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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-D-0154: Considerations in Demonstrating Interchangeability With a Reference Product: Draft Guidance for Industry; Notice of Availability, 82 Fed. Reg. 5579 (January 18, 2017)

Dear Sir or Madam:

Janssen Pharmaceutical Companies of Johnson & Johnson (Johnson & Johnson or the Company) is pleased to provide comments on the Draft Guidance for Industry released by the Food and Drug Administration (FDA or the agency), entitled "Considerations in Demonstrating Interchangeability With a Reference Product" (Draft Guidance),[1] which outlines the agency's proposed policy for how a biosimilar product may be demonstrated to be interchangeable with a reference product.

As a global leader in biotechnology, Johnson & Johnson has a valuable perspective at a time when the U.S. market is expanding to include FDA-approved biosimilars for the first time. We have many years of experience with the development, manufacture, and postmarketing monitoring of biologics. Our biologics portfolio spans immunology, cardiovascular disease, and oncology and includes ORTHOCLONE OKT3® (muromonab-CD3), the first monoclonal antibody ever approved; PROCRIT® (epoetin alfa); REMICADE® (infliximab); REOPRO® (abciximab); SIMPONI® (golimumab); SIMPONI® ARIA™ (golimumab); STELARA® (ustekinumab); SYLVANT® (siltuximab); and DARZALEX® (daratumumab).

Johnson & Johnson appreciates that the agency has issued the Draft Guidance and, as discussed below, supports many aspects of it, such as the agency's strong expectation that U.S. reference product be used in switching studies. However, we believe that the Draft Guidance can be significantly

[1] 82 Fed. Reg. 5579 (January 18, 2017).

improved by expecting that switching studies include immunogenicity as a primary endpoint and by addressing some additional topics, including label statements about interchangeability, nonproprietary naming of interchangeable products, and, perhaps most significantly, the challenging issue of the durability of interchangeability determinations given post determination changes to the reference product (e.g., new indications or presentations) and, for both products, manufacturing changes and drift.

I. The "Any Given Patient" Standard

The Draft Guidance does not attach any significance to the first standard for a biosimilar to be an interchangeable product, namely, that it "can be expected to produce the same clinical result as the reference product in any given patient." We believe, first, that this standard compels that a proposed interchangeable product be assessed in each condition of use of the reference product, and, second, that the agency should address when additional data beyond that necessary to demonstrate biosimilarity would be necessary to address this standard.

A. All Conditions of Use

The Draft Guidance allows that "a sponsor may seek licensure for a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed," while stating that the agency "recommend[s] that a sponsor seek licensure for all of the reference product's licensed conditions of use when possible" (lines 116-119).

A biosimilar should not receive an interchangeability determination unless the agency determines it is interchangeable for each condition of use (which includes for each presentation) for which the reference product is licensed, even where the agency may not lawfully license the biosimilar for one or more conditions of use (for example, for a reference product indication protected by orphan exclusivity). This approach is critical for patient safety because a biosimilar determined by FDA to be interchangeable likely will have pharmacy-level substitution for each of its reference product's conditions of use, and so no reference product use should lack data or FDA review to support interchangeability. Moreover, we believe that the first statutory standard for interchangeability—"can be expected to produce the same clinical result as the reference product in any given patient"—compels this conclusion.

Consider the following example: Although the Draft Guidance provides details on how to compare one potentially interchangeable delivery device to a reference delivery device and notes briefly in Section VIII that multiple delivery device presentations may be licensed and available for a reference product, it should also clarify that, if a biosimilar in a prefilled syringe presentation were found to meet the standard for interchangeability while that biosimilar with an auto-injector presentation were found not to meet the standard, the biosimilar could not be determined to be interchangeable.

Should it happen that an interchangeable biologic has not (yet) demonstrated interchangeability for a reference product condition of use licensed

after the interchangeability determination, the biologic should be clearly labeled regarding the limits of interchangeability (see section IV), and pharmacists should be educated. Similarly, should some of the reference product indications be covered by regulatory exclusivity preventing licensure of the biosimilar for those indications, while, as noted above, the biosimilar should demonstrate interchangeability for such uses, the product limitation should be prominently labeled lest substitution undermine exclusivity.

