Biosimilars
FORUM

Setting the Record Straight on Biosimilar Interchangeability

Biosimilars Amendment to Senate Bill S. 2840

As more biosimilars launch in the United States and achieve greater availability on formularies, many patients find themselves with increased access to safe, effective, and lower-cost biosimilars. Patients should understand that biosimilars are fully vetted through a vigorous, lengthy FDA review process, and offer the same clinical benefits and effectiveness of the originator biologic. If a patient's treatment plan includes biosimilars, they can be fully confident that the therapeutic outcome on a biosimilar will be the exact same as the originator biologic, supported by FDA reviews, academic studies, and guidelines from healthcare networks and physician societies.


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RESEARCH ARTICLE

Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis

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Abstract

Biosimilars are increasingly available for the treatment of many serious disorders, however some concerns persist about switching a patient to a biosimilar whose condition is stable while on the reference biologic. Randomized controlled studies and extension studies with a switch treatment period (STP) to or from a biosimilar and its reference biologic were identified from publicly available information maintained by the U.S. Food and Drug Administration (FDA). These findings were augmented with data from peer reviewed publications containing information not captured in FDA reviews. Forty-four STPs were identified from 31 unique studies for 21 different biosimilars. Data were extracted and synthesized following PRISMA guidelines. Meta-analysis was conducted to estimate the overall risk difference across studies. A total of 5,252 patients who were switched to or from a biosimilar and its reference biologic were identified. Safety data including deaths, serious adverse events, and treatment discontinuation showed an overall risk difference (95% CI) of -0.00 (-0.00, 0.00), 0.00 (-0.01, 0.01), -0.00 (-0.01, 0.00) across STPs, respectively. Immunogenicity data showed similar incidence of anti-drug antibodies and neutralizing antibodies in patients within a STP who were switched to or from a biosimilar to its reference biologic and patients who were not switched. Immune related adverse events such as anaphylaxis, hypersensitivity reactions, and injections site reactions were similar in switched and non-switched patients. This first systematic review using statistical methods to address the risk of switching patients between reference biologics and biosimilars finds no difference in the safety profiles or immunogenicity rates in patients who were switched and those who remained on a reference biologic or a biosimilar.

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Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis

READ THE PAPER

The FDA recently released a peer-reviewed scientific paper — ***Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis***[1] — that emphasizes that interchangeability has nothing to do with product quality, a point that FDA has been making for many years. An interchangeable biosimilar must meet the high FDA standards of a biosimilar — proven to be highly similar structurally to its reference product and no clinically meaningful differences in safety, potency, and purity.[2]

The U.S. biosimilar legislation in 2009 was drafted in a cautious manner. At the time it was drafted, there was no U.S. development experience and no FDA review experience. Given that no U.S. biosimilars had yet been approved, there was also no post-approval safety experience. The FDA is now on record as stating that based on what they have seen and now know, the theoretical safety and immunological concerns that were the basis for a separate interchangeability category have not been demonstrated in patients.

Still, much confusion exists about interchangeability, especially with a current bill working its way through Congress. Deeming biosimilars to be interchangeable upon approval clarifies FDA's position that irrespective of an interchangeability designation, all biosimilars are of the same product quality. If biosimilars are deemed to be interchangeable, it will deprive biosimilar opponents of the opportunity to sow fear confusion and doubt.

Frequently Asked Questions about the Biosimilars Amendment to Senate Bill S. 2840

QUESTION	ANSWER
What does the biosimilars amendment to S. 2840 do?	The amendment will allow the FDA to deem a biosimilar interchangeable without requiring additional data that is now acknowledged by FDA to be not necessary. It is important to remember that all FDA-approved biosimilars undergo a rigorous evaluation so that health care providers and patients can be confident of the safety, effectiveness, and quality of these products.
Does the biosimilars amendment to S. 2840 reflect current FDA standards and processes?	The statutory requirements themselves will not be impacted, and the FDA will retain the same flexibility that it has today. The biosimilars amendment streamlines the biosimilar approval process and provides greater clarity to FDA and biosimilar developers. The FDA has noted that the interchangeability designation has no clinical impact on patients. If biosimilars are deemed interchangeable when approved as a biosimilar, the FDA will evaluate potential interchangeability earlier in the approval process.
Does the biosimilars amendment to S. 2840 lower the scientific or safety standards for interchangeable biosimilars at the FDA?	No, all biosimilars, whether or not they are deemed interchangeable, are required to meet strict scientific standards for safety and efficacy regardless of interchangeability. Interchangeability is NOT a scientific standard. Interchangeability is merely a term that allows for automatic substitution at a retail pharmacy by a pharmacist without authorization of the physician. Both the U.S. FDA and the European Medicines Agency are on record that biosimilars provide patients with the same clinical experience as their reference products. Based on available data, no differences are observed in efficacy, safety or immunogenicity for patients starting on biosimilars or after being switched from a reference product to a biosimilar.
Are all biosimilars interchangeable now?	Yes, in the clinical setting, all biosimilars have the same safety and efficacy as their reference biologic and can be prescribed by physicians with confidence regardless of their interchangeability status. Interchangeability is only reflective of what a retail pharmacist, not a physician, may or may not do in a retail pharmacy.
What does the FDA say about the biosimilars amendment to S. 2840?	Recently the FDA weighed in on a similar Senate bill, the Biosimilar Red Tape Elimination Act, that would deem all biosimilars interchangeable. Specifically, the FDA noted: • "The Agency believes this change would expedite the development, approval, adoption by healthcare providers, and patients' usage of biosimilars." • "The distinction between the two categories [approved and interchangeable] no longer appears to serve a significant scientific purpose in the overwhelming majority of cases, as it does not reflect the current scientific understanding of the safety or efficacy of biosimilar products as it relates to substitutability at the pharmacy level." • "This legislation, coupled with the most recent Biosimilar User Fee Act (BsUFA) reauthorization's focus on interchangeable products, would make the U.S. biosimilar program more consistent with current scientific understanding."

