Biosimilars
FORUM

800 17th Street, NW Suite 1100, Washington, DC 20006

May 1, 2017

Dr. Stephen Ostroff
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Comments on January 2017 Draft Guidance: "Considerations in Demonstrating Interchangeability with a Reference Product" (Docket No. FDA-2017-D-0154)

Dear Acting Commissioner Ostroff:

The Biosimilars Forum appreciates the opportunity to comment on the Food and Drug Administration ("FDA") *Draft Guidance: Considerations in Demonstrating Interchangeability with a Reference Product*, as published in Docket No. FDA-2017-D-0154.

The Biosimilars Forum is a non-profit organization whose mission is to advance biosimilars in the United States with the intent of expanding access and availability of biological medicines and improving health care. The Forum works on a consensus basis to develop policy positions to ensure the United States has a competitive, safe and sustainable biosimilars market, providing more options to patients and physicians.

General Comments to the Draft Guidance

The Biosimilars Forum appreciates FDA's efforts to publish this Draft Guidance document clarifying its expectations with regard to the data required from a sponsor in order to demonstrate interchangeability. In addition to the specific comments to the Draft Guidance below, the Forum urges the FDA to consider, on a case-by-case basis, the practicality and feasibility of switching study expectations to support a determination of interchangeability, and to ensure there is flexibility in approach when appropriately justified.

The Forum believes it is critical for the Agency to clarify that a demonstration of interchangeability represents a distinct requirement for additional data compared to a demonstration of biosimilarity. It is important for stakeholders across the health care industry to understand that the FDA does not have more than one standard of product quality for the approval of biologics and that the safety and efficacy profiles of biosimilars and their corresponding interchangeable biologics are the same, so "patients and health care professionals are able to rely upon the safety and effectiveness of biosimilar products in the same manner as for the reference product."[1]

[1] SJ Lemery et al. *FDA's Approach to Regulating Biosimilars*. Clin Cancer Res (Jan 2017), doi: 10.1158/1078-0432.CCR-16-1354.

As discussed further below, the Forum notes that several terms appear in the Draft Guidance that have not been well-defined. Additionally, there are concepts which are not addressed that the Forum considers would be beneficial for the FDA to directly and proactively define. The Forum believes industry and the public would benefit from the adoption of a glossary to define particular terms related to interchangeability that would supplement the definitions provided in the recently finalized FDA *Guidance to Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (hereinafter, "Biosimilars Clinical Pharmacology Final Guidance").[2] For example, the difference between physician-initiated switching and independent pharmacy-level substitution has been the source of significant confusion that could hinder the uptake of biosimilars in the marketplace.

Specific Comments to the Draft Guidance

General Principles (Section III)

The Forum applauds FDA's application of the concept of extrapolation and extension of its "totality of the evidence" approach from biosimilar determinations to interchangeability determinations. We believe this approach is appropriate and provides needed efficiency and flexibility.

As noted in Lines 75-76, the statute requires that sufficient information be provided to show that the biological product *can be expected to produce the same clinical result as the reference product in any given patient*. The Forum does not interpret this language to mean that clinical data in each indication for which the reference product is licensed must be provided in order to secure an interchangeability determination. The Forum supports the Agency's approach, which requires sponsors seeking an interchangeability determination to scientifically justify extrapolation.

The Forum requests that the FDA clarify the language included at Lines 116-119 regarding licensure for fewer than all of the reference product indications. The Forum believes that regardless of whether licensure is sought for all indications, to meet the statutory definition of interchangeable, the sponsor must scientifically justify licensure for all indications – whether through testing or extrapolation. The Forum suggests changing the language to: "When seeking licensure for a proposed interchangeable product, we strongly recommend that a sponsor seek licensure for all of the reference product's licensed conditions of use which are not protected by patent or exclusivity."

