of data and information to support a demonstration of interchangeability. Extrapolation is further described in section VI.B of this guidance.

Generally, the data and information to support a showing under the "can be expected to produce the same clinical result as the reference product in any given patient" standard will likely not involve additional clinical studies other than those necessary to support other elements of demonstrating interchangeability, which are described in section VI. We note that although a sponsor may seek licensure for a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed, we recommend that a sponsor seek licensure for all of the reference product's licensed conditions of use when possible.

Further, for biological products administered more than once to a patient, section 351(k)(4)(B) of the PHS Act provides that another of the criteria for FDA to make a determination of interchangeability is a finding that information in the application is sufficient to show that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch." FDA expects that applications generally will include data from a switching study or studies[12] in one or more appropriate conditions of use. FDA anticipates that data and information acquired from a switching study or studies will be useful in assessing the risk, in terms of safety and diminished efficacy, of alternating or switching between the products. Considerations for the design of a switching study, including study endpoints, study design and analysis, study population, condition(s) of use, and routes of administration to be studied, are discussed in detail in section VI.A of this guidance.

V. FACTORS IMPACTING THE TYPE AND AMOUNT OF DATA AND INFORMATION NEEDED TO SUPPORT A DEMONSTRATION OF INTERCHANGEABILITY

The data and information needed to support a demonstration of interchangeability, beyond that needed to demonstrate biosimilarity,[13] may be dependent on and influenced by multiple factors, which are discussed in this section.

[12] The term *switching study or studies* as used throughout this guidance refers to a clinical study or studies used to determine the impact of alternating or switching between the proposed interchangeable product and the reference product.

[13] Data and information needed to demonstrate biosimilarity are discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

A. Product-Dependent Factors That May Impact the Data Needed to Support a Demonstration of Interchangeability

1. Product Complexity and the Extent of Comparative and Functional Characterization

This section provides general, prospective considerations for evaluating the types and extent of data needed to support a demonstration of interchangeability. These considerations may affect the study design and aid in the justification of a development program for a proposed interchangeable product. Consistent with the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015),[14] the Agency recommends that sponsors use a stepwise approach to generating data and information, which may allow the sponsor to address any uncertainty about demonstrating interchangeability that may arise at each stage of product development. At each stage, the sponsor should evaluate the extent to which there is uncertainty about the interchangeability of the proposed product with the reference product and identify a strategy to address that uncertainty.

Section 351(k)(4)(A)(i) of the PHS Act provides that one of the criteria for FDA to make a determination of interchangeability is a finding that information in the application is sufficient to show that the proposed interchangeable product is biosimilar to the reference product. Such information would include, in part, a showing that the proposed interchangeable product meets the *highly similar* standard for demonstrating biosimilarity.[15] The "highly similar" standard applies to both interchangeable and biosimilar products.

The product's degree of structural and functional complexity may influence the extent of clinical data needed to support a demonstration of interchangeability. For example, clinical data needed to support a demonstration of interchangeability of a product expected to have a single target (e.g., a receptor) may be more limited than the clinical data that may be needed for a product acting on multiple targets or less-defined biological pathways. In addition, the extent of clinical data needed may be affected by the presence of structural features that specifically impact interchangeability (e.g., features that influence patient response to one product after exposure to another product).

FDA acknowledges that there is a range of comparative analytical data that may be submitted to support licensure under section 351(k) of the PHS Act.[16] Data sets that include highly sensitive analytics and/or sequential analytical methods that can identify molecules with different combinations of attributes (e.g., charge variants and glycoforms), as well as a comprehensive assessment of the relationships between attributes, may provide information that reduces the

[14] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[15] Section 351(i)(2) of the PHS Act defines *biosimilarity*, in part, to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components."

[16] See the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* (April 2015) for the Agency's current thinking on factors to consider to support a demonstration that a proposed therapeutic protein product is *highly similar* to a reference product.

uncertainty about interchangeability. These approaches could be of greater importance for more complex products because these products would have a larger number of attributes and thus a potential for greater uncertainty regarding interchangeability. Advances in analytics may allow for extended analytical characterization that affect the extent of other data and information needed to support a demonstration of interchangeability and may in certain circumstances lead to a more selective and targeted approach to clinical studies intended to support a demonstration of interchangeability.

