January 20, 2026

Docket No. FDA-2011-D-0605
Submitted to: U.S. Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

To Whom It May Concern,

The Alliance for Safe Biologic Medicines (ASBM) appreciates the opportunity to comment on the October 2025 draft guidance, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies*. Founded in 2010, ASBM is a diverse coalition of physicians, pharmacists, patients, researchers, and manufacturers of biologic and biosimilar medicines working to advance patient-centered, science-based health policy in the United States and internationally.

ASBM supports efforts to modernize biosimilar development in ways that are consistent with evolving. We agree that comparative analytical assessments (CAA) have become increasingly powerful and, in many circumstances, more sensitive than traditional comparative clinical efficacy studies (CES) for detecting product differences. Thoughtful streamlining—applied on a fact-specific, case-by-case basis—can be appropriate and scientifically justified.

However, ASBM is deeply concerned that reducing CES requirements, when coupled with contemporaneous public messaging and policy initiatives that frame biosimilars as generic products, risks undermining hard-won physician and patient confidence in the U.S. biosimilar framework. That confidence is not incidental; it is critical to biosimilar uptake, ensuring treatment stability for millions of American patients, and achieving the savings biosimilars are intended to deliver.

FDA Is Correct That Analytics Have Advanced—but Also Correct in Recognizing Their Limits

The draft guidance appropriately reflects FDA's growing experience with comparative analytical assessments and acknowledges that, for many well-characterized therapeutic proteins, robust analytics, pharmacokinetic similarity, and immunogenicity assessment may sufficiently address residual uncertainty. ASBM agrees that CES can be blunt tools, often limited by plateau effects, dose saturation, and insensitive endpoints.

At the same time, FDA's own recent statements caution against interpreting these advances as support for an analytics-only approach to biosimilar approval. At the September 19, 2025 FDA Public Workshop, *Advancing the Development of Interchangeable Products: Identifying Future Needs*, FDA repeatedly emphasized[i] that clinically meaningful differences may arise from factors outside "what's in the vial." These include delivery devices, user interfaces, accessory products (such as pumps or diluents), and real-world use environments—factors that even the best analytics alone cannot fully capture.

FDA specifically noted that "additional considerations related to pharmacy substitution that may require more data are: differences in the user interface for combination products [and] accessory products (e.g., pumps, diluents)." FDA's human-factors experts further explained that human-factors validation studies may be required to demonstrate that a proposed product has "no clinically meaningful difference" in real-world use. FDA also acknowledged that a subset of biological products—such as complex mixtures or products with limited structure-function understanding—remain challenging to characterize comprehensively and are "likely to raise uncertainty around biosimilarity."[ii]

These acknowledgments underscore a critical point: while analytics are powerful, they do not resolve all clinically relevant questions in all contexts. The final guidance should make this explicit to avoid misinterpretation.

Today's Confidence in Biosimilars Was Built on a Data-Driven, Stepwise Approach

FDA itself has recognized that "the past 15 years brought increased scientific understanding and confidence in biosimilars." That confidence was not built on analytics alone. It emerged from a stepwise, totality-of-evidence framework integrating robust analytical similarity with clinical pharmacology, immunogenicity assessment, and **targeted clinical evidence where appropriate**.

FDA's September 2025 public workshop posed the following question in the context of pharmacy-level automatic substitution: *"Will patients and providers have what they need to be able to use the interchangeable product?"*

It is critical that physicians have **confidence in a third-party biosimilar substitution**. Physicians must trust that switching to a biosimilar will not introduce new risks in a given patient. The current interchangeable biosimilar approval process addresses this through case-by-case individual evaluations for interchangeables, including additional clinical data when appropriate- but FDA has expressed support for legislation which would deem all biosimilars "interchangeable" upon approval. Physicians must also be confident that differences in devices, instructions, accessories, or use conditions will not compromise switching outcomes- a challenge the FDA recognizes. Finally, they must be confident in and comfortable with relying on third-party automatic substitution without prescriber involvement.

Data from ASBM's recent national physician surveys[iii] gives us insight into how physician confidence is built, and what might jeopardize it. U.S. physicians report very high overall confidence in FDA-approved biosimilars, with nearly nine in ten prescribers (89%) expressing high confidence in their safety and effectiveness[iv]. At the same time, that confidence is conditional, particularly when it comes to third-party substitution. 69% of U.S. physicians surveyed are uncomfortable with non-medical switching or automatic substitution of biologics by third parties (such as insurers or pharmacies), particularly when patients are stable on therapy. In addition, 88% of U.S. physicians reported that clinical data- specifically switching studies- increase their confidence in interchangeable biosimilars, and the same proportion (88%) supported maintaining FDA's current case-by-case approach to granting interchangeability. **By contrast, only 11% favored treating all biosimilars as interchangeable by default.[v]**

These findings are consistent with earlier U.S.[vi] and European[vii] surveys showing strong physician support for biosimilars as treatment options, paired with sustained caution toward automatic, non-medical switching driven by parties other than the prescribing clinician. Together, the data suggest that physician confidence in biosimilars has been built through FDA's totality-of-evidence framework- **and could be undermined if biosimilars are treated as generics by default rather than evaluated in context.**

CES Reduction Combined With FDA's "Genericization" Messaging Creates a Compound Risk

