Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

DRAFT GUIDANCE

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

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Biosimilars

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Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product 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 product* or *proposed product*) with a reference product.

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

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

[2] 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)."

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 an 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"[4] 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."[5]

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."[6]

III. 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 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

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

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

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

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. The 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 may vary depending on the nature of the proposed interchangeable product and may include, but need not be limited to, an evaluation of data and information generated to support a demonstration of a biological product's biosimilarity, such as:

- The identification and analysis of the critical quality attributes
- 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(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)
- The pharmacokinetics and biodistribution of the product in different patient populations
- The immunogenicity risk of the product in different patient populations
- Differences 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

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 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 to extrapolate data and information supporting a demonstration of interchangeability in an appropriate condition of use to the remaining conditions of use for which the reference product is licensed. Extrapolation of data 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. 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.

In addition, 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 "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." FDA expects that applications generally will include data from a switching study or studies[7] 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.

An interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.[8] Sponsors of proposed interchangeable products should evaluate the proposed product's presentation, including product design and user interface, relative to the reference product. Considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products are discussed in detail in section VIII of this guidance.

IV. 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
- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability
- Recommendations regarding the use of a U.S.-licensed reference product in a switching study or studies

[7] 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.

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

- Considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products[9,10]

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,[11] may be dependent on and influenced by multiple factors, which are discussed in this section.

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

Consistent with the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, the Agency recommends that sponsors use a stepwise approach generating data and information to address residual uncertainty about demonstrating interchangeability during product development. At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the interchangeability of the proposed product with the reference product, and identify next steps to try 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

[9] 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). 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.

[10] 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 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.)

[11] 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*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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.[12] FDA acknowledges that there is a continuum of comparative analytical data that could support a demonstration that the highly similar standard is satisfied.[13] For example, a fingerprint-like characterization[14] may reduce residual uncertainty regarding interchangeability and inform the data and information needed to support a demonstration of interchangeability, which may lead to a more selective and targeted approach to clinical studies necessary to demonstrate interchangeability.

Despite significant improvements in analytical techniques, current analytical methodologies may not detect or characterize all relevant structural and functional differences between the reference product and the proposed interchangeable product.[15] There may also be some structural features that specifically impact interchangeability (e.g., features that influence patient response to one product after exposure to another product). 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 residual uncertainty about interchangeability and thus inform the data and information needed to support a demonstration of interchangeability between the two products.

The extent to which data and information provided by these advanced analytical approaches helps to reduce residual uncertainty about interchangeability depends on the degree of analytical similarity between the products and the strength of the evidence for the clinical relevance of the analytical data. Evidence of clinical relevance may range from a risk assessment describing the potential importance of the additional attributes evaluated to advanced modeling supported by functional and/or in vivo data. A clinically relevant and thus meaningful fingerprint-like characterization may reduce residual uncertainty regarding interchangeability and may lead to a more selective and targeted approach to the clinical studies necessary to demonstrate interchangeability.

[12] 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."

[13] See the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* for the Agency's current thinking on factors to consider when demonstrating that a proposed therapeutic protein product is *highly similar* to a reference product.

[14] For information regarding fingerprint-like characterization, see the guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*. Also see the draft guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. When final, this guidance will represent the Agency's current thinking on this topic. Also see Kozlowski S, Woodcock J, Midthun K, Sherman RB, 2011, Developing the Nation's Biosimilars Program, N Engl J Med, 365:385–388.

[15] See Section IV.A. Nature of Protein Products and Related Scientific Considerations in the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

The product's degree of structural and functional complexity may also influence the data and information needed to support a demonstration of interchangeability, because the product's structural complexity can affect the residual uncertainty regarding interchangeability. For example, products expected to have a single target (e.g., a receptor) may have less residual uncertainty regarding interchangeability than those acting on multiple or less-defined biological pathways.

Along the continuum of possible data sets that could support a demonstration of the highly similar standard, there may be extensive characterization approaches that have some, but not all, of the features of a meaningful fingerprint-like characterization. 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 residual uncertainty regarding interchangeability. Such extensive characterization approaches may reduce the residual uncertainty regarding interchangeability for complex products. Reducing residual uncertainty can impact what additional data and information would be needed 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)[16] 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 a consideration regarding residual uncertainty about the data and information needed to support a demonstration of interchangeability. Consider the following illustrative examples:

- Product A has relatively low structural complexity, has been demonstrated to have meaningful fingerprint-like analytical similarity to the reference product as a part of demonstrating biosimilarity, and has a low incidence of serious adverse events related to immunogenicity. Here, data derived from an appropriately designed switching study (see section VI.A) may be sufficient to support a demonstration of interchangeability.