To clarify these points in the Draft Guidance, we suggest the following changes to lines 116-119: ~~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~~ To meet the requirement that an interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient," a sponsor must seek licensure for all of the reference product's legally available licensed conditions of use and must demonstrate interchangeability for all conditions of use ~~when possible~~."

B. Additional Data

We note that FDA does not propose that the "can be expected to produce the same clinical result as the reference product in any given patient" standard for determining interchangeability creates any evidentiary burden beyond that for biosimilarity. For example, the criteria outlined for extrapolation (lines 519-558) for interchangeability are essentially the same as the criteria for extrapolation for biosimilars in the agency's 2015 guidance, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Although the biosimilarity standard for ensuring activity in subgroups should be high, interchangeability could raise additional concerns. For example, given the many contributory causes of immunogenicity (e.g., micro-aggregation, denaturation, adjuvants), a biosimilar and reference product could have very similar incidence of immunogenicity with similar clinical manifestations, but the reference product might be more immunogenic in one MHC type and the biosimilar in another. Such a situation would clearly fail to meet the "any given patient" standard so it is important that it be studied and excluded. Appropriately addressing this issue would require approaches that assess similarity of individual and subgroup variability with respect to immunogenicity and PK.

II. Immunogenicity Assessment in Switching Studies

The Draft Guidance says primary endpoints should assess the impact of switching on PK and, if available, PD, because these would be sensitive to differences in immunogenicity or exposure (lines 358-360). It suggests that direct measures of immunogenicity are secondary (lines 377-378, 444-445), while also noting the importance of immune response and adverse events to the assessment of interchangeability (lines 341—348). But direct measures of immunogenicity are more sensitive than PK/PD measures, and there is a reasonable expectation that substantial differences in immunogenicity would ultimately lead to clinical manifestations, even if the PK/PD measures in the study are not sufficiently sensitive to detect an impact. For example, a doubling

of the incidence of immunogenicity from 10% to 20%, where immunogenicity is associated with a clinically significant halving of the AUC, would only lower mean AUC by 5% (10% of 50%); so, the doubling of clinically significant immunogenicity may go undetected (or not be statistically significant) if immunogenicity is not a primary endpoint. Therefore, and because, as the Draft Guidance notes (lines 341-348), immunogenicity is a key concern regarding switching, immunogenicity should be among the primary endpoints, and any suggestion of higher immunogenicity with switching than with continuing the reference product should place a burden on the sponsor to demonstrate that the difference would have no impact on "clinical result."

Because the assessment of immunogenicity in switching studies should be another primary objective in addition to PK parameters, the study design for switching studies—including use of an appropriate, sensitive population (healthy volunteers versus patients; no concomitant immune-modulators) and sample size should be carefully considered for a robust assessment of immunogenicity. In addition, more specific guidance on how to perform immunogenicity comparisons would be helpful, as incidence rates alone are not adequate to characterize anti-drug immune responses nor to elucidate their impact on clinical outcomes. For example, the studies should compare titers levels in each arm and the correlations of titers to PK, efficacy, and safety at all switching time points, to allow comparisons of clinical impact at higher titers versus lower titers. Furthermore, it is important to determine whether antibodies cross-react with both products. Additionally, in some cases, comparing the characterization of antibodies in switched or unswitched patients (e.g., isotype, epitope) and/or the characteristics of the patients with antibodies (e.g., MHC type) may elucidate the implications of switching.

III. Use of U.S.-Licensed Reference Product in Clinical Switching Studies

Johnson & Johnson strongly supports the agency's strong recommendation that switching studies to demonstrate interchangeability should use only U.S.-licensed reference product.

A biologic approved in several countries typically exists in several versions (sometime called "flavors") specific for different countries as regulatory approvals may vary regarding matters such as specifications, shelf-life, and status of proposed changes in materials, process, or manufacturing sites. Generally, these differences are minor; but occasionally they may be substantial (e.g., when E.U. regulators requested and approved a reformulation of Eprex® to remove HSA and add a detergent, other regulators did not, and important differences in immunogenicity resulted). Whether differences are minor or larger, switching studies between "flavors" of a product available in various countries are neither required nor done and the standards of interchangeability are not addressed (nor need they be as patients are not switched back and forth between "flavors").