Scope (Section IV)

The Forum is concerned that the Draft Guidance uses the terms "switching" and "substitution" without precisely defining them. The Forum would like to take the opportunity to highlight common confusion with regard to physician-initiated switching of a biosimilar versus substitution of an interchangeable product without physician intervention. As noted above, providing a glossary of terms within this guidance would be useful in clarifying some of this uncertainty. Specifically, while FDA's expectations for a switching study to meet the statutory standard for demonstration of interchangeability is appropriate, we encourage the FDA to stress the importance of continuing to educate the public on the important distinction between physician-initiated switching and pharmacy-

[2] *Available at:* https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf (accessed March 9, 2017).

level substitution. The creation of a separate glossary for patients may prove useful to FDA's educational efforts.

Factors Impacting the Type and Amount of Data and Information Needed to Support a Demonstration of Interchangeability (Section V)

The Forum appreciates FDA's guidance on factors affecting the data needed to support an interchangeability finding. However, the discussion surrounding structural analysis in Section V.A.1. includes the concept of fingerprint-like characterization, which has not been sufficiently defined in any biosimilar guidance documents. While the Forum appreciates the definition of fingerprint-like similarity provided in FDA's newly published Biosimilars Clinical Pharmacology Final Guidance, the Forum continues to believe that a more robust definition is needed. The lack of a clear definition of "fingerprint-like similarity," and an explanation of what the FDA expects the sponsor to provide in order to demonstrate it, results in a lack of clarity regarding the additional requirement for analytical data, if there is any, and whether FDA contemplates the same standard applicable to biosimilars, or a different standard. Accordingly, the Forum requests that FDA provide a more precise explanation of how the Agency defines fingerprint-like characterization, how it relates to interchangeability, and how a sponsor may achieve it.

Further, the inclusion of statements such as a "meaningful fingerprint-like characterization may reduce residual uncertainty…" at Lines 207-210 may lead to inaccurate perceptions of the quality, safety, and effectiveness of biosimilar and interchangeable products. The Forum requests that the FDA make clear that biosimilars and interchangeable products have an equivalent level of quality, safety and efficacy. Further, FDA should specify that there is not an additional analytical standard for demonstration of interchangeability.

Additionally, while the Forum appreciates the need for flexibility in determining on a case-by-case basis the studies and data needed, the Forum believes more clarification is needed with regard to what considerations drive the decision to require particular study criteria. For example, what are the considerations that determine the number of exposure periods for switching studies as discussed at Lines 325-327 and 416-481? The Forum also believes that a graphic depicting the study design and illustrating the number of switches would be helpful.

With regard to biosimilar postmarketing data (Section V.B.), the Forum believes the current language in this section inadvertently conflates two separate concepts, and we request that the FDA provide more precise language to avoid confusion. It is the Forum's understanding that postmarketing data from a biosimilar will not always be required to demonstrate interchangeability, as sponsors may choose to submit a product for a determination of biosimilarity and interchangeability at the same time. However, the Forum understands that there may be circumstances under which the FDA may decide, on a case-by-case basis, that a determination of biosimilarity and the collection of postmarketing data is necessary in order to make an interchangeability determination about a particular product. The FDA should make clear that postmarketing data will not always be required in order to obtain a determination of interchangeability.

Separately, the sponsor of a licensed biosimilar who later decides to apply for interchangeability will have collected postmarketing data that may be used as a part of the submission package for interchangeability. While postmarketing data alone would not be sufficient to make an

interchangeability determination, the type of available postmarketing data (whether required or not) may play a role in the totality of evidence to support a demonstration of interchangeability. It may have an impact on the trial design and data set that FDA will require from such a sponsor and may also contribute to the overall dataset needed to support a demonstration of interchangeability.

Accordingly, the Forum believes that the title of the section (Lines 264-265) is imprecise and suggests that the FDA change it to: "The Role of Postmarketing Data in Supporting Demonstration of Interchangeability."

Data and Information Needed to Support a Demonstration of Interchangeability (Section VI)

Overall, the Forum believes that the FDA should ensure there is flexibility with respect to the particular data required to demonstrate interchangeability on a case-by-case basis and when appropriately justified. For example:

- The Forum suggests the language at Lines 350-354 of Section VI.A. (Considerations for the Design and Analysis of a Switching Study or Studies Needed to Support a Demonstration of Interchangeability) more explicitly clarify that sponsors may propose scientifically justified alternatives to clinical pharmacokinetics (PK) and pharmacodynamics (PD) testing design and discuss such proposals with the FDA. There may be situations related to a particular product, study population and indication when PK/PD studies are relatively insensitive or may be clinically irrelevant for detection of potential immunogenicity. As a result, it is important that the FDA be receptive to alternative study designs and endpoints.