2. Product-Specific Immunogenicity Risk

Clinical experience with the reference product and comprehensive product risk assessments (e.g., regarding immunogenicity)[17] may also affect the data and information needed to support a demonstration of interchangeability. For example, products with a documented history of inducing detrimental immune responses may require more data to support a demonstration of interchangeability than products with an extensive documented history that immunogenicity does not impact clinical outcomes.

3. Totality of Factors to Consider in Assessing the Data and Information Needed to Support a Demonstration of Interchangeability

The factors discussed in sections V.A.1 and V.A.2 of this guidance need to be considered together to inform the data and information needed to support a demonstration of interchangeability in a particular context. Consider the following illustrative examples:

- Product A and its associated reference product have relatively low structural complexity and the reference product has no history of inducing severe immune responses related to immunogenicity. Product A also has a low incidence of serious adverse events related to immunogenicity, similar in nature and frequency to those observed with the reference product, as demonstrated in clinical studies conducted as part of the development program for Product A. Here, sufficiently extensive comparative analytical data supporting a demonstration that the proposed interchangeable product (Product A) is highly similar to the reference product, in addition to data derived from an appropriately designed dedicated switching or integrated study (see section VI.A), may be sufficient to support a demonstration of interchangeability.

- Product B and its associated reference product have high structural complexity and the reference product has a history of rare, life-threatening adverse events related to immunogenicity. Here, postmarketing data for the product as a licensed biosimilar, in addition to an appropriately designed switching study (see section VI.A), may provide additional data and information necessary to support a demonstration of interchangeability. The collection of biosimilar postmarketing data is described further in section V.B of this guidance.

Based on the factors discussed in sections V.A.1 and V.A.2, the uncertainty regarding the interchangeability of the respective proposed interchangeable products (described in the

[17] Section VII.D.2 in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015) provides a discussion on clinical immunogenicity assessment.

preceding examples) would likely be different. Therefore, the data and information necessary to support a demonstration of interchangeability need to be considered on a case-by-case basis.

B. Biosimilar Product Postmarketing Data That May Impact the Data Needed to Support a Demonstration of Interchangeability

New tools and improved epidemiological approaches to evaluating postmarketing exposures and outcomes lend promise to the continued improvement of the capabilities of postmarketing surveillance and the collection of data related to the actual use of drug products in general. However, our current thinking is that postmarketing data collected from products first licensed and marketed as a biosimilar, without corresponding data derived from an appropriately designed, prospective, controlled switching study or studies, generally would not be sufficient to support a demonstration of interchangeability. For example, we generally would not expect postmarketing data to provide sufficient information related to the impact on clinical pharmacokinetics (PK) and pharmacodynamics (PD) of switching or alternating between the use of the proposed interchangeable product and the reference product, which we think are important study endpoint considerations in the switching studies for the reasons described in section VI.A.1 of this guidance.

Notwithstanding these limitations, we recognize that in certain circumstances, postmarketing data from a licensed biosimilar product may be helpful as a factor when considering what data is necessary to support a demonstration of interchangeability. For example, some sponsors may wish to submit postmarketing data describing the real-world use of the biosimilar product, including certain safety data related to patient experience with some switching scenarios. Such data may reduce uncertainty about interchangeability and thus the data needed to support a demonstration of interchangeability. FDA will evaluate proposals to include postmarketing data in applications to support demonstrations of interchangeability on a case-by-case basis.

In certain situations, postmarketing surveillance data from the licensed biosimilar product in addition to data from an appropriately designed switching study may be needed to address uncertainty regarding a demonstration of interchangeability and add to the totality of the evidence to support a demonstration of interchangeability. Further, there may be situations where a postmarketing study, in addition to postmarketing surveillance data, from the licensed biosimilar product may be needed to address uncertainty regarding a demonstration of interchangeability. For example, as a scientific matter, for a reference product with a history of severe immunogenicity-related adverse events, additional data and information may be needed to support a demonstration of interchangeability. Such additional data may be able to be obtained through collection of postmarketing information if the product has been licensed as a biosimilar. Sponsors are encouraged to discuss with FDA their plans for the use of postmarketing data to address any uncertainty about interchangeability and add to the totality of the evidence to support a demonstration of interchangeability.