- Product B has high structural complexity, has been demonstrated to be highly similar to the reference product as a part of demonstrating biosimilarity but has no demonstration of meaningful fingerprint-like analytical similarity, and has known serious adverse events related to immunogenicity. Here, postmarketing data for the product as a licensed

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

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 residual uncertainty regarding the interchangeability of the respective proposed products (described in the preceding examples) would be different. Therefore, the data and information necessary to support a demonstration of interchangeability needs 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, however, 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 postmarketing data may describe the real-world use of the biosimilar product, including certain safety data related to patient experience with some switching scenarios. Such data may impact residual uncertainty about interchangeability and thus the data needed to support a demonstration of interchangeability.

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 residual 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 residual uncertainty regarding a demonstration of interchangeability. For example, as a scientific matter, where there is residual uncertainty regarding interchangeability based on immunogenicity-related adverse events that could affect use of the product as an interchangeable, a sponsor may need to first obtain licensure as a biosimilar product and collect postmarketing data before interchangeability can be demonstrated. In such cases, the type and amount of biosimilar product postmarketing data needed would depend on the residual uncertainty regarding the demonstration of interchangeability. Sponsors are encouraged to discuss with FDA their plans for the use of postmarketing data to address

residual 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 advises 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.[17]

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

For biological products that are intended to be administered to an individual more than once, sponsors generally will be expected to conduct a switching study or studies to address the statutory provision "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.

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. However, FDA expects that a sponsor will provide a justification for not needing data from a switching study as a part of the demonstration of interchangeability, and sponsors are encouraged to meet with FDA to discuss their planned development approach.

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.

It is important to note that if patients experience an immune response or adverse event during the course of a switching study, a carryover effect may make it difficult to determine whether the proposed interchangeable product or the reference product caused the event. If an apparent

[17] See the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*, which provides recommendations to industry on all formal meetings between the FDA and sponsors or applicants for biosimilar biological products intended to be submitted under 351(k) of the PHS Act.

difference in immune response or adverse events 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, regardless of whether the proposed interchangeable product or the reference product or the switching of the two products actually caused the event.

FDA has outlined a flexible approach regarding the design of any necessary 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 pharmacokinetics and pharmacodynamics (if available), because these assessments are generally most likely to be sensitive to changes in immunogenicity and/or exposure that may arise as a result of alternating or switching. FDA recommends that clinical PK and PD test methods and assays be developed and validated early in product development. The validation should consider both the proposed interchangeable product and the reference product. Although assessments of efficacy endpoints can be supportive, at therapeutic doses many clinical efficacy outcomes would only be sensitive to large changes in exposure or immunogenicity, which may not be observed in a study of limited duration and with a limited number of switches.

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. 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 address residual uncertainty with respect to interchangeability.

In addition to PK and PD parameters, a switching study or studies would also be expected to assess immunogenicity and safety.

2. Study Design and Analysis

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. 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} should be primary considerations) and should be appropriately justified. As the switching study will likely require repeated patient monitoring, the 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 interval 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 (e.g., steady state of pharmacokinetics) before randomization to the switching period of the study.

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

  - The last switching interval should be from the reference product to the proposed interchangeable product, where the duration of exposure to the proposed interchangeable product after the last switch is sufficiently long to allow for washout of the reference product (i.e., at least three or more half-lives) to assess the pharmacokinetics of the proposed interchangeable product in the switching arm and compare it to the pharmacokinetics of the reference product in the non-switching arm.

- PK, PD, and immunogenicity sampling: To capture the full PK profile, intensive PK sampling should be performed during the last switch interval following the dose after which at least three half-lives of the reference product have elapsed. Trough PK sampling should be conducted after each switch to ensure that steady state is attained. The timing of PD[18] and immunogenicity[19] sampling should be appropriately justified.

[18] See Section IV.H. Defining the Appropriate Pharmacodynamic Time Profile in the draft guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. When final, this guidance will reflect FDA's current thinking on this topic.

- Study Analysis:

  - Primary analysis: The following PK data obtained during the intensive sampling interval should be reported: C_{max}, T_{max}, C_{trough}, and AUC_{tau}. The log-transformed AUC_{tau} and C_{max} data should be statistically analyzed using an analysis of the variance. The 90% confidence interval for the geometric mean ratio of AUC_{tau} and C_{max} between the proposed interchangeable product and the reference product should be within 80–125%. C_{trough} and T_{max} should also be analyzed as secondary endpoints. PD endpoints, when evaluated, should be measured at appropriate times during the PK sampling interval.

