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Marty Makary, MD
Administrator
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted at regulations.gov

RE: FDA-2011-D-0605-0060; Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies, Guidance for Industry

Dear Administrator Makary:

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies, Guidance for Industry," as published in the Federal Register on Nov. 20, 2025.

NASPGHAN represents more than 3,000 pediatric gastroenterologists, pediatric gastroenterology nurses and advanced practice providers, and pediatric registered dietitians in the United States, Canada, and Mexico and is the only organization singularly dedicated to advocating for children with gastrointestinal, pancreatic, liver and nutrition-related diseases and disorders.

EXECUTIVE SUMMARY

Biologics have revolutionized care for those affected by inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis. Faster market entry of biosimilars and, consequently, greater competition, offers the potential to improve access to and lower patient out-of-pocket cost for standard-of-care biologic therapies.

The following summary offers an overview of our primary comments in response to the FDA's draft guidance:

Non-medical Switching
The FDA's draft guidance to streamline biosimilar development by de-emphasizing the necessity of comparative effectiveness studies (CES), including switching studies, is intended to speed patient access to biosimilars and lower patient and health care system costs. However, as regulatory pathways increasingly facilitate biosimilar approval and interchangeability, safeguards are needed to protect pediatric patients from payer- or pharmacy-driven non-medical switching, particularly given limited pediatric-specific switching data and the potential clinical consequences of biologic substitution in this vulnerable population.

Shared Responsibility for Biosimilar Education
The responsibility to educate patients and families on biosimilars has largely fallen on physicians. Insurance companies and specialty pharmacies have not done a good job with this education causing patient/family/caregiver confusion and anxiety that is likely increasing the "nocebo effect" associated with biosimilar use. The lack of insurer and pharmacist education about biosimilars and the need for critical adjustments before a switch is made, such as enrollment in new co-pay assistance programs and adjusting to a new injection device, makes it imperative that non-medical switching (i.e., prescribing decisions made without the explicit approval of the treating physician) be expressly prohibited for pediatric patients.

Health Care Savings
Savings from the prescribing and use of biosimilars must accrue to patients. Even when list prices are reduced, the net cost patients face can vary due to rebates, contractual discounts, insurance coverage, and other system factors that must also be acknowledged and addressed.

NON-MEDICAL SWITCHING

In an Oct. 29, 2025 press release,[1] it was stated the FDA, through a separate initiative, plans to make it easier for biosimilars to be developed as interchangeable with brand-name biologics to achieve "massive cost reductions" for advanced treatments for cancer, autoimmune diseases, and rare disorders. Currently, manufacturers perform "switching studies" for biosimilars licensed as interchangeable. We acknowledge these additional studies can slow development and have the potential to create public confusion.

The practice of insurers forcing pediatric patients to switch their biologic therapy, typically without the approval or even awareness of their treating physician, is prolific. With each switch is a potential adherence disruption, especially when insurers and PBMs adjust "preferred" products annually, or even more frequently. Even when a physician marks a prescription "dispensed as written," too often that order is ignored and a patient gets switched to another biologic even if the patient is stable and doing well on current therapy. Because of these formulary changes and the resulting non-medical switching, therapeutic drug monitoring (TDM) is more important than ever to monitor patients for continuation of effective dosing as well as

[1] FDA Moves to Accelerate Biosimilar Development and Lower Drug Costs, Oct. 29, 2025. https://www.fda.gov/news-events/press-announcements/fda-moves-accelerate-biosimilar-development-and-lower-drug-costs

drug-related immunogenicity.[2] Unfortunately, many health insurance companies will not pay for TDM.

Even among biosimilars, "small" changes such as delivery device, needle size, injection volume, and pain caused by additives or preservatives can affect adherence to treatment in patients with IBD, especially pediatric patients. These differences matter and is why therapy changes in pediatric patients must not occur without the approval of the treating physician.