Were FDA to take the position that interchangeability to a U.S. reference product could be established through comparisons with a non-U.S. reference product, the resulting determination of interchangeability would rely upon

several assumptions, including that the non-U.S. reference product and the U.S. reference product are interchangeable. As noted above, there are typically no data (e.g., switching studies) to support such an assumption, and there is no basis to make it. Were the FDA to make such an assumption (i.e., that the non-U.S. and U.S. reference products are interchangeable), there would be no logical basis for the FDA not to allow introduction of the non-U.S. reference product into the U.S. as an interchangeable biosimilar to the U.S. product. Further, having assumed interchangeability of the U.S. and non-U.S. reference products, and given the "any given patient" and "switching" standards for interchangeability, it would be difficult for the FDA to take the position that the specifications, materials and process used for the non-U.S. reference product (as required by the non-U.S. health authority) remained unacceptable for the U.S. reference product.

Moreover, different immune response is a principle concern for interchangeability, and even minor differences between products may induce immune responses in different patients with switching. Use of a non-U.S.-licensed reference product would, therefore, serve to demonstrate interchangeability with the non-U.S.-licensed reference product, but not with the U.S.-licensed reference product. We cannot see how an adequate scientific justification for use of a non-U.S.-licensed reference product could be made. Indeed, as explained above, it would suggest there is no scientific basis for the agency's rejection of non-U.S. reference products, and their specifications, materials, and processes.

IV. Label Statements Related to Interchangeable Products

In commenting on the agency's draft guidance, Labeling of Biosimilar Products, Johnson & Johnson argued that both the highlights section and any patient labeling should include a statement about whether or not the biosimilar has been determined to be interchangeable with its reference product (https://www.regulations.gov/document?D=FDA-2016-D-0643-0049). As will be explained below in section VI.A, in any instance in which the reference product is licensed for a new condition of use (e.g., a new indication or a new presentation), this statement should be augmented by an additional description to assure that switching at the pharmacy level can occur as safely as possible for patients: a description of the conditions of use for which the product is not determined to be interchangeable.

In addition, the highlights section and patient labeling of each interchangeable product should include the statement: "This product is not interchangeable with any other [core name] product." Of course, sponsors of interchangeable products must justify, including by conducting switching studies as appropriate, that their product is interchangeable with the reference product, but there is no expectation that they will assess interchangeability with any other biosimilar to the reference product. Because interchangeability cannot be assumed without such an assessment, this statement will help assure patient safety and that neither health care providers nor patients mistakenly assume (as

they likely may, given their experience with generic drugs) that interchangeable biosimilars to a reference product are interchangeable with one another.

Relatedly, when finalized, the guidance should state explicitly that demonstration of interchangeability to the reference product is not a demonstration of interchangeability to other products that are interchangeable with the reference product, and that no such interchangeability should be assumed.

V. Postmarketing Safety Monitoring and Non-Proprietary Naming

Section IX of the Draft Guidance, Postmarketing Safety Monitoring Considerations, asserts the importance of robust postmarketing safety monitoring for assuring the safety of biological products, including biosimilar and interchangeable products. The agency also noted the importance of postmarketing pharmacovigilance as a rationale for distinguishable names for biological products in its final Guidance, Nonproprietary Naming of Biological Products.

In our comments on the draft of that guidance (https://www.regulations.gov/document?D=FDA-2013-D-1543-0153), we explained the need for distinct suffixes for interchangeable products to assure that there is correct attribution of safety reports to the reference product or the interchangeable product, as applicable. We reference those arguments here and request that the final naming guidance be modified to indicate that an interchangeable product will need a suffix that is distinct from the suffix of its reference product (and so distinct from the suffix of every other interchangeable product to the reference product). That expectation should also be referenced in the final interchangeability guidance.

In addition to facilitation of pharmacovigilance, the need for a unique suffix for an interchangeable biologic is also driven by other factors: new conditions of use may arise for which it is not interchangeable (and may or may not be biosimilar), and manufacturing drift may render the product still biosimilar but not interchangeable at some future date (see section VI. immediately below).

