AMA
AMERICAN MEDICAL ASSOCIATION

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The Honorable Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Draft Guidance for Industry, "Considerations in Demonstrating Interchangeability with a Reference Product: Update," Docket No. FDA-2017-D-0154

Dear Commissioner Califf:

On behalf of the physician and medical student members of the American Medical Association (AMA), I am writing in support of the FDA's draft Guidance for Industry, "Considerations for Demonstrating Interchangeability with a Reference Product: Update." Biologic drugs, and by extension their biosimilars, are a critically important class of medications for our patients, including those with autoimmune disorders or cancer. The proposed Guidance will increase the number of biosimilars available for pharmacy-level substitutions, which should lead to increased patient access and reduced cost. Having just passed the milestone of 50 biosimilar products approved for use in the United States, we now have additional data on biosimilars supporting the need and safety of the proposed change.

Biologic drug efficacy is very sensitive to the secondary, tertiary, and even quaternary structure, which describes how the molecule is folded and packed into shape. For example, many biosimilars are antibody-based drugs, which require very specific folding patterns to generate the receptor binding affinity needed to provide the drug's action in the body. The active portion of the biosimilar may be a tiny fraction of the overall molecule while they also may contain several large components that do not contribute meaningfully to the efficacy of the medication. As such, biosimilars may have different chemical structures than their reference product, but if the difference only exists in non-active portions of the structure and does not impact other elements such as folding or polarity, then in theory they will retain similar efficacy. Given the complexity of biologic drugs, biosimilar manufacturers are already required to prove that their product utilizes the same mechanism of action as the reference product, analytical studies proving similarity of the biologically active components, animal studies assessing toxicity, and clinical studies assessing efficacy, immunogenicity, pharmacokinetics, and pharmacodynamics.

Beyond the baseline evidence that manufacturers provide for biosimilar approval, to be deemed "interchangeable" and thus eligible for pharmacy-level substitutions, manufacturers have previously been required to perform a switching study—a two-arm clinical trial in which one-arm receives the reference product continuously and the other switches from the reference product to the biosimilar and back again. If there are no substantive differences in efficacy or immunogenicity upon switching back and forth between biosimilar and the reference product, the biosimilar may be deemed "interchangeable." It should be noted again that to receive the initial FDA approval as a biosimilar, the drug must already have proven

to have similar efficacy and immunogenicity to inefficacy and immunogenicity caused by the act of switching itself after a patient has already initiated treatment.

Previously, the AMA has been supportive of switching study requirements, finding them to be a prudent approach for a new class of medicines that may have immunogenicity concerns. However, as FDA scientists noted late last year in a meta-analysis of 5252 patients across 21 different biosimilars, "no differences in terms of major safety parameters such as deaths, [non-fatal serious adverse events], and discontinuations were observed when patients are switched (to or from a biosimilar and its reference biologic) or not switched."[1] Given the evolving state of the evidence and physician experience prescribing biosimilars, at the Annual Meeting of the AMA's House of Delegates in June 2024, the AMA rescinded its support for the interchangeability pathway and instead adopted a more nuanced approach that is aligned with proposed Guidance. Under our new policy, the AMA supports pharmacy substitution of biosimilars (in the absence of explicit physician authorization to the contrary) when the following three conditions are met:

> (a) the biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; (b) there are no data indicating clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product; and (c) the prescribing physician has been adequately notified by the pharmacist.

Through the proposed guidance, the FDA maintains the ability to take regulatory action in the event a specific biosimilar demonstrates safety or efficacy concerns upon switching, while simultaneously increasing access to these important medicines. Combined with other FDA activities in this space, such as the draft labeling guidance to remove the "interchangeability statement" from biosimilar labeling, we are confident that more patients will receive life-changing therapy moving forward.

For questions or to further discuss please contact Shannon Curtis, AMA Assistant Director of Federal Affairs at Shannon.Curtis@ama-assn.org.

Sincerely,

James L. Madara, MD

[1] Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. *PLOS ONE.* 2023;18(10):e0292231.