Alone, a science-based reduction in CES requirements may be reasonable in defined circumstances. In the current policy environment, however, CES reduction does not occur in isolation. It is unfolding alongside public statements by senior HHS and FDA leadership encouraging the public to "think of biosimilars as generics,"[viii] proposals to eliminate the practical distinction between biosimilars and interchangeable biosimilars[ix], and FDA support for legislative efforts such as the Biosimilar Red Tape Elimination Act.[x]

As former CDER Director George Tidmarsh stated at FDA's September 19, 2025 public workshop[xi], these developments amount to a de facto "genericization" of biosimilars—that is, collapsing a regulatory framework designed for complex biologic medicines into a small-molecule generic model optimized for automatic pharmacy substitution. While regulators in both the United States and Europe have appropriately streamlined certain development requirements, including reducing the routine use of comparative efficacy studies where science supports it[xii], European regulators have not paired those changes with widespread automatic substitution[xiii]. In the European Union, pharmacy-level substitution of biosimilars remains uncommon and is frequently prohibited by Member States[xiv]. By contrast, the existing U.S. statutory framework for interchangeable biosimilars, if coupled with further reductions in clinical confirmation, would enable a level of routine third-party automatic substitution that effectively creates a mass-substitution regime not observed in Europe or other advanced regulatory systems.

For physicians and patients, reducing or eliminating CES while publicly analogizing biosimilars to generics will be heard as **lowering standards to create a generics-style mass substitution system for biosimilars, regardless of FDA's internal scientific rationale.**

This is precisely the outcome clinicians and patients have consistently opposed. It risks eroding trust, destabilizing treatment for stable patients, and undermining the very uptake and savings these policies are intended to promote.

FDA Should Clarify Guardrails in the Final Guidance

To preserve confidence while modernizing biosimilar development, ASBM respectfully urges FDA to:

1. Explicitly state that the absence of a CES is a case-specific determination, not a presumption, and that FDA retains discretion to require additional clinical or human-use data when residual uncertainty exists.
2. Reaffirm that clinical evidence remains an integral component of the totality-of-evidence framework, particularly where device, human-factors, immunogenicity, or patient-specific variables may affect real-world outcomes.
3. Clarify that streamlining CES requirements does not imply that biosimilars are equivalent to small-molecule generics, nor that biosimilars should be treated as interchangeable by default.
4. Preserve the interchangeability designation as the gatekeeper for third-party automatic substitution, consistent with the scientific rationale and legislative assurances that underpinned state substitution laws.

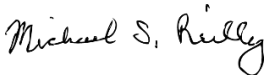
Conclusion

Biosimilars have already delivered substantial savings and expanded access for patients—without lowering FDA's scientific standards. The primary barriers to biosimilar uptake remain payer and PBM formulary practices, not the evidentiary rigor of the biosimilar approval pathway. Lowering or appearing to lower that rigor will not reform those market distortions; it will only undermine physician and patient confidence.

ASBM supports regulatory efficiency grounded in science. We do not support the genericization of biosimilars. FDA's final guidance should reflect both the power and the limits of modern analytics, preserve a data-driven, case-by-case approach, and communicate clearly that biosimilars remain distinct from generics—scientifically, clinically, and regulatorily.

Thank you for the opportunity to comment on this important guidance.

Sincerely,



Michael S. Reilly, Esq.
Executive Director
Alliance for Safe Biologic Medicines

ASBM Steering Committee Members:

Alliance for Patient Access
American Academy of Dermatology
Autoimmune Association
Association of Clinical Research Organizations
Colon Cancer Alliance
Global Colon Cancer Association
Global Healthy Living Foundation
Health HIV
International Cancer Advocacy Network
Kidney Cancer Association
Lupus and Allied Diseases Association, Inc.
National Hispanic Medical Association
National Psoriasis Foundation
ZeroCancer

REFERENCES

[i] https://www.fda.gov/industry/fda-public-workshop-future-needs-development-interchangeable-products-09192025
[ii] https://www.fda.gov/media/188971/download

[iii] www.safebiologics.org/surveys

[iv] https://safebiologics.org/wp-content/uploads/2023/08/ASBM-2021-US-Biologics-Prescribers-Survey-Specialty-Data.pdf

[v] https://safebiologics.org/wp-content/uploads/2024/09/ASBM-US-Physician-Survey-IC-Biosims.pdf

[vi] https://safebiologics.org/wp-content/uploads/2023/08/ASBM-2021-US-Biologics-Prescribers-Survey-Specialty-Data.pdf

[vii] https://safebiologics.org/wp-content/uploads/2020/06/EU-Survey-2019.pdf

[viii] https://www.rev.com/transcripts/rfk-jr-announces-fda-drug-approval-changes

[ix] https://www.congress.gov/bill/119th-congress/senate-bill/1954/text

[x] https://www.agencyiq.com/blog/the-fda-wants-to-kill-the-interchangeable-biosimilar-its-not-waiting-on-congress-to-start-the-burial-preparations/

[xi] https://www.fda.gov/media/188972/download

[xii] https://www.ema.europa.eu/en/reflection-paper-tailored-clinical-approach-biosimilar-development

[xiii] https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2024.1263472/full

[xiv] https://gabi-journal.net/key-factors-for-successful-uptake-of-biosimilars-europe-and-the-us.html