VI. Durability of Interchangeability Determinations

A key issue that the Draft Guidance does not address and that any final guidance must address is the durability of interchangeability determinations. After FDA has determined that a biosimilar is interchangeable with its reference product, changes may occur that would raise questions and concerns about interchangeability. FDA should specify its approach to this issue in the final guidance, whether it be that interchangeability determinations may expire or need reevaluation over time, or even if it is that such concerns need not be addressed.

This issue manifests itself in a few different ways, none of which is addressed by the Draft Guidance (though the agency asks questions about aspects of two of them in its Federal Register notice). Examples include when the reference product is licensed for a new indication after the biosimilar is determined to be interchangeable; when the reference product implements an innovative presentation after the biosimilar is determined to be interchangeable; as well as manufacturing changes and product drift with either product after an interchangeability determination.

A. New reference product conditions of use after an interchangeability determination

As noted, in the Federal Register notice announcing the availability of the Draft Guidance, the agency asks: "How, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed?" (82 Fed. Reg. 5580). As observed above in section I.A., interchangeable products will be used by some as if they are generic drugs, and FDA must determine interchangeability with respect to each condition of use for which the reference product is licensed to assure safe use of the product.

When the reference product is licensed for a new condition of use, any interchangeable product for that reference product should be considered misbranded under section 502(a) of the Federal Food, Drug, and Cosmetic Act and, accordingly, the sponsor of the interchangeable product should be expected to submit promptly an immediately effective Changes Being Effected (CBE-0) labeling supplement to include in its label a statement, in the highlights section of the professional label and in patient labeling, that the product has not been determined to be interchangeable with the reference product in that condition of use. In addition, the agency should consider requiring notice to healthcare providers and pharmacists that the product is not interchangeable in the new condition of use. (The label statement and notice should be reserved for these situations when a condition of use is added after initial interchangeability determination, and should not be used if a product is not shown to be interchangeable in one or more conditions of use at the initial evaluation—as we argue above in section I.A., in such a case, a determination that the biosimilar is interchangeable should not be possible.)

The sponsor may also, concurrently or subsequently, submit a preapproval supplement to the agency providing justification as necessary for why the product is interchangeable in the new condition of use. Indeed, whereas it is recommended that the sponsor address interchangeability of all conditions of use, there should be an expectation of such a supplement within a reasonable time limit. It may be that extrapolation of interchangeability to the new condition of use may be justified, but it should not be assumed, to assure patient safety. The statement that the biosimilar is not interchangeable in the new condition of use would of course be removed from the label if the biosimilar is determined to be interchangeable for the new condition of use. If the product is determined not to be interchangeable for the new condition of use and a label

statement indicating that limitation on interchangeability might be insufficient to protect patient safety, FDA should consider withdrawing the interchangeability determination for the product or other approaches to preventing inappropriate switching.

B. Manufacturing changes and product drift

The Federal Register notice also poses the following question: "With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating postapproval manufacturing changes of interchangeable products?" (82 Fed. Reg. 5580). As the notice suggests, neither a reference product nor a non-interchangeable biosimilar should be expected to perform anything beyond a standard comparability assessment when they implement manufacturing changes. In each case, the question is whether the product with the manufacturing change remains safe and effective, and a standard comparability assessment is sufficient to assure continuing safety and effectiveness. Moreover, there is typically a short period (3-6 months) during which the product before a manufacturing change and the product after a manufacturing change may both be on the market, with a comparatively low risk that there will be "switching" between the two versions of the product.

With an interchangeable product, however, the issue is not merely whether it remains safe and effective after the manufacturing change but whether it remains interchangeable with the reference product. Physicians, pharmacists, and patients will expect that patients can safely, and without risk of diminished efficacy, continue to switch between the reference product and the interchangeable biosimilar, yet a standard comparability assessment is not sufficient to assure this expectation. Consequently, a sponsor of an interchangeable product should be expected to justify that the product is highly likely to remain interchangeable when it makes a manufacturing change.

Interchangeability may be threatened not only by manufacturing changes implemented for the biosimilar, but also by changes implemented for the reference product, and by drift of either product over time. Hence, the sponsor of the biosimilar product should be expected periodically (such as no later than every 2 or 3 years after the previous such assessment) to reassess interchangeability.