VI. DATA AND INFORMATION NEEDED TO SUPPORT A DEMONSTRATION OF INTERCHANGEABILITY

FDA recommends sponsors intending to develop a proposed interchangeable product to meet with FDA to discuss their proposed product development plan. Early discussions with FDA about product development plans, including adequate scientific justification for the proposed development program, will facilitate development of interchangeable products.[18]

A. Considerations for the Design and Analysis of a Switching Study or Studies Needed to Support a Demonstration of Interchangeability

A switching study or studies will generally be expected to demonstrate that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" set forth in section 351(k)(4)(B) of the PHS Act. The main purpose of a switching study or studies is to demonstrate that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch. A switching study or studies should evaluate changes in treatment that result in two or more alternating exposures (switch intervals) to the proposed interchangeable product and to the reference product.

If a sponsor of a proposed interchangeable product believes that data from a switching study is not necessary, FDA expects the sponsor to provide a justification for not needing such data as a part of the demonstration of interchangeability. For biological products that are not intended to be administered to an individual more than once, FDA expects that switching studies would generally not be needed. For products intended to be administered more than once, sponsors are encouraged to meet with FDA to discuss the planned development approach, including any proposed justification of why data from a switching study is not needed.

Design of switching studies may be informed by how the proposed interchangeable product will be used in clinical practice, taking into consideration scenarios where alternating or switching products might cause the most clinical concern. For treatments that have a long course of therapy, sponsors should anticipate dropouts in the study and should use a scientifically justifiable method to address the increased possibility of missing data.

As described in more detail in this section, a switching study is typically designed to assess whether switching between the reference product and the proposed interchangeable product will present risk in terms of safety or diminished efficacy that is greater than using the reference product without such switching. A switching study should generally evaluate whether switching between the reference product and the proposed interchangeable product will affect clinical

[18] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018), which provides recommendations to industry on all formal meetings between the FDA and sponsors or applicants for proposed biosimilar products or proposed interchangeable products intended to be submitted under 351(k) of the PHS Act. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

response in terms of safety or diminished efficacy reflected, in part, through an assessment of whether switching results in differences in immunogenicity and PK and/or PD (if available), as compared to not switching. If an apparent difference in clinical response in terms of safety or diminished efficacy is noticed between the switching and non-switching arms of the study (see section VI.A.2.a of this guidance), it would raise concerns as to whether the proposed interchangeable product is interchangeable.

FDA has outlined a flexible approach regarding the design of a switching study. FDA will address program-specific scientific matters (e.g., the impact of small patient populations) on a case-by-case basis in interactions with sponsors. To facilitate development of interchangeable products, FDA encourages sponsors to have early discussions with FDA about their product development plans.

1. Study Endpoints

The primary endpoint in a switching study or studies should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on clinical PK and PD (if available). The PK and PD (if available) endpoints, as distinguished from clinical efficacy endpoints, are generally more likely to be sensitive to detect changes in exposure and/or activity that may arise as a result of alternating or switching. In addition to PK and/or PD parameters, a switching study would also be expected to descriptively assess immunogenicity and safety. A switching study may also incorporate the evaluation of efficacy endpoints. Although assessments of efficacy endpoints can be supportive, at therapeutic doses many clinical efficacy endpoints would generally be less sensitive to detect changes in exposure and/or activity that may arise as a result of alternating or switching.

Biologically relevant PD measures, if available, may be useful as shorter term, more sensitive indicators of the potential impact of alternating or switching on the risk of diminished efficacy as compared to efficacy endpoints. Relevant PD measures may also be useful to reflect multiple domains of activity, which could reduce residual uncertainty about interchangeability. Selection of PD endpoints should be scientifically justified for the intended purpose.[19] When PD endpoints that are sensitive to changes in drug concentration can be identified, PD analysis, in addition to PK analysis, may be useful to assess the impact of switching or alternating between the proposed interchangeable product and the reference product.

Study samples from the switching arm and non-switching arm should be assessed with the same PK, PD, or immunogenicity assay. FDA recommends that clinical PK, PD, and immunogenicity assays be developed and validated early in product development.[20,21] Sponsors are expected to demonstrate that the developed PK and/or PD assays are suitable for detecting changes on the selected PK and/or PD endpoint(s) as a result of alternating or switching between products. The

[19] See the guidance for industry, *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016).

