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Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
C/O Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted through https://www.regulations.gov

Dear Commissioner Califf:

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) appreciates the opportunity to comment on draft industry guidance for "Labeling for Biosimilar and Interchangeable Biosimilar Products" as published on September 17, 2023.

NASPGHAN represents 3,484 pediatric gastroenterologists, advanced practice practitioners, nurses and dietitians in the United States and is the only organization singularly dedicated to advocating for children with gastrointestinal, liver and nutrition-related disorders.

Biologic drugs have significantly advanced the pharmacological management of inflammatory bowel disease (IBD) and have substantially improved outcomes and quality of life for children with Crohn's disease and ulcerative colitis. NASPGHAN members who treat children with IBD have considerable experience with biologic and biosimilar products, and, therefore, we are well-positioned to provide comments on the Food and Drug Administration's (FDA) draft labeling guidance.

Biosimilar and interchangeable products are different from generic medications (i.e., pharmaceutical products). Therefore, it is critical that biological product labeling provide adequate and accurate information to enable physicians to prescribe a biologic medication safely and for its intended purposes. While NASPGHAN is generally supportive of the draft guidance, we offer the following observations and recommendations concerning:

- the definition of a "clinically meaningful difference" between a reference product and a biosimilar and interchangeable biologic;
- approaches to biologic product identification; and
- communicating biosimilar interchangeability for pediatric use.

Definition of a "Clinically Meaningful Difference" Between a Reference Product and a Biosimilar and Interchangeable Biologic

We acknowledge the *Public Health Service Act* defines a biosimilarity to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

While biosimilars may demonstrate efficacy, safety and immunogenicity similar to the originator, particularly in the adult populations in which they were originally studied, they may differ in terms of inactive substances, preservatives and device type (i.e., for medication administration) which may be information physicians need to know when making treatment decisions.[1] Some of these inactive substances can increase pain and cause reactions (Table 1). These differences must also be considered before an insurance company or pharmacist can substitute a biosimilar or interchangeable biologic product without the consultation with or approval from the prescribing provider.

For example, citrate is a "clinically inactive compound" that causes pain at the injection site for patients receiving adalimumab. Citrate was removed from the adalimumab originator (Humira) formulation to make it more tolerable, particularly for children, yet it is included in some of the new biosimilars to this compound. Some patients are allergic to latex or have intolerance to monosodium glutamate — both of which are present in some biosimilar products. These differences may seem minor, but they are very important, especially when treating children. These differences must not be overlooked and demonstrate why the substitution of any biologic product should be prohibited in pediatric patients without the consultation of the prescribing health care provider. We respectfully ask the FDA to acknowledge these important differences between biosimilar and interchangeable biologic products and consider ways in which product labeling can help prescribing providers navigate these product differences.

Table 1. Humira (adalimumab) biosimilars are not identical.

"Inactive ingredients"	Abrilada®	Hyrimoz®	*Hadlima®	Hulio®
Polysorbate 20			✓	
Citrate			✓	
Sodium EDTA	✓			
Monosodium glutamate				✓
Latex rubber		Needle cap		

*Not all forms of Hadlima contain citrate.

Approaches to Biologic Product Identification

We appreciate the FDA's recommended approach to biologic product identification depending on the context of the information being presented. However, the nomenclature for biologics is confusing to prescribers and to patients.[2] We believe that when a label mentions a product's proper name, it should also include the product's proprietary name (if available). Use and labeling of both a product's proper and proprietary names would help to alleviate confusion among prescribers and patients especially as more biologic products enter the market.

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[1] Abitbol V, Benkhalifa S, Habauzit C, Marotte H. Navigating adalimumab biosimilars: an expert opinion. J Comp Eff Res. 2023 Nov;12(11):e230117. doi: 10.57264/cer-2023-0117. Epub 2023 Oct 19. PMID: 37855223.