  - Safety, immunogenicity, and efficacy should be descriptively analyzed as secondary endpoints.

b. Integrated Study Design

If a sponsor is considering a study design using a single study intended to (1) support a demonstration of no clinically meaningful differences between the reference product and the proposed product for biosimilarity[20] and (2) evaluate the impact of switching or alternating between the reference product and the proposed product for interchangeability, 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 reference product arm) or to switch to the proposed product (switching arm) as described in section VI.A.2.a of this guidance. FDA recommends continuing the proposed product arm (non-switching proposed product arm) from the inception of the study, through the duration of the switching portion of the integrated study, to the completion of the study.

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 pharmacokinetics and pharmacodynamics (if available), following the last switch to support a demonstration of interchangeability, where the primary comparison is between the switching arm and the non-switching reference product arm.

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[19] See Section VII.A. Obtaining Patient Samples in the draft guidance for industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins*. 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*.

[20] 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*.

3. Study Population

The study population for switching studies should be adequately sensitive to allow for detection of differences in pharmacokinetics and/or pharmacodynamics, common adverse events, and immunogenicity between the switching and non-switching arms. Even though it is likely that the study population will generally have characteristics that are consistent with those of the population studied for licensure of the reference product for the same indication, sponsors may conduct switching studies in a patient population that is different from that used to support licensure of the reference product. Sponsors should provide adequate scientific justification to support that such a population is adequately sensitive to detect the impact of switching (e.g., differences in clinical pharmacokinetics and/or pharmacodynamics, common adverse events, and immunogenicity).

FDA strongly recommends that sponsors use patients in switching studies because these studies are designed to mimic how the proposed interchangeable product will be used in clinical practice. 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 during the course of 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, if needed. 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 of Use To Be Studied

As described in section VI.B of this guidance, sponsors should consider choosing a condition of use that would support subsequent extrapolation of data to other conditions of use.

In addition, it is important to note that a sponsor may obtain licensure only for a condition of use (or uses) for which the reference product is licensed. If a reference product has multiple conditions of use and one of those conditions of use was licensed under section 506(c) of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 601, subpart E (accelerated approval), and the reference product's clinical benefit in this condition of use has not yet been verified in postmarketing studies, then sponsors should consider studying another condition of use for which the reference product is licensed, to avoid complications in the event that postmarketing studies fail to verify the reference product's clinical benefit for the condition of use being considered under the accelerated approval provisions.

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 to support a determination of interchangeability for each condition of use for which the reference product is licensed and 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)
- The pharmacokinetics and biodistribution of the product in different patient populations (Relevant PD measures may also provide important information on the mechanism(s) of action.)
- The immunogenicity risk of the product in different patient populations
- Differences 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[21]

Differences between conditions of use with respect to the factors described 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

[21] 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.*

structural and functional characterization may also 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 choosing 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 and subsequently support extrapolation based on the factors described in this section.

VII. USE OF A U.S.-LICENSED REFERENCE PRODUCT IN A SWITCHING STUDY OR STUDIES

In the context of demonstrating biosimilarity to a reference product, FDA has advised 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."[22,23] 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. 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. Switching studies are designed to assess whether one product will affect the immune system's response to the other product, once the switch occurs, and whether this will result in differences in immunogenicity or PK profiles. Thus, using a non-U.S.-licensed comparator product generally would not be appropriate in a switching study for the following reasons:[24]

It is possible that the proposed interchangeable 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). The immune system reaction in terms of the overall level of antibody produced to each product could be similar, thereby supporting a demonstration of no clinically meaningful differences. Thus, these subtle differences would not preclude a demonstration of

[22] 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*.

[23] See Q.I.8 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, which discusses use of a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product.

[24] See Q.I.8 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, which explains that "[a]t this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product."

biosimilarity. However, with switching, multiple exposures to each product can prime the immune system to recognize subtle differences in structural features between products, and 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 (e.g., impurities). Because there may be subtle differences between the U.S.-licensed reference product and the non-U.S.-licensed comparator product, there is uncertainty as to whether the results observed in a switching study using a non-U.S.-licensed comparator product would also be observed if the U.S.-licensed reference product had been used instead.

Under the BPCI Act, an interchangeable product may be substituted for the reference product without the prescribing health care provider's intervention. There may be multiple versions of a non-U.S.-licensed comparator product on the international market, each approved for use by the relevant national regulatory authority and each with possible subtle differences in levels of structural features from the U.S.-licensed reference product and between each other. The goal of a switching study or studies is to determine a biosimilar product's interchangeability with a reference product that is licensed for use in U.S. clinical settings, thus establishing interchangeability with a product that patients will not receive in the United States would generally not be appropriate.

