PO Box 3691
Arlington, VA 22203
(703) 971-1700

May 22, 2017

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

Re: Docket Number FDA-2017-D-0154
Considerations in Demonstrating Interchangeability With a Reference Product;
Guidance for Industry, Draft Guidance

Dear Sir or Madam,

The Alliance for Safe Biologic Medicines (ASBM) respectfully submits the following comments in response to the recent draft guidance on *Considerations in Demonstrating Interchangeability With a Reference Product*, published to the Federal Register on January 18, 2017.

ASBM is an organization focused on promoting the increased availability and use of biologic medicines, while ensuring their safety and efficacy. It is our mission to serve as an authoritative resource of information for the general public as well as the healthcare and health policy communities on issues surrounding biologic medications. We provide information on the development, regulation, safety, and quality of biologics, advocate for policies that prioritize medical decisions between patients and physicians, and seek solutions that ensure affordability and accessibility of biologic medications, while never compromising patient safety.

We are both closely affiliated with ASBM: I (Harry Gewanter) am a pediatric rheumatologist practicing in Richmond, VA and ASBM's Chairman; Philip Schneider is Clinical Professor and Associate Dean for Academic and Professional Affairs for the University of Arizona, College of Pharmacy and Chairman of ASBM's Advisory Board.

ASBM appreciates the science-based approach that FDA has demonstrated to date in considering biosimilar policy. ASBM applauds FDA for the successful implementation of policies that allow safe and effective biosimilars to come to market, thereby increasing treatment options and broadening access to life changing medications for patients with serious grievous illnesses.

Biologic interchangeability is complex, but it is critically important to maintain patient safety, and ASBM commends FDA for the comprehensive, thoughtful methodology they have applied in developing this draft interchangeability guidance. ASBM agrees with all elements outlined in the draft guidance and suggests adding the following points for consideration.

I. General Principles

We agree with FDA's recommendation that a sponsor seek licensure for a proposed interchangeable product for all of the reference products licensed conditions of use[1]. We recommend that the FDA strengthen this position to ***require*** **sponsors to only seek an interchangeability designation if they can provide evidence to support interchangeability for all of the licensed conditions of use.** If they cannot, we recommend that the product is instead approved as a biosimilar and NOT an interchangeable biosimilar.

As practicing clinicians, we are familiar with the day-to-day aspects of treating patients with biologics. The clinical reality is that if a biologic is approved as interchangeable for one indication, it will be assumed that it is interchangeable for all conditions of use, regardless of whether the agency has considered sufficient supporting evidence. This assumption is hard-wired into clinician behavior as a result of decades of experience with generic medicines, where therapeutic equivalence, once demonstrated, applies across all indications. This approach is not appropriate for biologic medicines and has the potential to lead to inappropriate substitution that can put patient safety at risk. ASBM asks FDA to ensure that approval decisions related to interchangeability are limited to those supported by scientific evidence, which can include sound scientific justification for appropriate extrapolation.

Similarly, ASBM requests clarification on the Agency's plans should subsequent data emerge suggesting a detrimental impact associated with switching in one or more conditions of use. While it is evident that this would need to be handled on a case-by-case basis, we believe it important to create a process by which an interchangeability designation can be retracted. This retraction should be accompanied by a widespread communication strategy to ensure clinicians using these medicines are aware of the change in status so that they can adapt their clinical practice accordingly.

II. Factors Impacting the Type and Amount of Data and Information Needed to Support a Demonstration of Interchangeability

ASBM supports FDA's 'totality of evidence' approach applied to the approval of biosimilar and interchangeable biosimilar medicines. ASBM believes that, while critically important to the totality of evidence paradigm, the **use of analytical data should always be associated with clinical studies** that provide sufficient evidence that switching between biologic products does not result in an increased risk to patients in terms of safety or diminished efficacy.

The role of real-world data in evaluating long-term safety and efficacy of medicines is unparalleled. Specific to biosimilars, real-world evidence has the potential to provide a wealth of important information on the effects of switching between biologics of the same product class. ASBM does however support FDA's statement 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*

[1] Considerations in Demonstrating Interchangeability With a Reference Product; Guidance for Industry, Draft Guidance. Page 4, lines 116-119

[2] Considerations in Demonstrating Interchangeability With a Reference Product; Guidance for Industry, Draft

be sufficient to support a demonstration of interchangeability." [2] While postmarketing data are important for evaluating real-world safety and efficacy, it is unlikely they will provide either the critically important pharmacokinetic or pharmacodynamic data required to fully evaluate the impact of switching. For example, comparing neutralizing antibody and drug trough levels among patients who have either been switched or not switched, is a critical element in evaluating whether the switch has resulted in an increased risk to the patient in terms of safety or diminished efficacy. **ASBM believes that when evidence is needed to support an interchangeability designation, real-world evidence should not be used as a substitute for a randomized clinical study**.