[20] See guidance for industry, *Immunogenicity Testing of Therapeutic Protein Products—Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019).

[21] See guidance for industry, *Bioanalytical Method Validation* (May 2018).

validation study should demonstrate that the assay performs similarly for both the proposed interchangeable product and the reference product.

In summary, the primary endpoint(s) in a switching study or studies are recommended to be, in most cases, a comparison of PK and/or PD (if available) parameter(s) between the switching arm and non-switching arm following the final switch. In cases where PK and/or PD are not adequately sensitive endpoints (e.g., products with limited systemic exposure, or for which PD effects are not measurable), sponsors are expected to propose and justify selected endpoints other than PK or PD measures.

2. Study Design and Analysis

This section provides general recommendations and considerations related to study design and analysis. Sponsors may propose alternative approaches and are encouraged to discuss the proposed design and analysis of a switching study with FDA.

a. Dedicated Switching Study Design

A study with a lead-in period of treatment with the reference product, followed by a randomized two-arm period—with one arm incorporating switching between the proposed interchangeable product and the reference product (switching arm) and the other remaining as a non-switching arm receiving only the reference product (non-switching arm)—may be appropriate when designing a switching study. An illustrative example of switching study design is described in Attachment I. Considerations for the design and analysis of such a study are discussed as follows:

- Sample size: The sample size of the switching study should generally be based on PK considerations. Inter-subject variability in AUC_{tau} or C_{max} as described for the reference product should be primary considerations; however, prior information on product immunogenicity incidence and consequences should also be considered, and the sample size should be appropriately justified. When appropriate, inter-subject variability in PD endpoints may need to be considered. Study designers should anticipate the possibility of a considerable dropout rate for reasons unrelated to the study treatment arms. An anticipated high dropout rate due solely to an influence affecting all treatment arms could be assumed to be random. The negative impact on the statistical power of such a random influence could be precluded by factoring such influences into the sample size calculation. It should be noted that dropout rates or missing data rates that differentially affect the study treatment arms could represent treatment arm differences, and sponsors should provide adequate justification to FDA about any such differences and their possible causes. In addition, FDA will investigate possible causes of the noted differences in treatment arms.

- Number and duration of switches: The number and duration of switches between the reference product and the proposed interchangeable product should take into consideration the clinical condition to be treated, the therapeutic dosing of the product, and the duration of the exposure period to each product that would be expected to cause

the greatest concern in terms of immune response and resulting impact on safety and efficacy, if any.

- The lead-in period should be of sufficient duration to ensure an adequate baseline with respect to the study objectives before randomization to the switching period of the study.

- The switching arm is generally expected to incorporate at least two separate exposure periods (switch intervals) to each of the two products (i.e., at least three switches with each switch crossing over to the alternate product).

- In the switching arm, the final switch should be from the reference product to the proposed interchangeable product.

- The comparative assessment should occur during the final exposure period after a sufficient time (i.e., an adequate washout period of at least three or more half-lives) has elapsed following the last administration of the reference product in the switching arm. The number of doses of the proposed interchangeable product or reference product administered in the final exposure period will depend on the half-life and clinical dosing regimen.

- PK, PD, and immunogenicity sampling: To capture the full PK profile, intensive PK sampling should be performed during the final exposure period after at least three half-lives have elapsed following the last administration of the reference product in the switching arm. Trough PK sampling should be conducted at an appropriate time point during each exposure period to ensure that steady state is attained, when appropriate. The timing of PD[22] and immunogenicity[23] sampling should be appropriately justified.

- Study Analysis:

    - Primary analysis: For intravenous (IV) studies, AUC_{tau} will be considered a primary study endpoint. For subcutaneous (SC) studies, C_{max} and AUC_{tau} will be considered as co-primary study endpoints. The log-transformed AUC_{tau} and C_{max} data should be statistically analyzed using an average equivalence statistical approach.[24] The 90% confidence interval for the geometric mean ratio of AUC_{tau} (IV and SC data) and C_{max} (SC data) between the proposed interchangeable product and the reference product should be within 80% to 125%. C_{trough} and T_{max}

[22] See Section IV.H. Defining the Appropriate Pharmacodynamic Time Profile in the guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016).