To facilitate this exercise and minimize the burden of interchangeability determinations, the agency should, when it determines that a biosimilar is interchangeable, specify in its approval letter a panel of physico-chemical studies comparing the interchangeable product to the reference product that the biosimilar sponsor can perform to assess if interchangeability has been maintained. If these studies were to identify concerns (e.g., by failing performance criteria for the studies), the biosimilar would lose the interchangeability designation unless its sponsor justified retaining it with additional studies, which may on a case-by-case, fact-specific basis include a switching study or studies as described in the Draft Guidance.

C. Reference delivery device life cycle changes

It would not be unexpected that the manufacturer of a reference biologic would make significant design improvements to its delivery device(s) over the product's post-patent lifecycle to improve usability. It may also completely change the platform delivery technology (e.g., seek a sBLA for a new generation auto-injector). The final guidance should address these specific scenarios, including the need to include label statements and provide notice to pharmacies that the biosimilar is not considered interchangeable for the new presentation of the reference product, unless and until it is subsequently shown to be interchangeable in a sBLA.

VII. Presentations and Interchangeability

FDA fully appreciates that reference biologics are often associated with specific presentations including lyo- or liquid-in-vials for intravenous administration and a wide variety of delivery systems (e.g., auto-injectors, pen injectors, prefilled syringes) intended for subcutaneous administration by HCPs or patients at home. The mix of presentations and their use environments raise significant questions about interchangeability.

For biosimilar presentations intended for subcutaneous administration by patients or caregivers, interchangeability of a prefilled auto-injector, for example, presents significant challenges. At present, to avoid auto-injector usage errors, sponsors develop and validate training programs and materials for use by providers in training patients. Substitution of a reference auto-injector at the pharmacy level may result in a patient receiving a different auto-injector than prescribed by their physician and on which they were trained by their provider. Patients would then be expected to use a different device on which they had received no training, relying instead only on the interchangeable product's USPI's instructions for use, if accessed. This scenario, which is certain to occur, would have a high potential for use errors, because no training was provided for the interchangeable product's device, and use was not observed.

Reference product manufacturers have invested significant resources in providing HCP training to best support patient training on the use of these devices. To augment face-to-face instructions provided by the HCP, reference device manufacturers often develop "starter kits" for new patients that include quick reminder cards, instructional placemats, training videos, and auto-injector trainer simulator devices. These materials are submitted and reviewed by OPDP and are an important component in the support that manufacturers provide to facilitate successful use of these devices. The final guidance should discuss how a sponsor seeking an interchangeability determination for its biosimilar should address in their BLA or BLA supplement both this aspect of educational materials support and the potential impact on patients who may receive an unfamiliar device at the pharmacy level without this support.

Further, most biologic manufacturers have recognized the need for patient training and have explicitly stated in their approved prescribing information that physicians or HCPs need to evaluate each patient's ability to use these specific

devices and to receive training.[2] The need for training is also stated in the approved Medication Guides[3] for most reference biologics as well as in the approved patient Instructions for Use.[4] Presumably the label of a proposed interchangeable biosimilar will include the same statements, yet the Draft Guidance does not explain how a biological product, with this labeling, "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." (Emphasis added.) Although the issue of substitution without HCP intervention or training is discussed in Section VII B (lines 678-690), the Draft Guidance does not explain that the practice of this substitution without health care provider intervention would be contrary to the approved labeling or how this labeling restriction impacts interchangeability.

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The attached table includes additional comments and suggested edits to the Draft Guidance.

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Johnson & Johnson appreciates FDA's consideration of the challenging issue of interchangeability of biosimilar products with their reference products and would welcome the opportunity to discuss these comments further.

Sincerely,

JAY SIEGEL

Digitally signed by JAY SIEGEL
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Reason: I attest to the accuracy and integrity of this document.
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Jay P. Siegel, MD
Chief Biotechnology Officer and Head,
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Johnson & Johnson

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[2] For example, the Simponi® label states: "After proper training in subcutaneous injection technique, a patient may self-inject with SIMPONI if a physician determines that it is appropriate. Instruct patients to follow the directions provided below . . ." and, "The first self-injection should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer SIMPONI, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of SIMPONI."

[3] For example, the Simponi Medication Guide states: "If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI. Do not try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse."

