August 20, 2024

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Submitted electronically via https://www.regulations.gov/docket/FDA-2017-D-0154/

Re: Docket No. FDA-2017-D-0154- FDA Draft Guidance "Considerations in Demonstrating Interchangeability With a Reference Product: Update Guidance for Industry" (Oppose)

Dear Sir or Madam,

We write today as representatives of the Alliance for Safe Biologic Medicines, a coalition of physicians, patients, pharmacists, and manufacturers of both biologics and biosimilars, dedicated to advancing patient-centered health policy. We wish to share our concerns with the FDA's recent Draft Guidance[i] which proposes to eliminate the role of switching studies when making a determination of interchangeability for a biosimilar. We believe this to be an ill-advised and inappropriate move that could undermine the FDA's successful program of biosimilar approval and commercialization.

Importance of Switching Studies to Physicians and Patients

Switching studies are an important tool in the interchangeable biosimilar approval process as they provide robust evidence that switching between a reference product and a biosimilar does not compromise safety or efficacy, even over multiple switches.

Treatment plans are tailored to individual patients and generally do not fall into a one-size-fits-all approach. Treatment of chronic illnesses such as arthritis, Crohn's disease, psoriasis, and various forms of cancer has evolved over years of trial and error with different products before a patient becomes stable or in a state of disease remission. Newly diagnosed patients, those experiencing a flare of their disease and those with multiple diagnoses require intensive management and complex decision-making. This crucial process is the foundation of the patient–physician relationship. Physicians have historically expressed concerns about non-medical switches by third-parties such as insurers or pharmacy benefit managers (PBMs) as these are generally initiated for economic reasons other than achieving the best health outcome. This concern is particularly acute for stable patients experiencing an automatic substitution of a

[i] US Food and Drug Administration. Guidance for Industry. Considerations in demonstrating interchangeability with a reference product. May 2019 [homepage on the Internet]. [cited 2024 Jul 2]. Available from: https://www.fda.gov/media/124907/download

biosimilar for the originator biologic without physician involvement[ii],[iii], [iv],[v]. For this reason, legislatures in all 50 U.S. states passed laws permitting the automatic substitution of *interchangeable* biosimilars as these products had affirmatively demonstrated through robust data that a patient's treatment stability (neither safety nor efficacy) would be impacted even after multiple switches, relative to a patient who was not switched. In other words, **state medical societies were supportive of biosimilar substitution conditional *on its limitation to products approved under the FDA's current data requirements for interchangeable biosimilars, including switching studies.***

Current Data Standards Drive Physician Confidence in Interchangeable Biosimilars

In addition to the FDA Draft Guidance, several legislative and regulatory proposals have been introduced at the state[vi] and federal[vii] level that would reduce requirements for interchangeability, declare all biosimilars interchangeable (making all biosimilars pharmacy-substitutable in the manner of generics)[viii], and/or restrict the FDA's use of switching studies in determining interchangeability. ***Data has shown, however, that these policies are strongly opposed by physicians who prescribe biologics.***

A 2024 survey of 270 U.S. physicians[ix] shows the importance of maintaining the robust data requirements undergirding the interchangeable designation. Respondents were drawn from nine practice areas: Dermatology, Endocrinology, Gastrointestinal, Immunology, Nephrology, Neurology, Oncology, Ophthalmology, and Rheumatology. All prescribe biologics.

- 87% of respondents agreed that they are more comfortable switching a patient from an originator biologic to a biosimilar if that medicine has been specifically evaluated for the impact of switching on safety and efficacy.

- 88% of respondents believe each interchangeable biosimilar should be individually evaluated specifically for the impact of switching on safety and efficacy.

- Only 11% believe all biosimilars should be deemed interchangeable.

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ii Coleman C, Salam T, Duhig A, Patel AA, Cameron A, Voelker J, et al. Impact of non-medical switching of prescription medications on health outcomes: an e-survey of high-volume Medicare and Medicaid physician providers. J Mark Access Health Policy. 2020;8(1):1829883.

iii Teeple A, Ellis LA, Huff L, Reynolds C, Ginsburg S, et al. Physician attitudes about non-medical switching to biosimilars: results from an online physician survey in the United States. Curr Med Res Opin. 2019;35(4):611-7.

iv Sarnola K, Merikoski M, Jyrkkä J, Hämeen- Anttila K. Physicians' perceptions of the uptake of biosimilars: a systematic review. BMJ Open. 2020;10(5):e034183.

v Feagan BG, Marabani M, Wu JJ, Faccin F, Spronk C, Castañeda-Hernández G. The challenges of switching therapies in an evolving multiple biosimilars landscape: a narrative review of current evidence. Adv Ther. 2020;37(11):4491-518. doi: 10.1007/s12325-020-01472-1.

vi https://dfr.oregon.gov/pdab/Documents/reports/2023-PolicyRecommendations.pdf

vii https://www.govtrack.us/congress/bills/118/s2305/text

viii https://legiscan.com/LA/bill/HB403/2023

ix August 2024 survey of 270 U.S. prescribers of biologic medicines; conducted by Industry Standard Research on behalf of the Alliance for Safe Biologic Medicines, www.safebiologics.org.