[23] See Section VII.A. Obtaining Subject Samples in the guidance for industry *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019). Also see Section IV. Recommendations for Mitigating Immunogenicity Risk in the Clinical Phase of Development of Therapeutic Protein Products in the guidance for industry *Immunogenicity Assessment of Therapeutic Protein Product* (August 2014).

[24] See FDA's guidance for industry *Statistical Approaches to Establishing Bioequivalence* (February 2001).

should also be analyzed as secondary endpoints. The sponsor should propose margins and statistical analyses appropriate for the evaluation of the PD endpoints.

- Safety, immunogenicity, and efficacy should be descriptively assessed as secondary endpoints. Regarding safety, it could be reasonable for a sponsor to focus on an evaluation of all serious adverse events, immune-related safety events, and adverse events of interest (e.g., known cardinal adverse events previously described with use of the reference product). The immunogenicity assessment should include, but not necessarily be limited to, an assessment of anti-drug antibody (ADA) and neutralizing antibody (NAb) incidence, ADA and NAb titer, and an evaluation of the impact of the development of ADA and NAb on PK, PD, safety, and efficacy.[25] Immunogenicity assays should be adequately sensitive to detect ADA and NAb in the presence of drug concentrations in study samples. Sponsors should discuss with FDA their planned evaluation of safety and immunogenicity.

b. Integrated Study Design

If a sponsor is considering a single study to (1) support a demonstration of no clinically meaningful differences between the reference product and the proposed product for biosimilarity[26] and (2) evaluate the impact of switching or alternating between the reference product and the proposed product for interchangeability, then an integrated, two-part study design may be appropriate. Following the time point(s) for evaluation of the appropriate endpoint(s) to support the demonstration of no clinically meaningful differences for biosimilarity between the proposed product and the reference product in the first part of the study, the subjects in the reference product arm should be re-randomized in the second part of the study to continue to receive the reference product (non-switching arm) or to switch to the proposed interchangeable product (switching arm) as described in section VI.A.2.a of this guidance.

An integrated study needs to be adequately powered to evaluate the appropriate endpoint(s) to support the demonstration of no clinically meaningful differences for biosimilarity, where the primary comparison is between the proposed product arm and the reference product arm. In addition, the study needs to be adequately powered to evaluate PK and PD (if available) following the final switch to support a demonstration of interchangeability, where the primary comparison is between the switching arm and the non-switching arm.

3. Study Population

The study population for switching studies should be adequately sensitive to allow for detection of differences as a result of switching between the reference product and proposed interchangeable product in PK and/or PD, common adverse events, and immunogenicity between

[25] Refer to recommendations for immunogenicity assessments discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[26] Data and information needed to demonstrate biosimilarity are discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

the switching and non-switching arms. FDA generally recommends that sponsors use patients in switching studies because these studies are designed to assess the impact of switching and to mimic how the proposed interchangeable product will be used in clinical practice. With adequate scientific justification, however, sponsors may conduct switching studies in a patient population that is different from that used to support licensure of the reference product, or in healthy subjects. Sponsors should also provide adequate scientific justification to support that the study population is adequately sensitive to detect the impact of switching (e.g., differences in clinical PK and/or PD, common adverse events, and immunogenicity).

In a circumstance where a sponsor considers using healthy subjects, the sponsor should weigh the benefit of exposing healthy subjects to a proposed interchangeable product and/or the reference product during a clinical study against the risk of having them develop antibodies to the product, which in turn may preclude them from being able to receive the treatment in the future. However, there may be some limited situations where it is clinically and ethically appropriate to use healthy subjects in switching studies. Sponsors are strongly encouraged to discuss with FDA their rationale for conducting switching studies in healthy subjects before initiating studies, preferably before submitting a proposed protocol or protocol amendment.

4. Condition(s) of Use to Be Studied

A sponsor may obtain licensure only for a condition(s) of use for which the reference product is licensed. As described in section VI.B of this guidance, sponsors should consider choosing a condition of use to study that would support subsequent extrapolation of data to other conditions of use.