For these reasons, FDA strongly recommends that sponsors use a U.S.-licensed reference product in a switching study or studies. 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,[25] may also be influenced by the proposed product's presentation.[26] This section provides a framework for sponsors to determine the types of data and information related to a proposed presentation that might be necessary to support a demonstration of interchangeability. The considerations described in this section are intended to provide clarity and support flexibility, where appropriate.

[25] 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*.

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

- Clarity: The framework outlined in this section is designed to provide clear recommendations to guide the development of interchangeable product presentations. Often decisions regarding a presentation are made early in product development. The approach described is intended to reduce potential uncertainty during product development with respect to a proposed presentation and enable sponsors to conduct a product-specific evaluation of their proposed presentation.

- Flexibility: FDA anticipates that sponsors of proposed interchangeable products may develop presentations that have some differences in design from the presentations licensed for the reference product. FDA does not expect that all differences in the design of the presentation of a proposed interchangeable product, when compared to the presentation of a reference product, would negatively impact the appropriate use[27] of the product when substituted for the reference product. We intend this section to assist sponsors in tailoring the data and information needed to support a demonstration of interchangeability of their proposed product.

The threshold analyses described in section VIII.B.1.a of this guidance are recommended for all proposed interchangeable products to identify any differences in design between the proposed interchangeable product and the reference product. If there are differences other than minor as observed in the threshold analyses described in section VIII.B, sponsors can use the results from the threshold analyses to determine the need, if any, for additional data or information, such as data and information from a comparative human factors study. FDA expects that such additional studies will likely not be needed for many interchangeable products.

A. General Considerations

When developing a product for licensure as interchangeable 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.[28] 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. A sponsor planning to develop a presentation for which the reference product is not licensed should discuss its proposed presentation 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 entire container closure system should be provided in the chemistry, manufacturing, and controls (CMC) section of the application. There should be

[27] The terms *appropriate use* or *appropriately use* are sometimes used in this section for brevity to refer to use of the proposed interchangeable product in a manner that supports a demonstration of interchangeability under section 351(k) of the PHS Act.

[28] See Q.I.4 and Q.I.6 in the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

complete CMC information for the proposed product, including 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 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 product should be submitted.

B. Analysis of Proposed Presentations of Proposed Interchangeable Products

The use of a biological product generally involves a sequence of administration steps because biological products are generally injected or infused into the body. In addition, these products are administered by a variety of end users, including health care providers, patients, caregivers, or a combination of these end users.[29,30] The design of the presentation determines the specific tasks necessary to administer the product. These tasks can vary considerably depending on the type of presentation and its design characteristics. Differences in the design of the container closure system or delivery device constituent part between the proposed interchangeable product and the reference product may be acceptable provided that the design differences are analyzed appropriately and data are provided to demonstrate that the changes do not negatively impact the ability of end users, including patient and caregiver end-user groups, to appropriately use these products when the interchangeable product is substituted for the reference product without the intervention of the prescribing health care provider or additional training before use.

Because a proposed interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product, a proposed interchangeable product with a differently designed presentation than the reference product may raise uncertainty about whether the difference in presentations would impact the ability of end users, including patients or caregivers, to appropriately use the proposed product. Therefore, FDA recommends that sponsors analyze the presentations of a proposed interchangeable product to identify differences in design compared to the presentations licensed for the reference product using the threshold analysis outlined in this section. These threshold analyses may be used in the development of the proposed presentation to minimize differences between the proposed interchangeable product and the reference product as well as to identify whether additional data, including data from comparative use human factors studies (as described further in this section), may be needed in certain circumstances.

To conduct the analysis of the presentations of the proposed interchangeable product and reference product for the purposes of identifying differences between the presentations, sponsors should examine the external critical design attributes of the proposed interchangeable product in

[29] Administration steps at a high level include the aseptic technique to manipulate the product to prepare it for injection and to ensure that the right dose is administered, followed by a physical manipulation to inject the biologic in the correct site and by the correct route.

[30] As a scientific matter, FDA recognizes that the end users of biological products may have different training and expertise, and we provide some technical considerations in this section and in Appendix A for sponsors to consider, as appropriate.

comparison to those of the reference product. External critical design attributes are those features that directly affect the performance of critical tasks[31] that end users perform to appropriately use or administer the product. To identify these attributes, a sponsor should examine the overall external operating principles of the container closure system or delivery device constituent part by evaluating all the tasks that an end user needs to perform to prepare and administer the product. The external critical design attributes of the product would be those features that end users rely on to perform the tasks identified as critical to the appropriate use of the product. Because these attributes may impact appropriate use of the product, FDA recommends that sponsors consider the external critical design attributes of the reference product as part of their development program for a proposed interchangeable product.

