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June 1, 2014

The Honorable Fred Upton
Chairman
Energy and Commerce Committee
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Diana DeGette
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Upton and Congresswoman DeGette:

On behalf of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), I thank you for your leadership and commitment to advancing biomedical innovation and getting new treatments to patients more quickly. We applaud the launch of the 21st Century Cures Initiative and welcome the opportunity to be part of the dialogue. We therefore are pleased to offer the following thoughts in response to your first white paper, "21st Century Cures: A Call to Action" and look forward to working with you.

With more than 1,500 members, NASPGHAN is the leading society in the field of pediatric digestive diseases. NASPGHAN's mission is to improve quality of care and health outcomes for infants, children and adolescents with disorders of the gastrointestinal tract, the liver and nutritional conditions by promoting advances in clinical care, research and education.

What we hope to convey in these initial comments is that many aspects of the discovery, development and delivery process are unique to pediatrics. We therefore strongly encourage you to consider a future white paper and hearing or roundtable that specifically addresses issues associated with bringing drugs, devices, and other medical therapies to pediatric patients. NASPGHAN values its partnerships with the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) and supports their missions to advance research and to ensure the safety and efficacy of new and promising treatments. Still, barriers exist that hamper innovation and patient access to promising therapies. In these comments, we hope to shed light on some of these barriers as a basis for a future dialogue with you.

***Innovation***

The NIH is the central driver of innovation in this country, particularly in academic centers. Yet, the biggest barrier to innovation is the lack of adequate federal funding for biomedical research. Even though the scientific and public health need is great, the NIH budget has dropped 22 percent ($6 billion) since 2003 when accounting for inflation. A decade ago, the NIH funded nearly one out three grant applications. In

FY 2013, the NIH success rate was 16.8 percent. As NIH Director Francis Collins, MD described at an April 2, 2014 Senate hearing, "We are not limited by ideas, we are limited by resources." We ask Congress to commit to increasing the NIH budget starting with a $2 billion increase to the NIH budget in FY 2015 for a total funding level of $32 billion. We also urge Congress to consider the impact of budget instability, including the effect of sequestration and budget cuts, on our nation's researchers. An increase in the NIH budget must be accompanied by a stable trajectory of funding that will instill confidence in our research workforce, otherwise we risk losing a generation of scientists, as well as academic physician investigators, who are so vital to taking research from bench to bedside.

Last year, NASPGHAN released an updated pediatric gastroenterology research agenda which includes six key clinical categories: inflammatory bowel disease, functional and motility disorders, liver disorders, pancreatic disorders, allergy/intestinal failure/infection, and nutrition disorders. There are so many unanswered questions that remain in each of these areas and for which research is so desperately needed.

***Regulatory Issues***

Along an increased federal investment in medical research, maintaining our country's leadership in innovation requires a regulatory structure that promises safety and efficacy of drugs, devices, and therapies. The FDA is the government agency charged with evaluating safety and efficacy of drugs, and also ensuring the safety of patients who are enrolled in clinical trials. Over the last 15 years, the FDA has expanded its oversight greatly. Now, the FDA is actively regulating not only industry sponsored studies aimed at bringing drugs to market, but also small scale studies being conducted at academic medical centers. The process by which academic investigators now need to conduct interventional studies involves applying for an "investigational new drug" (IND) application and submitting reports similar to industry. The same pathway used for industries trying to get a new drug to market is being applied to physicians who want to study an old drug in their clinics or practices. The regulatory paperwork is a time-consuming process that cannot be easily overcome by academic researchers, especially for pediatric studies. Unlike companies with large budgets and regulatory departments, academic investigators have limited time and resources. Therefore, many of our talented young investigators are choosing to abandon interventional studies altogether, or to leave academia for industry where they have the resources to go through the FDA process. Innovation at a "grass roots" level is discouraged.

Recently, the FDA has developed draft guidance for clinical researchers for determining whether human research studies can be conducted without an IND application. In this guidance, even foods that are being studied to treat diseases may soon be required to file IND documents with the FDA. In the guidance, the FDA broadened its interpretation of when an IND is required for a food study, including studies related to infant formulas and probiotics. As NASPGHAN has conveyed to the FDA, its draft guidance establishes that an individual academic researcher who wants to study whether a dietary change may treat a specific condition (e.g., malnutrition or allergic colitis), now has the same IND responsibility as a drug company developing an investigational drug.

Very few academic physicians want to make labeling claims, including those for foods or dietary supplements. Researchers at universities have limited interest in marketing claims, or profits. They simply want to know if a treatment works. Such studies gather more formal data on interventions that are commonly being used in clinical practice. Researchers with access to limited research dollars cannot risk study delays and otherwise unanticipated added study requirements. If the FDA desires to regulate all academic investigational trials through the IND mechanism, NASPGHAN has encouraged the FDA to consider the limited resources academic investigators have and work closely with such investigators to simplify the IND process. The pediatric gastroenterologists within NASPGHAN will gladly partner with

FDA to educate the academic community about clinical research and about the regulatory pathways that serve as the foundation to protect the safety of the U.S. clinical trial participants.

