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NASPGHAN Annual Meeting
October 5-7, 2023
San Diego, CA

September 6, 2023

The Honorable Bernie Sanders
Chairman
Health, Education, Labor, and Pensions Committee
U.S. Senate
Washington, D.C. 20510

Dear Chairman Sanders:

On behalf of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), we write concerning Section 901 of *The Primary Care and Health Workforce Expansion Act.* Section 901 would remove the distinction between biosimilars and interchangeable biologics which we believe puts children with inflammatory bowel diseases (IBD) — which include Crohn's Disease and Ulcerative Colitis — at increased risk of adverse medical events. This is a particularly concerning because of the frequency that health care insurers force patients to switch their biologic therapy, typically without the approval or even awareness of their treating physician, and, despite well-controlled disease — a tactic otherwise referred to as "non-medical switching." Blurring the lines between biosimilarity and interchangeability increases the likelihood of multiple switches.

While we appreciate your leadership and efforts to make pharmacologic and biologic therapies more affordable, if the distinction between biosimilars and interchangeable biologics is eliminated, then Section 901 should be amended with very specific language to provide protection to pediatric patients for whom studies are lacking on biologic interchangeability. Specifically, Section 901 should be revised *to prohibit* an "interchangeable" biological product from being substituted for the reference product in children under 18 years of age without the intervention or approval of the health care provider who prescribed the reference product.

We believe Congress was correct when it made the clear distinction between a biosimilar and an interchangeable biologic. The Food and Drug Administration (FDA) has decided that for biosimilars, documentation of efficacy is not needed for all of the indications of the original molecule. However, there are **no** randomized controlled trials (RCTs) published on switching the use of infliximab (IFX) or other anti-TNF (Tumor Necrosis Factor) biosimilars in pediatric IBD patients. The only data on efficacy can be derived from three published RCTs in *adult patients* — one in patients with IBD and two of these trials in patients with rheumatoid arthritis and ankylosing spondylitis. This is important to recognize because pediatric IBD is clearly not identical in pathogenesis to either adult IBD or, even more importantly, to rheumatoid arthritis. There are several examples of biologics which are effective in rheumatoid arthritis but ineffective[1] or even harmful in IBD.[2] Further, there are significant differences in the efficacy in young children with IBD compared to adults with IBD, as well as pharmacokinetics of these compounds (i.e., the patient's metabolism of the medication);[3,4] therefore, a distinction has to be made between adult and pediatric IBD patient populations when considering broad application of these recommended changes.

Because the FDA does not require documentation of efficacy for all indications of the originator biologic and because pediatric patients have been subject to insurance company policies that force them to switch biologic treatments (often without their physician's input, even though the patient is stable on his/her current biologic therapy), the distinction between interchangeable biologic products and biosimilars in pediatric populations should not be confused or diluted.

Biologic drugs have significantly advanced the pharmacological management of IBD and have substantially improved outcomes and quality of life. As a result, the biggest threat to pediatric IBD patients is not the lack of effective treatments, but barriers to care imposed by insurance companies. Utilization management tactics such as step therapy, prior authorization and non-medical switching that limit access to biologic products are pervasive among insurance companies. As we expressed in an April 11 letter *(enclosed)* to you, we are gravely concerned about the increasing number of disturbing reports from NASPGHAN members (i.e., pediatric gastroenterologists around the United States) regarding insurance company obstacles and restrictions their pediatric patients are experiencing when attempting to access prescribed biologic therapies for IBD. It is increasingly common for patients who are doing well on their therapy — sometimes months to years on a specific therapy — only to receive a denial of care by an insurance company that changes the patient's treatment as biologic products move on and off formulary, sometimes even being switched back to the originator.[5,6]

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[1] Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088 – 94.
[2] Sandborn WJ, Colombel JF, Sands BE, et al. Abatacept for Crohn's disease and ulcerative colitis. Gastroenterology 2012;143:62 – 9.
[3] Assa A, Dorfman L, Shouval DS, Shamir R, Cohen S. Therapeutic Drug Monitoring-guided High-dose Infliximab for Infantile-onset Inflammatory Bowel Disease: A Case Series. J Pediatr Gastroenterol Nutr. 2020 Oct;71(4):516-520. doi: 10.1097/MPG.0000000000002832. PMID: 32639454.
[4] Matteo Bramuzzo1 M, Arrigo S, Romano C. et al. Efficacy and safety of infliximab in very early onset inflammatory bowel disease: a national comparative retrospective study. United European Gastroenterology Journal 2019, Vol. 7(6) 759–766
[5] Constant BD, de Zoeten EF, Stahl MG, et al. Delays Related to Prior Authorization in Inflammatory Bowel Disease. Pediatrics. 2022;149(3):e2021052501
[6] Constant BD, Albenberg L, Mitchel E, et al. Prior Authorizations for IBD Biologics Delay Therapy, Impact Decision Making, and Lead to Serious Adverse Events: 2022 Nationwide Provider Survey. 2023 Digestive Disease Week Annual Meeting, Chicago, IL, USA.

We have significant concerns about immunogenicity and loss of therapeutic response when pediatric patients are switched from a reference biologic to a biosimilar and vice versa. Switches between the originator and biosimilars or between different biosimilars are not recommended in pediatric IBD patients for multiple reasons until there are studies in this population, including long-term follow-up and post-marketing surveillance which can then determine the efficacy, safety, and immunogenicity of biosimilars.[7] There is also no published evidence on the safety or efficacy of switching back to the original biologic after switching from the original to a biosimilar in patients with IBD of any age. This is a situation in which there is likely to be an increased risk of developing anti-drug antibodies to the original biologic after discontinuing it. From studies of interrupted biologic therapy, 30 percent of patients fail therapy or develop allergic or more severe reactions after restarting the same biologic.[8]

Considering the young age of onset and earlier initiation of biologics in pediatrics, this is the population most vulnerable to potential immunogenicity from multiple non-medical switches throughout their lifetime. It is clearly established in well-documented, large epidemiologic studies that children with IBD have more severe disease phenotype than in adult-onset IBD[9] which further impacts how the pediatric patient will respond to biologic agents. Hence, one of the identified factors defining high risk in IBD, and thus the exception for insurance based, non-medical switching, should be pediatric-onset disease. Children have the unfortunate unique situation with a longer lifetime burden of disease, including increased risk for progression to certain types of intestinal cancer if inflammation is not kept under appropriate control.