The technical description of the threshold analysis appears in the next section, which may be of general use for sponsors in the development of proposed interchangeable products. In those circumstances where a threshold analysis indicates that further data may need to be gathered from comparative use human factors studies, Appendix A provides a technical description of comparative use human factors studies intended to support a demonstration of interchangeability.

1. Threshold Analyses

Three types of threshold analyses can be used in the development program for the purposes of identifying and evaluating differences in design and should be conducted after the presentation of the proposed interchangeable product, including product design and user interface,[32] have been finalized by the sponsor and are believed to be representative of the commercial product.

FDA recommends that sponsors carefully evaluate the risks associated with differences in the container closure system(s) and/or the delivery device constituent part(s) for proposed interchangeable products that may affect the patient or caregiver as the end user,[33] especially because interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider or additional training before use. The patient or caregiver end-user groups may not receive additional training in such circumstances and may lack the expertise that a health care provider user group is expected to possess. Patient and caregiver end-user groups may be less accustomed to navigating differences in container closure

[31] For additional information on critical tasks, see Section III.B.1. Critical Tasks in the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will reflect FDA's current thinking on this topic.

[32] The user interface includes all components of the delivery device constituent part with which the user interacts, such as controls and displays (i.e., those parts of the delivery device constituent part that users see, touch, and hear). The user interface also includes the delivery device constituent part labeling, which includes package labels, any instructions for use in user manuals, package inserts, instructions on the delivery device constituent part itself, and any accompanying informational materials. For additional insight, see the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices*.

[33] For additional information about end-user group considerations, see Section III.B.2. Intended Users and Use Environment in the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*. When final, this guidance will reflect FDA's current thinking on this topic.

systems and/or delivery device constituent parts for biological products than health care providers. As a result, there is concern that patients or caregivers who encounter different external critical design attributes between the container closure system and/or delivery device constituent part of a reference product and a proposed interchangeable product may be at increased risk for a use-related error that may impact their ability to appropriately use these products.

a. Types of threshold analyses

The following three types of analyses are recommended as part of the threshold analyses of proposed product presentation for all proposed interchangeable products:

i. Labeling comparison

FDA recommends a side-by-side, line-by-line comparison (between the reference product and the proposed interchangeable product) of the full prescribing information, instructions for use, and descriptions of the container closure systems and/or delivery device constituent parts.

ii. Comparative task analysis

FDA recommends that sponsors conduct a comparative task analysis between the reference product and the proposed interchangeable product.[34]

iii. Physical comparison of the interchangeable product and the reference product, along with their respective container closure system and/or delivery device constituent part

FDA recommends that sponsors of proposed interchangeable products acquire the reference product to examine (e.g., visual and tactile examination) the physical features of the reference product and compare them to those of the proposed interchangeable product.

b. Outcomes of threshold analyses

After completing the threshold analyses, the following outcomes are possible:

i. No design differences

When no differences are identified in the design of the presentation of the proposed interchangeable product and the reference product after the threshold analyses, it is likely that additional data to support the appropriate use of the proposed interchangeable product by the end

[34] To conduct a comparative task analysis, sponsors should systematically dissect the use process for each product (i.e., both the proposed interchangeable product and the reference product) and analyze and compare the sequential and simultaneous manual and intellectual activities for end users interacting with both products. FDA recommends that sponsors analyze the differences, with the goal of characterizing the potential for use error. Also see the American National Standards Institute/Association for the Advancement of Medical Instrumentation HE75, 2009(R)2013 Human Factor Engineering—Design of Medical Devices. The standard can be accessed at http://www.aami.org/productspublications/ProductDetail.aspx?ItemNumber=916.

users, including data from comparative use human factors studies, will not be necessary to support licensure as an interchangeable product. The sponsor should provide any analyses comparing the presentations for FDA's review and concurrence.

ii. Differences in design

If differences are identified between the design of the presentations of the proposed interchangeable product and the reference product, the sponsor should focus on whether the difference(s) involves an external critical design attribute that can negatively impact appropriate use by the patient and caregiver end-user groups and should seek to establish and categorize the differences as follows:

- Minor design differences: FDA views a design difference in product presentation as minor if the differences in the user interface of the proposed interchangeable product, in comparison to the user interface of the reference product, do not affect an external critical design attribute. Minor differences in design are likely to be viewed by FDA as acceptable provided that the data and information submitted by the sponsor demonstrate that the differences are in fact minor. For example, such data and information may be collected from thorough threshold analyses (described in sectionVIII.B.1.a of this guidance) that demonstrate that the differences in design do not involve an external critical design attribute that could negatively impact appropriate use. Similarly, for those products that would be expected to be administered only by a health care provider, the risks associated with substitution may be adequately addressed through threshold analyses rather than a comparative use human factors study. As mentioned previously, patient and caregiver end-user groups may be less accustomed to navigating differences in container closure systems and/or delivery device constituent parts for biological products than health care providers. The sponsor should provide this data and information for FDA's review and concurrence.