- 85% of respondents agreed that only biosimilars that have been individually evaluated specifically for the impact of switching on safety and efficacy should be deemed interchangeable.

Most critical to the Draft Guidance, these specialists supported the use of switching studies in an FDA determination of interchangeability by a factor of roughly 22:1.

- **88% of respondents agreed that biosimilar switching studies increase their confidence in the safety of moving their patients from an originator medicine to the biosimilar that has been studied and determined to be interchangeable with the originator. Only 4% disagreed. 7% neither agreed nor disagreed.**

These new data are consistent with previous findings demonstrating the value of the FDA's current data standards for interchangeable biosimilars in providing assurances to physicians that third-party substitution will not impact safety or efficacy. According to a 2021 survey[x], 89% of US prescribers have high confidence in the safety and efficacy of biosimilars; however, a majority (58%) of these prescribers oppose switching of a patient's biological medicine for non-medical (e.g. cost, coverage) reasons or without the consent of the prescribing physician. Further, 69% of physicians consider it very important or critical that patients and physicians decide together which biological is the most suitable.

The interchangeability designation for biosimilars was intended by legislators and FDA to promote confidence in the automatic, i.e. pharmacy-level substitution of biosimilars by third parties, e.g. insurers, pharmacy benefit managers (PBM). This approach has proven successful: data show that switching studies significantly enhance physician confidence in prescribing biosimilars. **The 2021 survey revealed that 57% are more likely to prescribe an interchangeable biosimilar when switching studies demonstrate that efficacy and safety are maintained. Furthermore, 59% of physicians feel more comfortable with pharmacy-level substitution of a biosimilar when such evidence is available.**

The Use of Switching Studies in Interchangeable Biosimilar Process Has Not Negatively Impacted Approval, Adoption

Looking at Europe for a baseline, we can see that biosimilar uptake ranges between 20% and 80%, varying by country and product[xi]. In the US, filgrastim, trastuzumab, and bevacizumab biosimilars have an uptake rate of 80%; Rituximab biosimilars 60%, and infliximab, pegfilgrastim, and erythropoietin-stimulating agent biosimilars have 40% market share[xii]. Adalimumab biosimilars, after a slow uptake in their first year, recently achieved 36% market share[xiii]. Given the faster rate of biosimilar adoption relative

[x] McKibbin RD, Reilly MS. US prescribers' attitudes and perceptions about biosimilars. Generics and Biosimilars Initiative Journal (GaBI Journal). 2022;11(3):96-103. doi:10.5639/gabij.2022.1103.016

[xi] Schneider PJ, Reilly MS. Policy recommendations for a sustainable biosimilars market: lessons from Europe Generics and Biosimilars Initiative Journal (GaBI Journal). 2020;9(2):76-83. doi:10.5639/gabij.2020.0902.013

xii Amgen Biosimilars. 2022 Biosimilar trends report [homepage on the Internet]. [cited 2024 May 9]. Available from: https://www.amgenbiosimilars.com/commitment/2022-Biosimilar-Trends-Report

xiii Humira biosimilar scripts take off. Axios. 16 April 2024.

to Europe, if the robust data standards under the current US interchangeable standard have any net effect on biosimilar uptake rates, it would appear to be a positive rather than a negative one [xiv]

Elimination of Switching Studies is Unsupported by Recent Data

The June 2024 Draft Guidance for Industry "Considerations in Demonstrating Interchangeability With a Reference Product: Update" relies upon and cites the conclusions of a recent systematic review and meta-analysis conducted by FDA (Herndon, et al) [11], in which the risk of switching mostly clinically stable patients between reference biologicals and biosimilars was evaluated. The meta-analysis is specifically cited to support the Guidance's assertion that 'the risk in terms of safety or diminished efficacy is insignificant following single or multiple switches between a reference product and a biosimilar product' [12]. This conclusion, however, is overly broad unsupported by the data provided in the meta-analysis. A recent whitepaper[xv] by McKibbin and Reilly identifies several concerns with the meta-analysis, including:

- **Highly selective and limited analysis.** the meta-analysis consisted of a highly selective review of abbreviated data from 44 randomized controlled trials and their extension studies from 21 different biosimilars with a switch treatment period in the study design. From this FDA came to the intended conclusion that there was no difference in the safety profiles or immunogenicity rates between patients who were switched to a biosimilar and those who remained on a reference biologic. Based on this highly selective and admittedly limited analysis, the authors of the study concluded that these findings support a reduction in the regulatory burden of switching studies as the default approach for addressing the switching standard for the interchangeable designation. They further concluded that the findings call for a reassessment in the need for switches to be included in clinical studies for candidate biosimilars since an approved biosimilar will be analytically highly similar to its reference product [11].

- **Efficacy Impacts Not Evaluated**
  FDA regulatory approval for interchangeable biosimilar products is based on demonstrating that neither safety nor treatment efficacy are negatively affected. Notably, while this meta-analysis white paper FDA looked at three safety profiles, **it did not evaluate any efficacy impacts of switching.** Comparing randomized controlled trials (RCTs) and extension studies of biological products for safety/immunogenicity does not equate to the other multifactorial considerations for switching patients from a reference product to a biosimilar product such as treatment efficacy or other treatment considerations.