Frequently Asked Questions about the Biosimilars Amendment to Senate Bill S. 2840 (cont.)

QUESTION	ANSWER
Will deeming all biosimilars interchangeable affect patient safety?	All biosimilars have been through rigorous testing and declared safe and effective by the FDA. In fact, the FDA recently released a peer-reviewed scientific paper — ***Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis***[1] — on the safety of switching patients to biosimilars. The research emphasizes that interchangeability has nothing to do with product quality or safety, a point that FDA has been making for many years. In a systematic review published by in the scientific journal PLOS One, FDA researchers found no difference in the safety outcomes of patients who switched to a reference biologic or a biosimilar and those who remained on their original drug. There has been confusion around the use of interchangeable biosimilar drugs compared to their reference product. Misperceptions exist that without the interchangeability designation, biosimilars cannot be switched with the reference product. The peer-reviewed publication from FDA notes that the interchangeability designation does not provide clinical benefits for patients. The research concluded that the safety results were consistent with the current evidence of interchangeability between the reference biologic and the biosimilar drug. **Key Finding** "This first systematic review using statistical methods to address the risk of switching patients between reference biologics and biosimilars finds no difference in the safety profiles or immunogenicity rates in patients who were switched and those who remained on a reference biologic or a biosimilar."
What about the recently passed BsUFA III Commitment Letter? Under BsUFA III, FDA has committed to conducting a Regulatory Science Pilot Program that will focus on advancing the development of interchangeable biosimilars. Should we wait until this program is completed?	Nothing in the proposed language will interrupt the BsUFA III commitments for the Regulatory Science Pilot Program. The Regulatory Science Pilot Program is a long-term program that includes applied research on the core concepts of biosimilars, including interchangeable biologics. Nor does the BsUFA III Regulatory Science Pilot Program serve as a prerequisite for the proposal to the biosimilars amendment to S. 2840. The biosimilar language proposed the biosimilars amendment to S. 2840 reflects the FDA's current scientific thinking on biosimilar interchangeability. The BsUFA III Regulatory Science Pilot Program will only add to the FDA's and industry's thinking on future regulatory science related to biosimilars and does not impact FDA's current thinking as reflected in the language.
Does the biosimilars amendment to S. 2840 change the FDA requirements for pediatric assessments of biosimilars?	No. The amendment to S. 2840 makes no changes to the language of the Biologics Price Competition and Innovation Act (BPCIA). Biosimilars applicants will continue to be required to follow FDA requirements and conduct pediatric assessments on any reference biologic pediatric indication for which they seek approval. In addition, as per the BPCIA, biosimilar applicants are limited to seeking approval of only indications previously approved for the reference biologic. In fact, seven pediatric IBD observational studies have been completed. Additionally, the FDA recently conducted a statistical analysis of randomized clinical trials of reference biologic to biosimilar switches. They identified forty-four switch treatment periods (STP) from 31 unique studies for 21 different biosimilars and showed that there was "no difference in the safety profiles or immunogenicity rates in patients who were switched and those who remained on a reference biologic or a biosimilar."

All Biosimilars are Safe and Effective

The Body of Research Finds No Difference in Outcome Between Biosimilars and their Reference Biologics and Between Biosimilars to the Same Reference Product

A review conducted in 2018 counted 90 clinical trials and real-world observational studies in 14 indications that cumulatively enrolled over 14,000 patients or healthy individuals. The publication concludes that "the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine."[4]

90 clinical trials
14 indications
14,000 patients or healthy individuals

Another review published in 2020 identified 178 clinical trials and real-world observational studies that cumulatively enrolled approximately 21,000 patients or healthy individuals. The review concluded that "the available switching data do not indicate that switching from a reference product to a biosimilar is associated with any major efficacy, safety, or immunogenicity issues."[5]

178 clinical trials
21,000 patients or healthy individuals

Biosimilars have already been used extensively in the U.S. and Europe with over 5 billion patient days of experience to date. No biosimilar approved in the U.S. or Europe has been withdrawn or suspended for reasons of safety or efficacy. Health authorities have concluded that the monitoring systems for safety concerns "**have not identified any relevant difference in the nature, severity or frequency of adverse events between biosimilar medicines and their reference medicines**."

No biosimilar approved in the U.S. or Europe has been withdrawn or suspended for reasons of safety or efficacy.

[1] Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. Published October 3, 2023. Accessed October 2023. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0292231.

[2] Biosimilar and Interchangeable Products in the United States: Scientific Concepts, Clinical Use, and Practical Considerations. U.S. Food and Drug Administration. Accessed October 2023. https://www.fda.gov/media/122832/download.

[3] Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. Published October 3, 2023. Accessed October 2023. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0292231.

[4] Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Published March 2018. Accessed October 2023. https://pubmed.ncbi.nlm.nih.gov/29500555/.

[5] The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Published October 2020. Accessed October 2023. https://pubmed.ncbi.nlm.nih.gov/32236956/.

The Biosimilars Forum

The Biosimilars Forum is a nonprofit organization working to advance biosimilars in the United States with the goals of expanding access and availability and improving healthcare outcomes. Since its inception, the Forum has worked to expand the uptake of biosimilars throughout the healthcare system through policies that will increase access for patients and lower costs through increased competition. Forum members represent companies with the most significant U.S. biosimilars development portfolios.