- Other design differences: FDA may not view a design difference as minor if any aspect of the threshold analyses suggests that differences in the design of the presentation of the proposed interchangeable product as compared to the reference product *may* impact an external critical design attribute that involves patient use or caregiver administration of the product. In such cases, the sponsor may consider modifying the design of the proposed presentation to minimize differences from the reference product, which could reduce the data that might be needed to support a demonstration of interchangeability.[35] Alternatively, if such differences are present

[35] FDA recognizes that, in certain circumstances, a sponsor may elect to retain a difference in design of an interchangeable product compared to the reference product to reduce difficulty with use or to minimize risk associated with the design of the reference product's presentation. FDA generally encourages the optimization of the design of the delivery device constituent part to enhance the safety of the product. However, there may be circumstances where an interchangeable product may be substituted for the reference product without additional end-user training. Thus, it is important that sponsors identify differences between their proposed presentation and the reference product's presentation, as described in this guidance, including identifying any differences intended to optimize the design of the delivery device constituent part to enhance the safety of the product. The sponsor should also characterize any identified differences in design that may impact the end user's ability (particularly patients and

in the final design of the presentation of the proposed interchangeable product, FDA recommends that sponsors provide appropriate data from additional studies, such as from a comparative use human factors study, to address whether such differences might negatively affect the appropriate use of the biological product in circumstances where the interchangeable product is substituted for the reference product. The data from additional studies should seek to characterize whether the difference(s) could negatively affect the appropriate use of the products by patients and caregivers (see section VIII.B.2 of this guidance for types of studies). Based on the results of additional studies, FDA may or may not determine that the design difference between the presentation of the proposed interchangeable product and the reference product is acceptable for a proposed interchangeable product.

2. Studies to Evaluate Differences That May Not Be Minor as Observed in Threshold Analyses

If the threshold analyses determine that a design difference may not be minor, as described in section VIII.B.1.b.ii of this guidance, sufficient evidence should be provided to permit FDA to evaluate the design difference for purposes of interchangeability. Alternatively, as mentioned previously, the sponsor may consider modifying the design of the proposed presentation to minimize differences from the reference product, which could reduce the data that might be needed to support a demonstration of interchangeability. However, if differences that may not be minor are present in the final design of the presentation of the proposed interchangeable product, FDA recommends that sponsors provide appropriate data from additional studies to support these differences. Such data may be gathered in a focused comparative use human factors study that evaluates the critical tasks related to the external critical design attributes that are found to be different or to focus on the patient and caregiver end-user group(s) that are most likely to be negatively impacted by the differences in the design of the presentation of the proposed interchangeable product and the reference product.

a. Comparative use human factors studies

Comparative use human factors studies may be needed to provide the evidence necessary to assess whether differences that may not be minor in the design of the presentation of the proposed interchangeable product prevent licensure of the proposed product as interchangeable with the reference product. The objective of the comparative use human factors studies described in this guidance is to assess any differences in the use error rate between the reference product and the proposed interchangeable product. This objective differs from the objective of human factors validation studies, which are conducted to evaluate how a product's user interface supports safe and effective use; such studies are not designed to assess differences in use error rates between two products. Therefore, the human factors validation studies described in the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* generally do not apply when evaluating interchangeability.

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caregivers) to appropriately use an interchangeable product when substituted for the reference product. (See sectionVIII.B.2 of this guidance.)

See Appendix A of this guidance for considerations for comparative use human factors studies (if needed) to evaluate differences that may not be minor, as observed in threshold analyses.

b. Additional studies

The need for additional data or information to support a presentation beyond what is described in this guidance may depend on a risk-based analysis and will be determined on a case-by-case basis. Additional studies such as comparative in vivo or in vitro performance testing may be warranted to support a demonstration of interchangeability under section 351(k) of the PHS Act.[36] FDA recommends that sponsors define specifications for each testing parameter before studies are initiated. Sponsors are encouraged to discuss appropriate testing with FDA as early during product development as feasible.

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.[37] 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 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.[38]

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.

[36] Comparative in vivo or in vitro performance testing may include the critical elements in establishing dose accuracy; for example, extended needle length, needle integrity, activation force, dispensing time, and dispensing volume. Additional types of performance specification testing, such as activation force, breakloose force, extrusion force, needle gauge, and needle protrusion, may need to be considered as well.

