NASPGHAN
PO Box 6
Flourtown PA 19031
215-233-0808
Fax 215-233-3918
Email:
naspghan@naspghan.org

April 7, 2014

Margaret Hamburg, M.D.
Commissioner
Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm.1061
Rockville, MD 20852

Re: FDA-2010-D-0503; Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug (IND) Applications – Determining Whether Human Research Studies Can Be Conducted Without an IND; Reopening of the Comment Period

Dear Commissioner Hamburg:

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) thanks the Food and Drug Administration (FDA) for re-opening for public comment Section VI, Part D of the Guidance for Clinical Investigators, Sponsors, and IRBs for determining when an IND is needed for human research studies.

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.

NASPGHAN appreciates that the September 2013 Guidance was issued in an attempt to provide potential sponsors, clinical investigators, and sponsor-investigators an overview and some clarity of IND requirements. On March 5, NAPSGHAN was a participant at a meeting with representatives from the Center for Food Safety and Applied Nutrition (CFSAN). Per our understanding, the Guidance was not issued as a response to safety concerns, but rather as an interpretation of the law and does not constitute new policy.

However, we are concerned that the consequence of the FDA's broadened interpretation of what food studies require an IND will be the establishment by IRBs at academic institutions of blanket policies that will require all food studies to obtain an IND. Most IRB administrators and members will not be able to sift through the legal

and regulatory nuances of food research. Without expertise in regulatory background, it is challenging to differentiate between what research studies intend to "evaluate the nutritional effects of a food" and what studies intend to "evaluate other effects of a food on the structure or function of the body." Thus, the consequences of the Guidance may result in a reduction of investigator initiated nutrition studies at academic medical centers due to additional regulatory burden. This has the potential to slow the advancement of nutritional research, especially in pediatric populations. **We, therefore, hope the FDA will carefully reconsider its Guidance with the premise that food, nutrition and dietary supplement research should be supported using the established framework for safety (i.e., the IRB process) and best clinical practice as determined by physicians.**

At the core of our concerns is the definition of a drug under the Food, Drug and Cosmetic Act to include "articles (other than food) intended to affect the structure or any function of the body," and, more significantly, the interpretation of the "other than food" exception. As the Guidance highlights, infant formula is not a drug when it is intended to affect the structure or function of the body as food and the desired effect is derived from the product's character as a food (its taste, aroma or nutritive value). However, a clinical investigation of the same formula will require an IND if its intended use is other than providing taste, aroma or nutritive value because it is no longer considered a food, but, instead, a drug. Consequently, a 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.

The IND Guidance may require an academic investigator studying food's impact of disease to use the same pathway for an IND as a company developing a drug. This single IND pathway constitutes a costly and 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. In addition, very few academic physicians want to make labeling claims for foods that will result in commercial benefits, marketing claims, or profits. They simply want to gather more formal data on interventions that are commonly being used in clinical practice, such as changing infant formulas in colic or food allergy.

At times with studies of dietary supplements, such as probiotics, FDA IND reviews have requested that adult safety studies be conducted before a pediatric study. Such requests provide a major impediment to investigators at children's hospitals, who have a limited ability to enroll adults in studies. For example, there are many studies of probiotics in pediatric disease that are conducted in Europe. Some U.S. investigators are skeptical about the results and would like to replicate them here, as the products are already widely available and being used here. If FDA requires an adult study before an IND will be granted for a pediatric study, it is highly likely the pediatric investigator will abandon his/her plan and focus on other research efforts. Therefore, these dietary and nutritional products will continue to be used by parents and children based on the European data, without independent validation by U.S. investigators. We would encourage the FDA to evaluate the medical literature and examine the major discrepancy between the number of pediatric probiotic studies being performed in Europe compared to those being performed in the United States in the last decade. While the regulatory issues are only a part of the impediment to doing such research in this country, they are a major part.

As a more specific example, a pediatric gastroenterologist researcher has recently successfully treated several of his patients with recurrent *Clostridium difficile* (*C. difficile*) infection with an over-the-counter prebiotic. This was preferable to families, who had expressed concern about repeatedly exposing their children to antibiotics. In the spirit of advocating for other patients with recurrent *C. difficile* infections and to advance generalizable science, the physician drafted a research protocol and submitted it to an institutional IRB. The physician knew an IND exemption from the FDA would be needed because the product being studied was a dietary supplement as per 21 CFR Part 312.2. To delineate: 1) the product

was labeled and marketed as a nutritional supplement; 2) the intended study was not to support any change in the manufacturer's labeling after the study; 3) the study did not involve any change in the recommended administration of the product; 4) the study would be in full compliance with IRB requirements; and 5) the study results would not be used to expand promotional claims of the product. In this case the FDA did not grant an exemption, and IRB approval was never obtained. The physician continues to use the commercially available product with continued clinical success as part of his standard of care treatment plan for patients with recurrent *C. difficile* infections. However, because of the FDA ruling, the research will not be conducted. Clinicians and investigators would benefit from the "crowd-sourced" fund of knowledge that is publically available, generalizable, and applicable from reported scientific findings of studied dietary products that are IND exempt – 21 CFR Part 312.7. Unfortunately, the proposed Guidance results in the reduced ability to translate this knowledge through clinical research to the benefit of society.

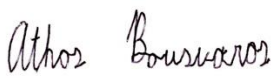
Researchers with access to limited research dollars cannot risk study delays and otherwise unanticipated added study requirements. In fact, our fear is not only that U.S. pediatric gastroenterologists will abandon research, but that the limited funding that is currently available will no longer be able fully support pediatric food and nutrition studies, or will fund fewer studies, because of the increased direct and indirect costs due to IND requirements. **If the FDA desires to regulate all academic investigational trials through the IND mechanism, we would encourage our FDA colleagues to consider the limited resources academic investigators have and work closely with such investigators to simplify the 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.

Based on the Guidance, most food studies will require an IND with the exception of those intended to evaluate the safety of a food ingredient. Per the Guidance, food and nutrition research endpoints are limited to the taste, aroma and nutritional effect. Consequently, U.S. researchers are not allowed to determine the strength of relationships between food components and the important functional endpoints they provide for the general population absent an IND. **We believe further discussion should occur by researchers and regulators before the proposed IND Guidance is implemented.**

Finally, NASPGHAN suggests that CFSAN should serve as the lead FDA center to determine when an IND is needed for food or dietary supplement research. At this time, it is unclear whether CFSAN, CBER, or CDER is the principal group developing these regulations. We look forward to further dialogue.

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