[4] For example, the Simponi IFU includes the statement: "Do not try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse."

Comments on FDA Draft Guidance: Considerations in Demonstrating Interchangeability to a Reference Product

COMMENTS FROM: Janssen Pharmaceutical Companies of Johnson & Johnson

SPECIFIC COMMENTS ON TEXT

Line Numbers	Comment and Rationale	Proposed change (if applicable)
184-189 205-210	This Draft Guidance, like the final 2015 guidance, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, describes the use of fingerprint-like characterization to reduce residual uncertainty, but it fails to note that, for the purpose of interchangeability, the critical issue of immunogenicity (same in any patient, no impact of switching) is not well-addressed, even when fingerprint similarity is shown. Many factors not necessary identified in physicochemical analysis (egg, containers, leachates from stoppers or needles, trace contaminants, trance denaturing or microaggregation on storage) can cause immunogenicity differences that would preclude interchangeability unless ruled out directly.	When mentioning fingerprint-like similarity, the final guidance should point out that key focusses with interchangeability, unlike biosimilarity, is to avoid excess immunogenicity with switching, and to ensure that immunogenicity will not be different in any given patient. The guidance should therefore point out that, because of these concerns, even with fingerprint-like similarity, it would generally be expected that additionally studies assessing immunogenicity, including switching studies, would be needed to support a claim of interchangeability.
193-200	Because the Draft Guidance acknowledges there may be some structural features that specifically impact interchangeability, we recommend that the final guidance place greater emphasis on the importance of the comprehensive assessment of relationships between attributes for each of the licensed	We suggest the following changes to lines 195-200: "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 for each of the licensed

	indications of the reference product.	indications of the reference product, 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."
233-236	The Draft Guidance states that clinical experience with the reference product and comprehensive product risk assessments (e.g., regarding immunogenicity) may affect the data and information needed to support a demonstration of interchangeability, and provides an example. That example, however, involves "products with a documented history of inducing detrimental immune responses" and suggests only that it "may require" more data to demonstrate interchangeability. Given that increased immunogenicity risk is the significant concern with switching, the final guidance should state that additional data will generally be required in such situations. In addition, although the clinical impact of immunogenicity of different products may vary, it is rare that immunogenicity would not impact clinical outcomes (adverse events and/or diminished efficacy) at all.	We suggest the following changes to lines 233-236: "For example, products with a documented history of inducing detrimental immune responses ~~may~~ will generally require more data to support a demonstration of interchangeability than products with an extensive documented history that immunogenicity ~~does not~~ has little or no impact on clinical outcomes."
246-258	The only apparent difference indicated for evidence needed to demonstrate interchangeability for Product A, a low structural complexity biosimilar with fingerprint-like analytical similarity and a low incidence of serious adverse events related to immunogenicity, versus Product B, a high structural complexity biosimilar without fingerprint-like analytical similarity and known serious adverse events related to immunogenicity, is the need in the latter case for postmarketing data for the product licensed only as a biosimilar. The guidance should be revised to indicate that the switching studies will take into account the	We suggest the following changes to lines 251-258: "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 its reference product has known serious adverse events related to immunogenicity. Here, rigorously collected postmarketing data (e.g., from a post-market study or registry) for the product as a licensed biosimilar, in addition to an appropriately designed switching study that would take account of the known serious

	different immunogenicity of the products, so that the premarket testing of the more complex product would likely also be more extensive. In addition, given the limitation of post marketing data (lines 273-278), including for detecting differences in immunogenicity reactions, it would generally be more appropriate for postmarketing data with the biosimilar to be collected more rigorously, such as in a postmarketing study or registry. Finally, the example seems unartfully worded, to suggest that Product B has known serious adverse events when its reference product may not. Presumably, it is meant that both have known serious adverse events related to immunogenicity, as Product B would presumably not be biosimilar to its reference product if that were not the case.	adverse events related to immunogenicity and associated with each product, 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."
280- 286	Even given their limitations in reducing residual uncertainty, postmarketing data may identify a potential safety issue that must be addressed by other data to make an interchangeability determination, or one that precludes such a determination. For this reason, FDA should always consider postmarketing safety data, when available, in making a determination about interchangeability. Moreover, these data should be considered to determine if they reduce uncertainty remaining after clinical switching data are considered, but not as a means to reduce the clinical switching data requirement itself.	We suggest the following changes to lines 280-286: "Notwithstanding these limitations, however, ~~we recognize that in certain circumstances,~~ postmarketing data from a licensed biosimilar product, when available, should always be considered as part of the totality of evidence to support an interchangeability assessment ~~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~~ add to the totality of evidence to support ~~a demonstration~~ an evaluation of interchangeability."
291-294	The Draft Guidance refers to "situations" in which a	