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

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

APPENDIX A: COMPARATIVE USE HUMAN FACTORS STUDIES

Considerations for Comparative Use Human Factors Studies, if needed, to evaluate differences that may not be minor as observed in threshold analyses:

1. Study Design Considerations

To support a demonstration of interchangeability under section 351(k) of the PHS Act, a comparative use human factors study should be designed to provide data supporting that the use error rate for the proposed interchangeable product is not worse than the use error rate for the reference product when used by patients and caregivers (as applicable) in representative use scenarios and use environments. The comparative use human factors studies described in this guidance would generally be simulated-use studies[39] where the participants, who are representative of the patients and caregivers, are asked to simulate the use of the product presentations (container closure systems and/or delivery device constituent parts) without actually administering the product.

For many aspects of demonstrating interchangeability under section 351(k) of the PHS Act, data is best collected using an equivalence study design. For example, it would be unlikely for FDA to determine that a proposed product is interchangeable with a reference product if data showed it to have lower or higher exposure than the reference product. In such cases, there could be a negative impact to the patient associated with a substantial deviation from equivalence. However, for the purpose of the comparative use human factors studies described in this appendix, the risks associated with container closure systems and delivery device constituent parts are derived from errors that occur in using the container closure system and/or delivery device constituent part. FDA would generally accept a proposed interchangeable product that had the same rates of error as the reference product, as demonstrated by an adequately designed comparative use human factors study or studies. However, we also recognize that lower error rates for a proposed interchangeable product compared to error rates for the reference product would likely not be considered to negatively impact the interchangeability assessment. Therefore, lower bounds on error rates are generally not necessary in comparative use human factors studies described in this appendix. For this reason, instead of using equivalence designs, noninferiority (NI) study designs are generally appropriate in such situations. NI tests comparing use of the presentation of a proposed interchangeable product to that of the reference product are similar to usual statistical tests for a difference, but translated to account for allowable differences in design between the presentation of the proposed interchangeable product and the reference product.

In comparing pharmaceutical products, NI tests are often conducted to indirectly demonstrate that a proposed product is more efficacious than a placebo. A standard way of approaching this goal is to fix an NI margin (referred to as *d* in this appendix) at some fraction of the difference

[39] For more information on simulation techniques, see Section D.1. Human Factors Simulated Use Validation Studies in the draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.* When final, this guidance will reflect FDA's current thinking on this topic.

between the placebo effect and the effect of the proposed product. Showing the effect of the proposed product to be significantly better than the margin demonstrates NI. The draft guidance for industry *Non-Inferiority Clinical Trials* discusses meta-analyses and margin selection in detail.[40] A comparative human factors study with an NI design for the purpose of demonstrating interchangeability under section 351(k) of the PHS Act will typically be less complicated than those described in the guidance on NI clinical trials because the endpoints of these NI studies will not be dependent on therapy and the placebo effect will not be a confounding factor.

The choice of comparative use human factors study endpoint(s) will depend on the nature of the presentation being evaluated and the associated differences between presentation of the proposed interchangeable product and the reference product identified in the threshold analyses. Although there may be many possible endpoints, a study evaluating performance of a critical task can often be reduced to a binary endpoint that considers whether or not the end user makes an error in performing the task. One possible endpoint for such a study may be the rates of errors observed when using the presentations of the proposed interchangeable product and the reference product. In this guidance, we show ER_{IP} and ER_{RP} as error rates observed when using the presentation associated with the proposed interchangeable product and that of the reference product, respectively.

Using the result of the threshold analyses described earlier as a guide, a risk assessment should be done to identify the external critical design attributes, end-user group(s), use scenarios, and use environments on which to focus the comparative use human factors study intended to support a demonstration of interchangeability. FDA recommends that patient and caregiver end users (as applicable) of the reference product be considered for inclusion in the comparative use human factors study. The risk assessment should explore risks for the various subgroups of the current patient and caregiver end-user groups and may identify an appropriate subpopulation on which to focus the comparative use human factors study. For example, in some cases, the risk assessment may determine that only a certain patient subpopulation (or subpopulations) is likely to experience difficulty administering the product, and thus the comparative use human factors study may be most appropriately focused on the identified patient subpopulation(s).

The goal of a comparative use human factors study intended to support a demonstration of interchangeability with an NI design is to demonstrate that ER_{IP} is no greater than $ER_{RP} + d$, where d is some acceptable deviance above ER_{RP}. In determining the margin d, the variability in ER_{RP} should be considered as well as the risk any difference in outcomes will pose to patients. The results of the risk assessment should be considered when determining the NI margin (*d)* between ER_{RP} and ER_{IP}.