For example, if a reference product is licensed for multiple indications, one of which was approved under section 506(c) of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 601, subpart E (accelerated approval), but the anticipated clinical benefit in that indication has not yet been verified in postmarketing studies, then sponsors should consider studying another indication for which the reference product is licensed, to avoid complications in the event that postmarketing studies of the reference product fail to verify the anticipated clinical benefit in the indication approved under accelerated approval.

5. Route of Administration

If a product is approved for more than one route of administration, sponsors should study the route of administration that will best assess how a patient's immune response will impact the clinical performance of the proposed interchangeable product, including changes in safety risk and efficacy. Choosing a more immunogenic route of administration (e.g., subcutaneous rather than intravenous) for use in switching studies may help sponsors anticipate the clinical implications of real-world use in clinical practice.

B. Extrapolation of Data

If the proposed product meets the statutory requirements for licensure as an interchangeable product under section 351(k) of the PHS Act based on, among other things, data and information sufficient to demonstrate interchangeability in an appropriate condition of use, the sponsor may seek licensure of the proposed product as an interchangeable product for one or more additional

conditions of use for which the reference product is licensed. The sponsor would need to provide sufficient scientific justification for extrapolating data and information to support a determination of interchangeability for each condition of use for which licensure as an interchangeable product is sought. The scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use for which the reference product is licensed, which may include the following:
  - The target receptor(s) for each relevant activity/function of the product
  - The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target receptor(s)
  - The relationship between product structure and target/receptor interactions
  - The location and expression of target receptor(s)
- Differences, if any, in the expected PK and biodistribution of the product in different patient populations (relevant PD measures may also provide important information on the mechanism(s) of action)
- Differences, if any, in the expected immunogenicity risk of the product in different patient populations
- Differences, if any, in expected toxicities in each condition of use and patient population (including whether the expected toxicities are related to the pharmacological activity of the product or to off-target activities)
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which the reference product is licensed[27]

Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of interchangeability. Advanced structural and functional characterization may provide additional support for the justification for extrapolation.

In choosing a condition of use to study that would permit subsequent extrapolation of data to other conditions of use, FDA recommends that a sponsor consider a condition of use that would be adequately sensitive to assess the risk of alternating or switching between the products, in terms of safety or diminished efficacy, in a switching study.

[27] These factors are also discussed in section VII.D.4. Extrapolation of Clinical Data Across Indications in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

VII. CONSIDERATIONS REGARDING THE COMPARATOR PRODUCT IN A SWITCHING STUDY OR STUDIES

As defined in section 351(i)(3) of the PHS Act, an interchangeable product may be substituted for the reference product without the prescribing health care provider's intervention. As described above, sponsors will generally be expected to conduct a switching study or studies to address section 351(k)(4)(B) of the PHS Act: "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch." The goal of a switching study or studies is to support a determination that a biosimilar product is interchangeable with a reference product that is licensed for use in the United States.

If a sponsor seeks to use data derived from a switching study or studies comparing a proposed interchangeable product with a non-U.S.-licensed comparator product as part of the demonstration that the proposed interchangeable product meets the standard described in section 351(k)(4)(B) of the PHS Act, the sponsor should provide adequate data and information to establish a "bridge" between the non-U.S.-licensed comparator and the U.S.-licensed reference product and thereby justify the relevance of the data obtained using the non-U.S.-licensed comparator to an evaluation of whether the requirements of section 351(k)(4)(B) have been met. This section describes considerations for the type and extent of data needed to establish an adequate bridge in this context.

In the context of demonstrating biosimilarity to a reference product, FDA has stated that "sponsors may seek to use data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed comparator product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act."[28,29] In clinical studies used to support a demonstration of no clinically meaningful differences as a part of demonstrating biosimilarity, the comparator product (whether it is a non-U.S.-licensed product or a U.S.-licensed reference product) serves as a control against which the proposed product is evaluated. However, in a switching study that is designed to evaluate the impact of switching or alternating to support a determination of interchangeability, the comparator product plays a different role.