	"postmarketing study" may be needed to address residual uncertainty. We suggest that, because of the limitations of postmarketing data collected from real-world use of a biosimilar product in detecting immunogenicity differences that may affect safety or result in diminished efficacy, there will be more frequent need for postmarketing studies than suggested by the text. We recommend that the final guidance provide examples of such "situations" as well as descriptions of related postmarketing studies.	
377-378	Because switching may reveal patient-level differences in efficacy that preclude interchangeability but not biosimilarity, efficacy data should be added to the listing of types of data generally to be collected in switching studies. This change would be consistent with lines 444-445. In addition to the possibility that some individuals respond better to one product and some to the other, in the case of drugs titrated to an endpoint (e.g., insulins, erythropoietins), potency differences in some patients may be obscured by titration (and be irrelevant for biosimilarity) but may be clinically important when patients switch (and are under- or over-treated), precluding interchangeability and switching without physician notification.	We suggest the following changes to lines 377-378: "In addition to PK and PD parameters, a switching study or studies would also be expected to assess immunogenicity, ~~and~~ safety, and, where appropriate, efficacy." It would also be useful to add some information about why and where efficacy could be a concern and, for such cases, where PD measures may suffice.
391-393	Because immunogenicity is of major concern with switching, the sample size for a switching study should not only be determined by the requirement for demonstrating PK equivalence, but should also be chosen so as to result in sufficient number of ADA-positive subjects to allow for a reasonable comparison of immunogenicity differences that may result from product switches.	We suggest the following changes to lines 391-393: "The sample size of the switching study should generally be based on the ability to compare immunogenicity differences and PK considerations (inter-subject variability in AUCtau or Cmax should be primary considerations) and should be appropriately justified.
512-517	The Draft Guidance states that "Choosing a more immunogenic	We suggest the following changes to lines 515-517: "~~Choosing~~

	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." While true, this statement underappreciates the factors other than route that may drive differences in immunogenicity. While subcutaneous route carries specific immunogenicity risk and thus, should be studied, it is also possible that the IV product will have differences in formulation/excipients that impact the immunogenicity of switching. In such cases, choosing to study only one route of administration (e.g., the more immunogenic SC route) would be inappropriate.	~~a more~~ FDA recommends that a sponsor choose the most immunogenic route of administration with the largest intersubject variability of exposures (e.g., subcutaneous rather than intravenous where applicable) for use in switching studies ~~may help sponsors anticipate~~ and to best reflect the clinical implications of real-world use in clinical practice. In addition, when formulations are different between routes of administration, studying only one route of administration would need scientific justification."
576-577	The statement that "switching studies are designed to assess whether one product will affect the immune system's response to the other product . . ." is an incomplete statement of underlying concerns. Even if neither product affects the response to the other, and even when both have similar immunogenicity rates and consequences, switching could increase the risk of immunogenicity and adverse clinical sequelae. Suppose, for example, each product has a 10% incidence of clinically significant immunogenicity, but they are immunogenic in different patients (e.g., if the cause of immunogenicity varies–e.g., denaturation, microaggregates, adjuvants in the formulation–then immunogenicity may manifest in different HLA types). Then in a typical population, 10% would have a response if treated with the reference, 10% if treated with the biosimilar, and 20% if switched. Hence, switching increases risk even though neither product affects the response to the other.	Language that better captures the broader immunogenicity concerns of switching would be: "Switching studies should be designed to assess whether switching between products might lead to immune responses in some patients who would not have had the same response if not switched."