- We appreciate FDA's recognition at Lines 393-395 that repeated blood sampling can be burdensome in some patient populations and treatment regimes. Accordingly, when defining the blood sampling time points for "intensive PK sampling," there should be some flexibility to consider the practical, ethical, and logistical issues for frequent PK blood sampling in such a patient population.

The Forum also requests that the FDA reconsider the organization of Section VI.A.2. The Draft Guidance includes separate sections for dedicated study design and integrated study design. However, there is some overlap between the two study types (e.g., Lines 390-445) and the Forum suggests that the section be reorganized to more clearly reflect which items apply to both types of designs, versus those items that apply to one or the other.

Use of a U.S.-Licensed Reference Product in a Switching Study or Studies (Section VII)

The Draft Guidance suggests that it may be possible for a sponsor to provide scientific justification to support the use of data generated in a switching study using a non-U.S.-licensed comparator to support a demonstration of interchangeability (Lines 608-612). However, there is not specific guidance regarding what data and information the scientific justification should include. The Draft Guidance should be modified to more clearly outline what the Agency's expectations are for scientific justification of use of a non-U.S.-licensed comparator.

Considerations for Developing Presentations for Proposed Interchangeable Products (Section VIII)

The Forum is concerned that Section VIII, as written, could limit innovation, such as the use of novel delivery methods that may reduce user error or otherwise improve patient usage. The Forum therefore respectfully urges the FDA to focus the requested threshold analyses more on the potential for, or likelihood of, negative impact on patients, rather than on design differences between the reference product and the proposed interchangeable product presentations. To that end, the Forum recommends that the FDA move footnote 35 to the main body of the Draft Guidance in order to emphasize that sponsors should not be relegated to utilizing obsolete presentations solely in order to meet interchangeability criteria.

Responses to Specific Draft Guidance Questions

1. **Q: Since the mid-1990s, FDA has approved manufacturing changes for biological products based on data from comparability assessments comparing the pre-change and post-change product using comparative analytical, and, when necessary, animal and/or clinical (e.g., pharmacokinetic, immunogenicity) studies. A demonstration of comparability between pre- and postchange product supports a determination that the safety and efficacy profile remains the same for the product.**

   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? Your comments should include the scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

   A: Manufacturing changes after approval of a biologic should be regulated consistently across all classes of biologics: originator, biosimilar and interchangeable. The sponsor of the product should be required to demonstrate to the satisfaction of the Agency that, as per ICH Q5E and current FDA regulations, the change has *no adverse impact on safety or efficacy*. With regard to a designation of interchangeability, FDA should be clear that post approval changes generally would not be expected to require a reexamination of a designation of interchangeability.

   The Forum notes that industry is awaiting a Draft Guidance on post-approval manufacturing changes for biosimilar biological products, which is currently planned under BsUFA II and slated for publication in 2019. The Forum encourages the FDA to prioritize the publication of this guidance to the extent possible.

2. **Q: As explained in the guidance ‘‘Considerations in Demonstrating Interchangeability With a Reference Product,’’ 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? Your comments should include the scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

A: In the event the sponsor of a reference product obtains a new indication that is not covered by pediatric or orphan exclusivity, the Forum proposes that sponsors of interchangeable biologics should be permitted to submit a supplemental BLA request to the agency to obtain the new indication by providing the information necessary to apply the concept of extrapolation. The scientific justification for extrapolation should address factors outlined in the Draft Guidance at Lines 519-558. The Forum notes that there is already a process in place for 505(b)(2) products that can be used as a model.

Conclusion

The Forum appreciates the publication of this vital Draft Guidance, and appreciates the opportunity to provide comments. The Forum asks the FDA to carefully consider its comments and concerns as it takes action to issue a final guidance.

If you have any questions or need any additional information, please contact Michael Werner at 202.419.2515 or at michael.werner@hklaw.com.