As described in section VI.A., a switching study is typically designed to assess whether switching between the reference product and the proposed interchangeable product will present risk in terms of safety or diminished efficacy that is greater than using the reference product without such switching. A switching study should generally evaluate whether switching between the reference product and the proposed interchangeable product will affect clinical response in terms of safety or diminished efficacy reflected, in part, through an assessment of whether switching results in differences in immunogenicity and PK and/or PD (if available), as compared

[28] See section V on U.S.-licensed reference product and other comparators in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[29] See Q.I.8 in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (December 2018), which discusses use of a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product.

to not switching. Hence, rather than being used only as a control, the comparator product is used in a switching study in both the active switching arm and the control non-switching arm. Therefore, the type and extent of bridging data needed to justify the use of a non-U.S.-licensed comparator in a switching study may be different or more extensive than is needed in other contexts.

It is possible that the reference product and the non-U.S.-licensed comparator product have, for example, subtle differences in levels of specific structural features (e.g., acidic variants, deamidations), process related impurities, or formulation. These subtle differences may not preclude use of the non-U.S.-licensed product as a comparator in certain studies to support a demonstration of biosimilarity because the comparator is being used as a control in an evaluation that does not involve switching back and forth. However, in the context of switching between the products, multiple exposures to each product may potentially prime the immune system to recognize subtle differences in structural features between products. The overall immune response could be increased under these conditions. This immunologic response is highly dependent on the structural differences between the proposed interchangeable product and the comparator product used in the switching study, in addition to other potential differences between the products such as impurities and formulation.

For the reasons described above, the type and extent of data needed to justify the use of a non-U.S.-licensed comparator in a switching study may be different or more extensive than is needed in other contexts in which a non-U.S.-licensed comparator is used. However, FDA believes that when supported by adequate data and information, it may be reasonable to use a non-U.S.-licensed comparator in a switching study. Sponsors are encouraged to contact FDA early in the product development process to discuss the design of a switching study, including any proposal to provide adequate scientific justification to support the use of data generated in a switching study using a non-U.S.-licensed comparator product to support a demonstration of interchangeability.

VIII. CONSIDERATIONS FOR DEVELOPING PRESENTATIONS FOR PROPOSED INTERCHANGEABLE PRODUCTS

The data and information needed to support a demonstration of interchangeability, beyond that needed to demonstrate biosimilarity,[30] may also be influenced by the proposed product's presentation.[31] Sponsors are encouraged to contact FDA early during product development to discuss the proposed presentation and specific considerations related to licensure of the proposed product as an interchangeable under section 351(k) of the PHS Act.

[30] Data and information needed to demonstrate biosimilarity are discussed in section VII of the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[31] For the purposes of this guidance, the term *presentation* means the container closure system and any delivery device constituent part of the product.

When developing a product for licensure as an interchangeable product under section 351(k) of the PHS Act, it is important that sponsors carefully consider the presentation of the proposed interchangeable product relative to the reference product.[32] A sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed. For example, if the reference product is only marketed in a vial and a prefilled syringe, a sponsor should not seek licensure for the proposed interchangeable product for a different presentation, such as an auto-injector. However, if a sponsor is considering the development of a presentation for which the reference product is not licensed, this should be discussed with FDA. In such cases, FDA will evaluate whether the proposed presentation could support a demonstration of interchangeability.

As applicable, a general description of the presentation should be provided in the chemistry, manufacturing, and controls section of the application. There should be complete chemistry, manufacturing, and controls information for the proposed interchangeable product, including, if applicable, delivery device constituent part design, and development information. The presentation should be shown to be compatible for use with the final formulation of the proposed interchangeable product through appropriate studies, including, for example, extractable/leachable studies, performance testing, and stability studies. Data and information supporting the appropriate use and performance testing of the delivery device constituent part of the proposed interchangeable product should be submitted.

IX. POSTMARKETING SAFETY MONITORING CONSIDERATIONS

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

Postmarketing safety monitoring for interchangeable products should first take into consideration any particular safety or effectiveness concerns associated with the use of the reference product and its class, the proposed interchangeable product in its development and clinical use (if marketed outside the United States), the specific condition of use and patient population, and patient exposure in the interchangeability development program. Postmarketing safety monitoring for an interchangeable product should also have adequate pharmacovigilance mechanisms in place.[33] Rare but potentially serious safety risks may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events. In particular cases, such risks may need to be evaluated through

[32] See Q.I.4 and Q.I.6 in the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (December 2018).

[33] For general pharmacovigilance considerations, see the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) and the guidance for industry *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report* (August 1997).