Without restrictions of non-medical switching, children are at risk of being repeatedly forced to switch on and off biologic therapies. Anecdotally, we all have cases where our patients have been forced to switch biosimilars multiple times and sometimes back to the originator biologic with the result being loss of efficacy or adverse reactions. The lack of data in children with IBD should not be misconstrued for safety, and it is our concern that the lack of data on biologic interchangeability in the pediatric population is not being thoughtfully considered by policymakers or regulators.

Additionally, there are differences in the medium and constituent ingredients of biological products that can increase pain and cause reactions and must be considered before switching a patient from one biological product to another. The table below highlights those differences. Citrate, for example, is an additive ingredient which results in greater pain at the injection site, and some patients are allergic to latex or have intolerance to monosodium glutamate (MSG). These differences may seem minor, but they are very important, especially when treating pediatric patients.

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[7] Dipasquale V, Cicala G, Spina E, Romano C. Biosimilars in Pediatric Inflammatory Bowel Diseases: A Systematic Review and Real Life-Based Evidence. Front Pharmacol. 2022 Mar 17;13:846151. doi: 10.3389/fphar.2022.846151. PMID: 35370732; PMCID: PMC8970685.

[8] Reenaers C, Mary JY, Nachury M, Bouhnik Y, Laharie D, Allez M, Fumery M, Amiot A, Savoye G, Altwegg R, Devos M, Malamut G, Bourreille A, Flourie B, Marteau P, Vuitton L, Coffin B, Viennot S, Lambert J, Colombel JF, Louis E; Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif. Outcomes 7 Years After Infliximab Withdrawal for Patients With Crohn's Disease in Sustained Remission. Clin Gastroenterol Hepatol. 2018 Feb;16(2):234-243.e2. doi: 10.1016/j.cgh.2017.09.061. Epub 2017 Oct 7. PMID: 28993262.

[9] M Malham, C Jakobsen, MK. Vester- Andersen, A Paerregaard, I Vind, V Wewer GastroHep. Paediatric onset inflammatory bowel disease is a distinct and aggressive phenotype—a comparative population- based study. 2019;1:266–273.DOI: 10.1002/ygh2.368 .

Table 1. Humira biosimilars are not identical.

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

Because biologic products, including biosimilars, are expensive, many patients rely on copay assistance programs. We share your goal of making biologic products more affordable for patients, but at this time, for many patients and their families, copay assistance programs are a necessity. Far too often, patients are forced to switch biologics, often without their knowledge, which requires them to apply for copay assistance with a new pharmaceutical company. This adds paperwork to physician practices and can result in delays to care when families must wait for approval of copay assistance before following through on treatment. Importantly, not all biosimilars have copay assistance programs, potentially leaving patients with increased out-of-pocket expenses after switching to a different biologic product.

We want to be clear. We do not oppose initiating a patient on a biosimilar or an interchangeable biological product. We do object to insurance companies forcing pediatric patients to switch biologic therapies against the recommendation of their treating physician and/or without the physician's knowledge and consent. The option for a physician to write "dispense as written" (DAW) and maintain the patient on the original biologic is an illusion. Insurers routinely respond to such requests stating they are not mandating switches but will no longer pay for the original biologic medication. This practice essentially mandates the switch from a financial perspective, regardless of DAW prescription.

There are actions Congress can take to improve patient timely access to prescribed care, including prior authorization reform and passage of the *Safe Step Act.* We believe the exceptions to step therapy protocols in the *Safe Step Act* will help patients access their recommended therapies faster, thereby avoiding adverse treatment reactions and medical complications. We believe the bill could be improved by making the following changes:

- at (b)(3) "Any treatments otherwise required under the protocol are contraindicated for the participant or beneficiary or have caused, or ~~are likely~~ have the potential to cause, based on clinical, peer-reviewed evidence, an adverse reaction or other physical harm to the participant or beneficiary.

- at (b)(5) "The participant or beneficiary is stable for his or her disease or condition on the prescription drug or drugs selected by the prescribing health care provider and has previously received approval for coverage of the relevant drug or drugs for the disease or condition by any group health plan or health insurance issuer, including the participant's or beneficiary's current group health plan or health insurance issuer.

- add the following new section at (b) as a circumstance for exceptions approval: "The participant or beneficiary is under 18 years of age."

We also believe there is an urgent need for reform of prior authorization practices used by payers, including blanket denials for use of a drug for an indication that is not approved by the FDA for use in pediatrics. We welcome an opportunity to offer recommendations to ensure pediatric patients are also protected from egregious prior authorization practices which frequently delay or obstruct necessary medical care. We appreciate the inclusion of prior authorization reforms under Section 801 of *The Primary Care and Health Workforce Expansion Act* and ask that it be made clear the language also applies to office-administered drugs and biologics.

We appreciate the opportunity to share our concerns on behalf of our patients and offer ourselves as a resource. Should you have questions, please do not hesitate to reach us by contacting Camille Bonta, NASPGHAN policy advisor, at 202-320-3658 or cbonta@summithealthconsulting.com

Sincerely,

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