ASBM supports FDA's recommendation that any population selected for study is **sufficiently sensitive to detect differences between the switched and non-switched arms.**[3] An important indicator of decreased efficacy or increased risk associated with a switch is the elevation of neutralizing antibodies and their effect on drug trough levels. Detection of this type of response is dependent on a patient's ability to mount an immune response. Since many patients treated with these biologic medicines are immunocompromised as a result of their disease and/or treatment, those patients are not the ideal population to evaluate in a switching study.

III. Use of a US-licensed Reference Product in a Switching Study or Studies

ASBM supports FDA's positon that while a non-US comparator is appropriate for a demonstration of biosimilarity, this would NOT be appropriate in a study designed to evaluate the impact of switching[4]. As FDA points out, the purpose of a switching study is to evaluate whether one product will affect the immune system's response to the other product once the switch occurs and what impact this has on the patient. In clinical practice, patients treated with a licensed biologic product approved in the US will be switched to a US-licensed interchangeable biosimilar. **The only appropriate way to investigate the effects of a switch and to confidently designate a biosimilar as interchangeable is to mirror clinical practice and use US-licensed products.**

ASBM agrees that because of the possibility of subtle differences between the US-licensed product and the non-US licensed product, evaluating the effects of the switch using a non-US licensed product is inappropriate.

IV. Considerations for Developing Presentations for Proposed Interchangeable Products

ASBM supports FDA's recommendations regarding product presentations for interchangeable products and would like to commend FDA for its in-depth guidance on this topic. To minimize confusion among clinicians, ASBM believes it important that **an interchangeability**

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[2] Considerations in Demonstrating Interchangeability With a Reference Product; Guidance for Industry, Draft Guidance. Page 8, lines 270-273

[3] Considerations in Demonstrating Interchangeability With a Reference Product; Guidance for Industry, Draft Guidance Page 13, lines 473-475

[4] Considerations in Demonstrating Interchangeability With a Reference Product; Guidance for Industry, Draft Guidance, Page 15, lines 578-579

designation is sought for all presentations (e.g. pre-filled syringe, vial, device) for which the biosimilar product is marketed. In day-to-day clinical practice, it would be almost impossible to prescribe and dispense the appropriate biologic medicine if, for example, the prefilled syringe was licensed as an interchangeable biosimilar and the vial was licensed as a biosimilar (but not interchangeable). While this scenario seems unlikely, we believe it important that the final interchangeability guidance explicitly state that the sponsor seek an interchangeability designation for all the presentations which will be available to clinicians. If this is not possible, ASBM believes there should be a clear notification placed either on the vial or pre-filled syringe directly, or on the packaging, or both, indicating whether or not the presentation is a biosimilar, or an interchangeable biosimilar.

V. Addressing the questions outlined in the Federal Register

1. *With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products?*

It is ASBM's opinion, that, once approved, manufacturing changes for either the reference product or the interchangeable product should be addressed independently and managed by the Agency's existing process for manufacturing changes.

2. *FDA expects that sponsors seeking an interchangeability determination 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. 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?*

As outlined in the sections above, it is ASBM's view that a biosimilar can only be deemed interchangeable if there is sufficient evidence to support safe switching in each of the conditions of use licensed for the reference product. This applies both at the time of initial licensure, and for additional conditions of use licensed the reference product after the interchangeable biosimilar has been licensed. This opinion is based on how interchangeable products will likely be used in real-world clinical practice. That is, if a product is deemed interchangeable, clinicians will assume it is interchangeable for all the indications for which the reference product is licensed.

In the draft interchangeability guidance, FDA suggests that data used to support a determination of interchangeability can be extrapolated to support additional conditions of use, provided there is scientific justification. One possible way to address additional indications sought for the reference product after initial approval of the interchangeable biosimilar is to apply this approach; specifically, to require the biosimilar sponsor to provide scientific justification to support extrapolation to the new indication licensed for the reference product.

If the scientific justification is deemed inadequate by the Agency however, ASBM recommends that the interchangeability designation is reconsidered to protect patient safety. It is also important that both the reference product and the interchangeable biosimilar receive approval for the new indication in the same timeframe. This could likely be achieved by setting a time limit for the sponsor of the interchangeable biosimilar to submit evidence to support the new indication and/or ensuring that the new indication sought by the sponsor of the reference product is not approved until the sponsor of the interchangeable biosimilar submits evidence.