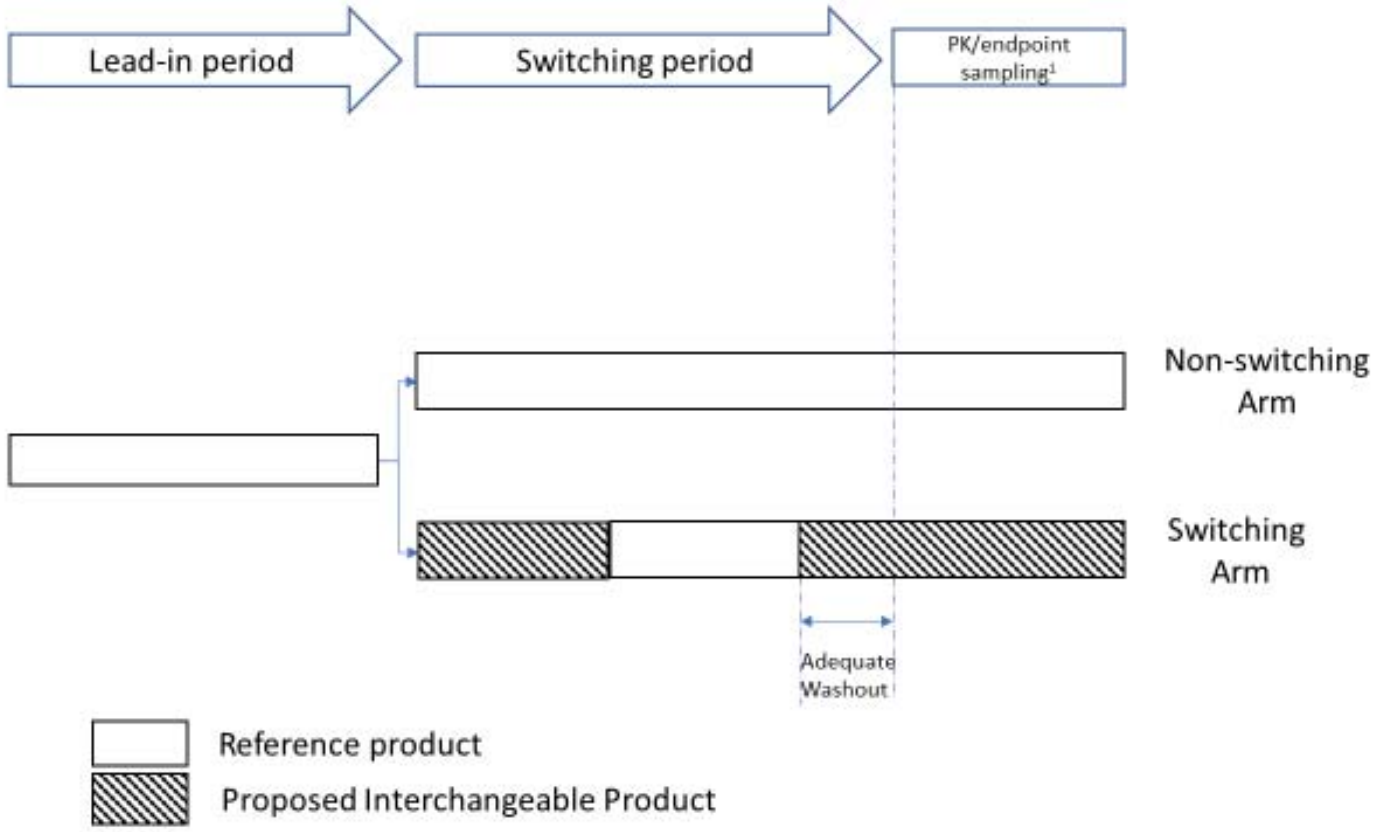
postmarketing surveillance or studies. In addition, as with any other biological product, FDA may require a postmarketing study or a clinical trial to evaluate certain safety risks.[34]

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

[34] See section 505(o)(3) and 505(p)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act.

ATTACHMENT I

Example of a **Switching Study Design**



[1]Appropriate PK parameters and other endpoints (e.g., PD) also collected and analyzed in previous switch intervals.

Figure is not drawn to scale.