Efforts by the FDA to make it easier for biosimilars to be developed as interchangeable with brand-name biologics must be accompanied by protections for pediatric patients against payer- or pharmacy-driven biologic substitution. These protections are especially important when a biologic for pediatric IBD is used off-label and because there is a dearth of data on the potential for immunogenicity with multiple treatment switches. Several single-center cohorts and a few multicenter adolescent/young adult series have reported that a *one-time nonmedical switch* (e.g., infliximab → CT-P13) did not significantly change remission rates, drug levels, or anti-drug antibodies signals in the short term.[3] However, because IBD is chronic and life-long, pediatric IBD patients may experience multiple biologic switches over their lifetime, and often multiple switches before reaching 18 years of age. There is a particular need for data on loss of response when a patient is moved back to the biologic used when treatment was first initiated after multiple switches. **We strongly support utilizing extrapolation to speed the entry of new products to market, but because pediatric data on multiple switches are limited, the FDA should require prospective pediatric registries and mandated post-marketing switching surveillance.**

SHARED RESPONSIBILITY FOR BIOSIMILAR EDUCATION

Letters insurance companies send to patients informing them that they are being switched to another biologic are often poorly written, provide minimal biosimilar education, and are confusing. Consequently, the responsibility to educate patients and families on biosimilars has largely fallen on physicians and their team of health care professionals.

Patients get anxious about biologic therapy switches, which can create a phenomenon known as the "nocebo effect" — a situation where a negative outcome occurs due to a belief that the intervention will cause harm.[4] For adverse reactions to medicines, nocebo implies that patients are more likely to experience an adverse effect if they expect or are worried about the adverse effect. The adverse effects may be physically experienced by the patient and are often clinically diagnosable. A 2015 Finnish report showed that around a quarter of patients discontinued an approved infliximab biosimilar due to a perceived loss of efficacy or an increase in side effects.[5]

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[2] Felipez LM, Ali S, De Zoeten EF, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the therapeutic drug monitoring in pediatric inflammatory bowel disease. J pediatr gastroenterol nutr. 2025;81(4):1100-1117. doi:10.1002/jpn3.70158

[3] McNicol M, Abdel-Rasoul M, McClinchie MG, Morris GA, Boyle B, Dotson JL, Michel HK, Maltz RM. Clinical outcomes and cost savings of a nonmedical switch to a biosimilar in children/young adults with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2024 Mar;78(3):644-652. doi: 10.1002/jpn3.12153. Epub 2024 Feb 9. PMID: 38334232.

[4] Prescriber Update; Vol. 40 No. 1, March 2019. https://www.medsafe.govt.nz/profs/PUArticles/PDF/Prescriber_update_Vo_40_No_ 1_March_2019.pdf

[5] Nikiphorou E, Kautiainen H, Hannonen P, et al. 2015. Clinical effectiveness of CT-p13 (infliximab biosimilar)

Most pediatric gastroenterologists make it a point to educate their patients about biosimilar efficacy and safety and to call them in advance any time a therapeutic switch is made. Without clinician counseling when therapy switches are made, the patient's perceived loss of benefit and discontinuation of treatment may increase, and these effects are hard to separate from pharmacologic causes in observational data. For this reason, non-medical switching must be expressly prohibited for pediatric patients.

When pharmacists swap biologic products without the advanced knowledge of the treating physician, it does not afford the provider the opportunity to educate the patient/family and make critical adjustments, like proper education about different injection devices or choosing a citrate-free formulation. Citrate can cause more pain at the injection site — a significant and important issue for pediatric patients and which can impact therapeutic compliance. Ensuring the treating physician has advance notice of a therapeutic switch can also allow them to help the patient/family sign up for a new copay assistance program, if necessary. **Non-medical switching without the approval of the treating physician results in unnecessary stress and anxiety for patients/families, potential delays in care due to affordability, and can unnecessarily lead to a nocebo effect which unnecessarily complicates patient treatment and management.**

POTENTIAL FOR HEALTH CARE SAVINGS

At the center of the conversation about biosimilars should be the overall health care cost savings. As noted in the FDA's Oct. 29, 2025 press release, biosimilars are considered lower-cost, but their market share remains below 20 percent.[6,7]