[2] Kim, A. Biosimilars: What's In a Name. Hosp Pharm 2015;50(10):847–848 2015. doi: 10.1310/hpj5010-847

Communicating Biosimilar Interchangeability for Pediatric Use

Increasingly, insurance companies are using utilization management tactics such as step-therapy, prior authorization, and non-medical switching — including *multiple* switches which are occurring with alarming frequency and oftentimes without the knowledge of the treating physician or patient — to control the prescribing, and thereby cost, of biologic products. These insurance company tactics restrict pediatric access to new medicines and cause medical harm. While not under the jurisdiction of the FDA, insurance companies and pharmacists should be *explicitly prohibited* from substituting a biosimilar or interchangeable biologic product in pediatric patients (i.e. under the 18 years of age) without the oversight and approval of the prescribing provider because of the *lack* of pediatric studies for biologics and the absence of both short- and long-term studies evaluating the effect of multiple biologic therapeutic switches on children. The lack of data and evidence constitutes a significant deficit considering these insurance company practices. Insurance companies leverage the absence of pediatric indications or the lack of labeling of pediatric-appropriate biologic dosing to deny access of children with IBD to effective biologic therapies or medically appropriate dosing.

There are no randomized controlled trials (RCTs) published on switching the use of infliximab or other anti-TNF (Tumor Necrosis Factor) biosimilars in pediatric patients with IBD. Further, there are no prospective studies which characterize or evaluate the immunogenicity, safety, and effectiveness of the biosimilars in children with IBD over time, particularly after switching has occurred. The only data on efficacy after non-medical switching can be derived from three published RCTs in *adult patients* — one in patients with IBD and two of these trials were conducted in adult patients with rheumatoid arthritis and ankylosing spondylitis. This is important to recognize because *pediatric IBD is not identical* in pathogenesis to either adult IBD or, even more importantly, to rheumatologic disease in adults, particularly, rheumatoid arthritis and ankylosing spondylitis. There is no published RCT evidence of safety or efficacy, particularly enduring efficacy (i.e., effectiveness over time) of switching biosimilars in children with IBD. In the absence of this evidence, we cannot conclude that biosimilar switching is either safe or effective in children with diseases of different physiology than those of the trial participants. To be clear, NASPGHAN supports the initiation of a biosimilar or an interchangeable biologic in pediatric patients. However, considering the young age of onset and earlier initiation of biologics in pediatrics, this is the population most vulnerable to potential immunogenicity, loss of efficacy, and adverse effects from multiple non-medical switches throughout their lifetime.

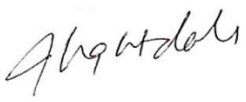
Considering the lack of studies showing safety or efficacy of switching biosimilars in children with IBD, biosimilar manufacturers should be provided instruction in the FDA's guidance about how to communicate biosimilar interchangeability for products that qualify for such designation. It is critically important that providers who prescribe biologics for children clearly understand when a product has been provided the designation of interchangeability. Further, it is important that insurance companies and pharmacy benefit managers (PBMs) that adjudicate requests for treatment authorization understand the significance of the distinction between biosimilars and interchangeable biologics in the pediatric population. While the FDA may believe the Purple Book Database of Licensed Biological Products is a more appropriate resource to convey information regarding interchangeability, we strongly recommend that pediatric use information for a biosimilar product's label include an interchangeable designation when and if clinically applicable.

Conclusion

Biologics have significantly advanced the management of children with IBD. However, the current common practice of insurance companies mandating multiple switches between biosimilars risks loss of efficacy from these important medications, and risks endangering access to the limited effective medications currently available for the vulnerable population of children with IBD. NASPGHAN is seeking the FDA's help. Specifically, pediatric short- and long-term studies are needed for biologics and biosimilars to evaluate safety, efficacy, bio-therapeutic-equivalence, and immunogenicity. Further, there is a need for studies to assess the risk of multiple biologic switches, considering the earlier initiation of biologic and more severe, long term disease burden in pediatrics.

NASPGHAN is eager to engage with the FDA to ensure that pediatric IBD patients have safe access to effective biologic therapies. The mere availability of biologic products does not equal access. NASPGHAN needs the FDA's help to ensure these biologic products are accessible without barriers that persist due to absence of pediatric indications. For more information, please contact NASPGHAN Executive Director Margaret Stallings at mstallings@naspghan.org.

Sincerely,



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