***Access to Medications for Children***

In considering urgent changes that are needed so children under 18 years of age can access new therapies already proven to work in adults, we suggest evaluating the current mechanisms by which drugs are tested and approved in children under 18 years. Currently, in order for a new drug to be approved for pediatric use, the current regulatory pathway requires that separate, phase 3 pivotal pediatric trials be performed to demonstrate safety and efficacy in children. The consequence has been that after a drug is FDA approved, licensed and available to adults with the same disease, it can take more than a decade until the drug is tested for children suffering from the same condition. As an example, the only drugs FDA approved for treatment of irritable bowel syndrome (a very common pediatric disorder) have only been approved for use in adults, despite one of these drugs having been on the market for more than six years.

In 1982, the FDA published a statement on "off -label" use of medications (see Appendix 1) that, to the best of our knowledge, has not been updated. The FDA statement wisely concluded that "'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature." In other words, drugs approved in adults could be utilized in children if medically appropriate. Recently, however, insurance companies have begun denying the use of newer drugs in that have been proven to be effective in patients over 18 years to patients under 18 years on the grounds of "off-label use," even though the FDA does not state such use is inappropriate. Physicians must then go through an elaborate process of appeals to get the medication for their patients.

The end result of this current state of affairs has been the emergence of a two-tiered health system. Those families with resources will find physicians with the skill set to use these medications off-label, often times at great expense to families since insurers often consider such use as "experimental" and not covered. Those without such access to care continue to suffer without these therapies. Therefore, the most vulnerable of our children remain at greatest risk.

It is important to note that while the current system emerged out of an "abundance of caution" for our children, it is rooted more in emotion than science. For many conditions, the biology of the disease is similar whether an individual is six or 60 years old—although the severity of the condition is often most impactful on the young necessitating a greater need for newer therapies. Also, using 18 years of age as a division between pediatric and adult drug development has its roots in law and not physiology. We would propose that along with adult drug development, new agents undergo phase 2 testing in young patients to establish dose-exposure relationships. Phase 3 trials that demonstrate efficacy can proceed and pediatric efficacy can be extrapolated from adult data. Having established the dose-response from pediatric phase 2 testing, an approval pathway with known pediatric dosing can then go forward for agents with disease-specific proven efficacy.

The remaining issue will be establishing pediatric safety. The current state of drug delivery is that once a drug is available, there is an off-label pediatric use that often outnumbers any given number of subjects that have been included in phase 3 pediatric trials. Rather than capturing this real-world potential repository for long-term pediatric safety, the data go uncollected. It is proposed that pediatric safety continue to be partly inferred from phase 3 testing, as is the current practice. Pediatric specific safety issues have always been best established through post-marketing surveillance. As such, the suggested pathway should also require drug companies to establish and maintain a well-designed, long-term patient

outcome registry. This would be a more effective expenditure of drug company resource investment than a separate, likely small, pediatric phase 3 trial and, in this way, rare pediatric specific events can be captured.

***Conclusion***

Over the past four decades, major breakthroughs and achievements in basic biomedical science have supplied unprecedented potential information for improving human health. The need for properly designed and conducted pediatric clinical trials and pathways to encourage individual investigator-initiative research has never been greater. We hope the 21st Century Cures Initiative will prominently feature children, help encourage innovation, and speed the delivery of new treatments to pediatric patients. Our organization, NASPGHAN, is pre-eminent pediatric professional organization focused on the treatment of children with digestive and liver diseases. As the voice for pediatric digestive health, we look forward to serving as a resource to you as you continue your mission to improve our nation's health care.

NASPGHAN appreciates consideration of our comments, and we hope that you will look toward our organization as a resource on this issue. Please contact NASPGHAN's Washington representative, Camille Bonta, at cbonta@summithealthconsulting.com or (202) 320-3658 should you have any questions or desire additional information.

Sincerely,

Athos Bousvaros, MD
President
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

**Appendix 1**

April, 1982, FDA Drug Bulletin
re: "Use of Approved Drugs for Unlabeled Indications"

Department of Health and Human Services
Public Health Service Food and Drug Administration, HFI-22
Rockville, Maryland, 20857
FDA Drug Bulletin: Information of Importance To Physicians and Other Health Professionals

April 1982, Volume 12 Number 1, Pages 4-5

"Use of Approved Drugs for Unlabeled Indications"

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners. Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which the FDA has approved. These are commonly referred to as the "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by the FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacture to the FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.