VI. Interchangeability: naming and labeling

Finally, ASBM would like to take this opportunity to reiterate previous comments submitted to FDA on biosimilar naming and labeling, as they relate to interchangeability.

As FDA finalizes the draft guidance on *Labeling for Biosimilar Products Guidance for Industry,* published to the Federal Register on April 4, 2016, ASBM urges the Agency to include a **statement of interchangeability in the product label** of interchangeable biosimilars.

FDA has long recognized the immunogenic potential of biologic medicines and the possibility of unwanted immune reactions that may occur as a result of switching between two similar, but not identical, biologics. For healthcare practitioners to be able to quickly and easily grasp how these medicines should be used clinically, a clear statement in the label indicating either biosimilarity or interchangeability is critical. This will ensure the patient and all healthcare practitioners, from the prescribing physician to the dispensing pharmacist, will understand whether or not a given medication can be safely switched. Clear definitions of 'biosimilar medicine' and 'interchangeable biosimilar medicine' will help ensure that patients receive these medicines appropriately. Importantly, 79% to 88% of physicians and pharmacists consider a statement of interchangeability in a biosimilar product label **important or very important**.[5]

ASBM also believes it is important to make it clear in the final interchangeability guidance and the product label that the interchangeability designation only **applies to an interchangeable biosimilar and the reference product**. The switching studies supporting an interchangeability designation will likely evaluate the effects of switching between the interchangeable biosimilar and the reference product. They will not evaluate the effects of switching between the reference product and more than one interchangeable biosimilar, or between interchangeable biosimilars, both of which are potential clinical scenarios. As more interchangeable biosimilars come to market, it is important that clinicians have a clear understanding of what the interchangeability designation means to facilitate evidence-based clinical decision-making.

Further, we believe it is important that the **data used to demonstrate interchangeability are included** in the product label. It is ASBM's view that including these data will create increased trust among physicians prescribing these medications and **foster clinician and patient confidence** in their use, thereby increasing uptake.

ASBM supports FDA's guidance on nonproprietary naming for biosimilars as it pertains to the use of distinguishable suffixes added to the end of a shared root name, as outlined in the recent

[5] ASBM survey data; 2015. Available at https://safebiologics.org/surveys/

guidance.[6] **We ask that FDA ensures that this guidance is also applied to interchangeable biosimilars**. Further, we would like to take this opportunity to ask that the FDA re-consider the use of random suffixes. ASBM believes that **memorable suffixes related to the name of the biologic manufacturer will minimize confusion** while enabling a connection to the biologic manufacturer, facilitating traceability and accountability. This view is supported by members of the healthcare community who use these products. In 2015, ASBM conducted a survey of **400 US prescribers of biologics** and found that 66% supported FDA issuing distinct names for all biologics, including biosimilars. **Sixty percent of respondents preferred suffixes based on the manufacturer's name**. Similarly, among **401 US pharmacists** surveyed in October 2015, 68% supported FDA issuing distinct names, with **77% supporting manufacturer-based suffixes**. It is ASBM's view that the introduction of interchangeable biosimilars, and the resulting clinical environment where patients can be switched back and forth between biologic medicines of the same class, creates a need for robust pharmacovigilance. This could be more efficiently facilitated by the use of meaningful suffixes related to the manufacturer of the biologic medicine.

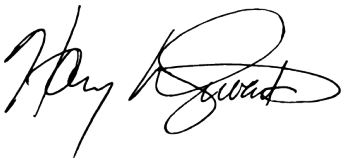
In Summary

ASBM thanks the FDA for applying such a rigorous and scientifically robust approach to the complicated topic of interchangeability. The availability of biosimilars in the US represents an opportunity for many more patients to gain access to these lifesaving medicines, but clinician confidence is critical to their success. Knowing the FDA is applying robust, evidence-based principles to the licensure of interchangeable biosimilars will bolster clinician and patient comfort with this important class of medications.

As this draft interchangeability guidance is finalized, ASBM encourages FDA to consider the points outlined in this document, as we believe they are in the best interests of patient safety.

ASBM thanks you for the opportunity to weigh in on these important issues.

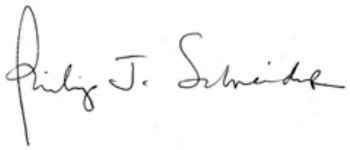
Sincerely,



Harry L. Gewanter, M.D., FAAP, FACR

Chairman
The Alliance for Safe Biologic Medicine

[6] Non-proprietary naming for biological products, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf



Philip Schneider, MS, FASHP
Advisory Board Chairman
The Alliance for Safe Biologic Medicines

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