- **Inappropriate Pooling of Data**: The conclusions of the meta-analysis are over-reaching as they are based on the pooling of data from studies across therapeutic areas. These limitations do not support the broad generalized recommendations. The data were not grouped by individual therapies, indications, or by the number of switches between biosimilar and reference biological [11]. Also,

xiv Caffrey M. Report biosimilar uptake accelerates in US and so do the savings. Am J Manag Care. 13 July 2022.

[xv] https://gabi-journal.net/misinformation-about-interchangeable-biosimilars-undermines-us-health-policy-physician-confidence-and-patient-health.html

pooled data management across large populations fails to address individual patient variability, history, and needs. Drawing overly broad conclusions based on pooled data is especially concerning for vulnerable populations such as pediatric and marginalized patients. For example, multi-disease patients or those who are at an increased risk for hypersensitivity, anaphylaxis, neutralizing antibody, or other reactions may have been included in the study but were not evaluated separately.

- **Extrapolates Multi-Switch Safety from Largely Single-Switch Studies:** Moreover, the inclusion of 28 single-switch studies and 16 multi-switch studies in a combined analysis results in an inappropriate extrapolation of multi-switch safety based on the disproportionate use of single-switch studies.

- **Neglects Real World Considerations of Patient Variability:** A further limitation of the analysis is that real-world outcomes of non-medical switching, such as the nocebo and placebo effects, were not considered. This is an important consideration as studies suggest that the risk of a nocebo effect is higher following a mandated non-medical switch [13]. The authors of the meta-analysis recognized the potential for confounding of results due to the recognized nocebo effects observed in real-world studies of biosimilars and therefore included only randomized clinical trials and their extension studies. While clinical trials minimize confounding with strict eligibility criteria that results in a more homogenous population, real-world studies can lack robustness and consistency due to heterogeneity in patient demographics and physician prescribing patterns. Since randomized clinical trials are unlikely to capture the complexity of responses observed in the real-world experience, the recommendation to change evidence standards for biosimilars based on the findings of this meta-analysis are risky and short-sighted [14].

Weakening Data Requirements for Interchangeable Biosimilars Undermines Physician, Patient Confidence in Third-Party Substitution

Data supported by good clinical evidence (e.g. double-blind controlled studies able to be reviewed by stakeholders and including diverse populations) is particularly critical to public and stakeholder confidence in biological medicines due to their size and complexity as well as their capacity to cause unwanted immune response. Furthermore, unlike traditional chemical drugs that are structurally stable and uniform, biologicals are created as a product of biological activity in living cells, and while biological products are held to manufacturing and characterization specifications per product label, there is potential to drift in molecular characteristics over time [26]. As it stands, the abbreviated approval pathway for biosimilars already relies more on analytical data and post-marketing surveillance than it does on clinical data. Therefore, reducing biosimilar evidence requirements even further – whether for approval or interchangeability status – can undermine the confidence thus established in this class of medicines.

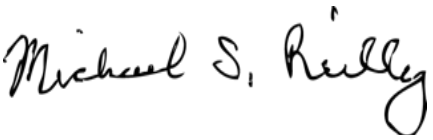
Confidence in biosimilars is crucial to their acceptance and widespread adoption. Physicians need assurance that treatment plans tailored to individual patient needs will not be disrupted by unforeseen issues arising from switching. Switching studies can provide this assurance by addressing variability among patients and confirming that therapeutic outcomes remain consistent, even with multiple switches.

The aphorism “absence of evidence is not evidence of absence” is acutely applicable to the importance of switching studies in the demonstration of interchangeability. Without conducting switching studies, it is

unknown whether efficacy diminishes or if side effects arise more frequently following a switch. Given the complexity of the human immune system and the challenges of treating patients with chronic disease and comorbidities, these less optimal outcomes are likely to be seen as individual patient responses rather than a pattern of concern. Therefore, the elimination of studies to identify negative outcomes (i.e. switching studies) is very different from the absence of negative outcomes in studies conducted to identify them (i.e. an affirmative demonstration that switching does not diminish safety and/or efficacy). Again, in the case of the meta-analysis by Herndon et al.; the authors confine their analysis only to safety and do not evaluate any impacts of switching on efficacy. Diminishing or eliminating clinical data requirements for third-party pharmacy substitution of biosimilars inappropriately conflates two classes of biosimilars that are currently distinguishable by their data requirements. This does not serve the needs of patients and policymakers and legislators should not go beyond the limitations of this study.

We urge the FDA to reconsider the recommendations in its Draft Guidance and instead preserve the important role of switching studies in the interchangeable biosimilar approval process. These studies play an essential role in ensuring that biosimilars can be safely and effectively substituted without compromising treatment stability. Eliminating them would not only potentially risk patient treatment stability but undermine trust in biosimilars (including interchangeable biosimilars) among patients, physicians and other stakeholders which could ultimately hinder biosimilar acceptance and associated savings to our health system.

Thank you for considering our perspective on this critical issue.



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