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Director, Center for Drug Evaluation and Research

Peter Marks, MD, PhD
Director, Center for Biologics Evaluation

Nikolay Nikolov, MD
Director, Office of Immunology

Robert Califf, MD
Commissioner, Food and Drug Administration

Re: Drug approval for children with Inflammatory Bowel Disease

Dear Drs. Cavazzoni, Marks, Nikolov, Califf:

The past 25 years have witnessed remarkable advances in treating inflammatory bowel disease (IBD), from the introduction of monoclonal antibodies to the recent advances in small-molecule therapy. Unfortunately, these life-altering therapies have been almost exclusively approved for adult patients and because of inordinate delays in pediatric drug approval, children continue to be therapeutic orphans. Two anti-TNF biologics, infliximab and adalimumab, received pediatric approval for Crohn's disease eight (2006) and six years (2012), respectively, after adult approval. Subsequently, these two drugs received approval for ulcerative colitis six (2011) and nine (2021) years, respectively, after adult approval. No other advanced therapies have been approved for children. It is now 10 years since adult approval of vedolizumab and eight years since the approval of ustekinumab, and neither are close to being approved for pediatric use. Both agents are considered safe and effective in adults with ulcerative colitis, yet children with corticosteroid-dependent ulcerative colitis are invariably denied these medications by payers unless they have failed anti-TNF therapy. None of the recently approved or emerging biologic and small molecule therapies currently used to treat adults are within a decade of approval in children. These ongoing delays significantly compromise the care of children with IBD as off-label use occurs without the benefit of adequate dosing and safety data. Extrapolation of efficacy and dosing is configured by pediatric gastroenterology experts based on knowledge and experience in use of drugs but is far from optimal management or the expected standard for any adult patient, let alone a vulnerable child. Third party payers refuse or delay approval of effective medications. Over the past two decades, the pediatric IBD community has repeatedly engaged with regulatory agencies as well as pharmaceutical and biotechnology companies to remedy this situation with minimal success.

There are many reasons for this shameful situation. Although the PREA legislation supports the concept of adults first, it does not decrease the burden on FDA to accelerate pediatric drug development. Accountability and enforcement by the FDA or the Division of Gastroenterology are

minimal, and timelines are not followed. Despite incentives through BPCA, pharmaceutical and biopharmaceutical companies have little interest in advancing pediatric initiatives in a timely manner. The financial return for pharmaceutical companies comes from use in adults not children, and anything perceived as slowing down adult approval quickly becomes unacceptable for pharma and regulators.

Previously, the Division of Gastroenterology and Inborn Errors Products made progress in facilitating and expediting pediatric drug development globally. EMA, PMDA and FDA published a series of articles on the issues impacting pediatric drug development in IBD. Many of these efforts culminated in the Gastroenterology Endpoints and Advancement in Therapeutics (GREAT) conferences at FDA discussing and presenting these issues with cross-functional stakeholders. However, the momentum from these important efforts has dwindled with the current FDA administration resulting in the existing unacceptable *status quo*. The EMA, on the other hand, has engaged in substantive discussions with clinicians on how to move trials forward. Very recently, Hiroshi Suzuki, director of the Japanese PMDA explicitly stated PMDA's goal of accelerating pediatric drug development. "It would be great if we could promote the simultaneous development of adult and pediatric drugs and the number of medicines that can be used in children increases," The FDA Division of Gastroenterology is now an outlier in correcting the disparity in regulatory approaches in pediatric IBD. Project Orbis, the initiative of the FDA's Oncology Center of Excellence, provides a framework for the collaborative review of promising new cancer treatments among international regulatory partners and could serve as a model for expediting the approval of medications to treat children with IBD.

We have actively participated in drug development for pediatric IBD since the start of the biologic era in 1998. Sadly, we now realize that the system in the U.S. is broken and that we can no longer support efforts that maintain a culture that denies children with inflammatory bowel diseases timely access to effective and safe medications. The fix to this situation is not difficult to conceptualize or operationalize. Timely availability of new therapies for children can **only** occur with adoption of **"full extrapolation"** of efficacy from well-powered placebo-controlled trials in adults, dosing and exposure response studies performed in children **prior** to adult approval, and post-marketing real-world safety monitoring. The Division of Rheumatology has used this paradigm for children with arthritis along with the phase 4 safety registry (CARRA) to meet regulatory requirements for over a decade. Ironically, the therapeutic agents used in management of JIA are often the same as the medications used to treat children with IBD. There can be no justification for the same medications being approved for children with arthritis while being denied for children with IBD.

We are cautiously encouraged by the recent publication of Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment Guidance for Industry by the Division of Gastroenterology. We anticipate a robust discussion on the utility of various endpoints and are optimistic that these discussions will result in agreement on what is both feasible and meaningful. At the same time, we are disheartened by the lack of progress in statements in support of full extrapolation of efficacy.

To quote from the Guidance:

"For drugs intended to be administered chronically, we recommend a blinded treatment period of at least 52 weeks to assess both efficacy and durability of response over time and to ensure adequate longer-term exposure to characterize safety"

"Sample size should be sufficient to ensure collection of data on an adequate number of subjects through week 52 to inform the efficacy and safety of the drug. FDA recommends a sample size of at least 50 to 60 subjects per treatment arm…."

The writers of this letter believe it is imperative that the emphasis of pediatric studies should be on PK/PD in children of varying ages with inclusion of adequate numbers of children <30 kg. Working out doses that provide data on exposure response in children are critical and can be guided by previous adult studies. This approach has been repeatedly emphasized in numerous peer reviewed publications. The pediatric community and patients/families will support the completion of these studies.

With the burgeoning number of available therapies in adults there is little chance that any currently licensed drug for adults with IBD will successfully enroll 100 or more children in a trial. Families will not agree to participation in a clinical trial if their child can obtain off-label medication. Furthermore, the opportunity to accrue PK/PD data will be lost. The requirement for extra unnecessary procedures in current pediatric trials is an additional disincentive to enrollment. We have squandered precious time. but there is no reason that the current failed paradigm cannot change. Without significant modification of the current approval process, it is quite possible **no** new therapies will be approved for children with IBD.

The lengthy process of approval for current and future therapies for children with IBD needs to be reformed. Tolerating a lower standard of care for children with IBD than that required for adults is unacceptable. Children are being harmed. Meaningful, transparent, collaborative discussions with the FDA along with families, healthcare providers, and pharmaceutical /biological manufacturers are essential to identify and implement effective solutions to rapidly remedy this situation.

Respectfully,

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