A recently published article showed the introduction of multiple infliximab products created price competition in the marketplace, which was correlated with the decreasing commercial costs of the infliximab originator, as well as the infliximab biosimilar.[8] From December 2017 to December 2021, the cost of the infliximab originator per infusion and per vial decreased by 53 percent and 62 percent, respectively.[9] These are significant savings; however, savings to patients were minimal. The median patient out-of-pocket costs per year for all infliximab products increased from $840 in 2015 to $1333 in 2020, then decreased to $950 per year in 2021.[10] While patient out-of-pocket costs are hard to study because so many variables can affect patients' costs, another paper[11] showed initially when patients switched from the originator to the biosimilar

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used as switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opinion on Biological Therapy 15(12): 1677–83. DOI: 10.1517/14712598.2015.1103733 (accessed 22 January 2019).

[6] FDA Moves to Accelerate Biosimilar Development and Lower Drug Costs, Oct. 29, 2025. https://www.fda.gov/news-events/press-announcements/fda-moves-accelerate-biosimilar-development-and-lower-drug-costs

[7] Maltz RM, Saeed SA, Adler J. Infliximab Biosimilar Utilization in a Large Pediatric Learning Health System. Children. 2025;12(5):656. doi:10.3390/children12050656

[8] Paglinco SR, Abdel-Rasoul M, McNicol M, Mouslim MC, Boyle B, Dotson JL, Michel HK, Maltz RM. The biosimilar shift: trending infliximab biosimilar utilization and associated cost savings for commercial insurance. Am J Manag Care. 2025 Oct 1;31(10):e295-e301. doi: 10.37765/ajmc.2025.89811. PMID: 41143667.

[9] Ibid.

[10] Ibid.

[11] In Press; Am J Manag Care

there were cost savings, but by 2021 those savings were negligible because the cost of the originator and biosimilars decreased and were similar.

Even when list prices of biologic products are reduced, the net cost that payers or patients face can vary due to rebates, contractual discounts, insurance coverage and other system factors. One article found that an adalimumab biosimilar with a 55 percent list price discount still cost more than double the original launch price of the reference adalimumab product once rebates were considered.[12] **More pricing transparency and policy changes are needed to ensure any savings produced by biosimilars are realized by consumers.**

Lastly, many patients/families rely on copay assistance programs to afford biologic therapy, both originator biologic products and biosimilars. Out-of-pocket costs may worsen or improve depending on which product a plan "prefers" and whether and how much copay assistance is available. When insurance companies mandate therapy switches due to formulary changes, it can take time for patients to sign up for a new copay assistance program. Put simply, it is not enough to just bring more biosimilar products to market in a timely manner. There are numerous systemic factors and considerations that must be accounted for to ensure that biosimilars are reducing costs for patients, not just insurance companies.

CONCLUSION

Many of the concerns about safety and efficacy of biologic products in pediatric populations can be assuaged by collecting post-market surveillance data that will allow physicians and patients to move beyond presumption to assurance that switching of biologic products in pediatric populations is safe and will not lead to long-term adverse medical outcomes. Absent this data and patient education, the uptake of biosimilars in pediatric populations will remain underutilized.

NASPGHAN also looks forward to future discussions with the Agency to improve the clinical development pathway for drugs to treat pediatric patients with IBD. We refer the FDA to comments submitted on Sept. 17, 2024 by NASPGHAN, the American Gastroenterological Association, the American Academy of Pediatrics, the Crohn's and Colitis Foundation, and Improve Care Now in response to the draft FDA guidance "Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment."[13]

NASPGHAN thanks you in advance for consideration of its concerns and recommendations. Questions or requests for additional information should be directed to Camille Bonta, NASPGHAN policy advisor, at cbonta@summithealthconsulting.com or (202) 320-3658.

Sincerely,

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[12] Pine, L. Adalimumab Biosimilars May Not be as Cost-Effective Based on Previous Rebates, July 19, 2023. https://www.hcplive.com/view/adalimumab-biosimilars-may-not-be-as-cost-effective-based-on-previous-rebates

[13] https://www.regulations.gov/comment/FDA-2024-D-2682-0026

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