An example of a simple and direct approach to an NI test comparing ER_{IP} and ER_{RP} can be summarized as follows:

- Determine the allowable margin (d) by which ER_{IP} could exceed ER_{RP}.

[40] For additional insight, see the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will reflect FDA's current thinking on this topic.

- Calculate the study sample size, considering assumed error rates and *d*.
- Observe error rates for the critical task(s) during the experiment.
- Perform the statistical hypothesis test:
    - H_0: $ER_{IP} - ER_{RP} > d$
    - H_A: $ER_{IP} - ER_{RP} \leq d$

Rejecting the null hypothesis (H_0) in favor of the alternative hypothesis (H_A) supports the claim of NI as defined by *d*.

Typically, the acceptable Type I error probability (α) will be set at 5%.

The NI test may be performed by comparing the upper bound of the appropriate confidence interval level for the difference in event rates to *d*. If the upper bound is less than *d*, NI is demonstrated.

Paired designs and parallel designs are appropriate approaches to the NI studies discussed in this appendix. A paired design in which each end user uses both presentations and acts as his or her own control will generally be applicable and more efficient with respect to resources than a parallel design. Parallel group designs in which end users are randomized to groups using one or the other presentation are also viable in situations where paired designs are not possible. Sponsors are advised to propose and discuss study designs with FDA before initiating studies.

2. Sample Size Considerations

Sample sizes for a comparative use human factors study should be adequate to support a demonstration of interchangeability. Sample sizes needed to adequately compare the presentations of the reference product and the proposed interchangeable product may be larger than those described generally in the human factors study literature. In general, small sample sizes are likely to be inadequate in this context because the goals of the comparative use human factors studies to support a demonstration of interchangeability may be different than the goals of typical human factors/usability studies discussed in the literature and certain FDA guidances. The literature on human factors studies holds a variety of opinions with respect to sample sizes. Some references dedicated to qualitative, non-comparative human factors studies suggest small samples sizes (5 to 25 participants), while other studies suggest that greater numbers of test subjects should be included.[41,42,43]

[41] Faulkner, L, 2003, Beyond the five-user assumption: Benefits of increased sample sizes in usability testing, Behavior Research Methods, Instruments, and Computers, 35(3), 379–383.

[42] Nielsen, J, 2000, Why You Only Need to Test With 5 Users, Jakob Nielsen's Alertbox, Retrieved October 13, 2015, from http://www.useit.com/alertbox/20000319.html.

[43] Spool, J, Schroeder, W, 2001, Testing web sites: Five users is nowhere near enough, in CHI 2001 Extended Abstracts (p. 285-286), New York: ACM Press.

The comparative use human factors studies described in this appendix are intended to ensure that design differences other than minor design differences found in the threshold analyses (described in section VIII.B.1 of the guidance) do not preclude a demonstration of interchangeability under section 351(k) of the PHS Act. Thus, as a scientific matter, a larger sample size may be necessary. Consider, for example, a failure in a critical task that can result in under-dosing that has a negative impact on a patient. If a study of 50 users showed no such failures, the upper bound of the 90% confidence interval for the error rate would be 0.058. This means that an error rate of approximately 6% at a reasonable confidence level could not be ruled out. If 50 subjects were asked to operate two delivery device constituent parts, one being the reference product and another being the proposed interchangeable product, and no subject failed using either delivery device constituent part, the 90% confidence interval for the difference in error rates would be (-0.051, 0.051). Although the observed difference in error rates is zero, such a demonstration does not rule out a 5% difference in error rates at the 90% confidence level. Putting these numbers into the context of the under-dosing example, the question is whether it is acceptable to expect up to 58 out of 1,000 users to be under-dosed. The risk associated with the specific error in question will determine the acceptability of error rates. In some cases, a 6% error rate or a 5% difference in error rates would be untenable, even though there could be other contexts in which such rates or differences would be acceptable. This example illustrates the importance of the risk analysis portion of the comparative use human factors study design, as well as the importance of properly sizing the study.

If extremely small error rates are expected, an adaptive design may be used to minimize sample size, while allowing for an adequate sample size if error rates are higher than initially assumed. Group sequential designs that are designed to stop early or a study design that adapts sample size may be considered. Consult the appropriate FDA guidance documents for detailed advice on designing studies using adaptive designs.[44]

[44] For detailed advice on designing studies using adaptive designs, see the draft guidances for industry *Adaptive Designs for Medical Device Clinical Studies* and *Adaptive Design Clinical Trials for Drugs and Biologics.* When final, these guidances will reflect FDA's current thinking on this topic.