597-598	The BPCI Act does not permit the substitution of interchangeable products as implied by this text. The pharmacy practice laws of the various States govern substitution.	We suggest the following changes to lines 597-598: "~~Under t~~ The BPCI Act defines~~,~~ an interchangeable product as a product that may be substituted for the reference product without the prescribing health care provider's intervention. Such substitution of biological products is governed by State pharmacy practice laws."
662-669	The guidance regarding including within the CMC section "design and development information" – including performance testing and stability studies— seems like good general advice for biologics presentations and delivery systems. However, it is not clear with regard to how it applies to an interchangeable biologic. Is the applicant also being asked to present such data for the reference product or conduct comparisons of such data between products? Additional details and examples would be appreciated including what CMC information would be needed in a supplement to an approved biosimilar presentation to demonstrate interchangeability. Do the side-by-side feature and performance comparisons (Section VIII and footnote 36) needed to demonstrate interchangeability differ from those that are needed to demonstrate biosimilarity?	We suggest adding a discussion of what comparisons and conclusions are needed to demonstrate interchangeability versus biosimilarity for a delivery device.
678-684	The Draft Guidance emphasizes tasks necessary to administer the product and adds that these "tasks can vary considerably depending on the type of presentation and its design characteristics" and that "[d]ifferences in the design of the container closure system or delivery device constituent part . . . without the intervention of the prescribing health care provider or additional training before use." While the design differences are important, the final guidance should also emphasize the importance of labeling, including validated Instructions for Use	Additional discussion is needed on what differences in instructions, graphics, or layouts for IFUs for a biosimilar product would raise new concerns about interchangeability with a reference delivery device and how such concerns might be addressed.

	(IFU), which are key to safe and effective use of these devices.	
845-852 and Appendix A	The Draft Guidance explains that the principles of human factors validation studies (HFVS) described in FDA CDRH guidance "generally do not apply when evaluating interchangeability," and goes on to describe, in Appendix A, a non-inferiority (NI) inter-device comparative study design. However, HFVSs are behavioral studies where understanding a participant's reason for a use error is as important as the fact that it occurred. Per the cited FDA guidance, percentages of successful use and use error rates themselves are less important than in detecting, in a limited number of subjects, low frequency use errors of high criticality - even if there is a single occurrence in the study. It is not clear then whether a NI HFVS approach, based on principles used in placebo controlled clinical trials, and in this case comparing use error rates, would fully address the question of interchangeability risks especially where different (multiple) types of use errors may have different criticality. In contrast, risk based assessments of use errors detected in HFVSs, the post study implementation of mitigations, and the sponsor's justification for the acceptability of specific residual risks have been the hallmarks of product approvability, and this standard should continue to be applied to the question of interchangeability.	We recommend that, in addition to describing the NI study approach, FDA also discuss when and how alternative approaches such as a comparability HF study might be advised.
868-888	Regarding the postmarketing safety monitoring considerations section, newly introduced auto-injectors often have high field complaint rates associated with use errors (e.g., failure to actuate, premature withdrawal of the injector from the skin). The root causes of these complaints and potential adverse events) can be associated with design, labeling or training factors that are not necessarily predictable or revealed in design	To ensure interchangeability, periodic postmarketing assessments should be provided to FDA as a postmarketing commitment to assess complaints and review potential corrective actions under consideration by biosimilar licensees to address use errors that may impact interchangeability.

	verification testing or in human factors studies with a limited number of participants that are reviewed for the initial approval.	
940-949	The Draft Guidance explains the need for a study evaluating performance of a critical task (or several critical tasks) and comparing the rates of errors for them. It would be helpful to clarify what is meant by critical tasks, i.e., those that are dependent on the design (e.g., auto-injector actuation) versus those that may be critical but are associated with any administration (e.g., checking expiration dates).	We recommend adding a sentence such as: Critical tasks studied and assessed should be those dependent on the design of the device.
951-961	The Draft Guidance explains the need to assess patient and caregiver end users as defined study groups. However, it does not discuss the need to include user groups that have received training on the reference delivery device but receive the biosimilar device as a substitute with no training, or where no training has been provided on either device. Users very familiar with the reference device may transfer inappropriate actions to use of the biosimilar device. This study aspect would be key to the study of interchangeability.	We recommend adding and describing a defined user group whereby patients trained on the reference device(s) would be assessed for task deviations and use errors when the delivery device of the biosimilar is presented for simulated use with training and with no training.