American Society for Nutrition
*Excellence in Nutrition Research and Practice*

April 6, 2014

Paul L. Ferrari
Center for Food Safety and Applied Nutrition (HFS-024)
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Docket No. FDA-2010-D-0503; Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND; Reopening of the Comment Period

Dear Mr. Ferrari,

The American Society for Nutrition (ASN) has serious concerns with the Foods portion (Section VI, D) of the September 2013 Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards (IRBs): Investigational New Drug Applications (INDs). ASN is dedicated to bringing together the world's top researchers to advance our knowledge and application of nutrition. ASN has more than 5,000 members who conduct and apply cutting-edge food and nutrition research to help all individuals live healthier lives, who might all be negatively impacted in some way by the current guidance. The purpose of this letter is to share ASN's concerns with requiring an IND for studies that will not result (nor are intended to result) in the development of new drugs or drug claims. The guidance highlights an extremely narrow view of nutrition research and presents multiple issues for the food and nutrition research community, including many possible unintended consequences, which are outlined below.

**Unintended Consequences**

***Narrow IRB Interpretation***
Traditional institutional review board (IRB) oversight has been adequate to ensure the safety of human nutrition research. The IND guidance on Foods does not respond to safety concerns and does not provide additional safety benefits beyond IRB review; the guidance may actually confuse the role of IRBs. University and medical facility IRB's may find it difficult to discern when INDs are *NOT* required for nutrition research studies and will err on the side of caution, enforcing the recommendations in this guidance for most human nutrition studies. Thus, investigators might be required to prepare an IND even when one is not needed. Similarly, the guidance creates complexities related to data safety monitoring board (DSMB) interpretation. For multi-site clinical trials, INDs will need to be shared and DSMBs for all sites of clinical trials must interpret the guidance in the same way. Additional FDA resources may be necessary to assist DSMBs and IRBs and help ensure that INDs for human research on food, nutrition and dietary supplements

9650 Rockville Pike | Bethesda, MD 20814
T: 301.634.7050 | F: 301.634.7892
info@nutrition.org | www.nutrition.org

are not prescribed if the research will not result (nor is intended to result) in the development of new drugs or drug claims.

***Negative Effect on National Policy Making***

Research to support health claims and other credible product claims designed to help consumers make healthier food choices will be diminished. Similarly, research conducted in the U.S. to support the *Dietary Guidelines for Americans,* Dietary Reference Intakes, and other dietary recommendations and policies will also be diminished. Most, if not all, studies to support health claim petitions since the enactment of the 1990 Nutrition Labeling and Education Act (NLEA) have been conducted without an IND and have been used by FDA in its decision-making process for health claims.

Health claims allowed on food products help consumers understand the demonstrated relationship between the food and its reduction of the risk of disease. The IND guidance requires that studies to demonstrate such a reduction be conducted under an IND in many circumstances, which, by definition, renders the substance a drug and therefore unable to be added to any food or dietary supplement. Without the ability to conduct human research to demonstrate such a reduction, new health claims cannot be substantiated. For new foods or food components, research conducted under an IND will render the substance a drug and therefore unable to be added to any food or dietary supplement. This creates a very circular process; substantiated health claims on food products are allowed by law, but one can only get there by following a drug approach which ultimately means one cannot market the product as a food. The guidance will severely limit nutrition research in the U.S. to support future health claims and federal dietary recommendations and policies.

***Inappropriate Research Barriers***

Filing an IND requires significant human and financial resources. The increased paperwork, time and uncertainty in filing INDs present additional research barriers for human nutrition investigators. This is particularly true when no benefit can be derived from the requirement of burdensome paperwork for research that has no intention of leading to drug development. INDs frequently lead to delayed or terminated research and increased costs. A delay in the start date of human nutrition research while IND paperwork is processed will reduce the productivity of investigators and their subsequent potential for funding. A delay may also reduce or eliminate the activity and viability of certain food components, such as a probiotics. While INDs were once the exception to the rule for human nutrition research, the IND guidance now exacerbates the burdens human nutrition investigators face. While the IND process is indeed burdensome to researchers, the primary concern is that the IND will not result in a drug or drug claim, inappropriately sets up the food or food component as a drug, and is therefore inappropriate for food and nutrition research, particularly when safety is not an issue.

***Research and Innovation Hindered***

Research in many emerging areas, including bioactives found in foods, pre/probiotics, and functional and medical foods, will be significantly and inappropriately reduced given the increased burden of an IND for research not intended to result in a drug. Filing an IND for studies on products that are intended to be marketed as foods (not drugs) will severely limit innovation and product development that is based on nutrition research in such important areas as bioactives and pre/probiotics. Filing an IND often disqualifies a substance from becoming a new dietary ingredient (NDI). Consequently, human nutrition research on food components such as bioactives found in foods would be difficult to conduct, and may not be feasible to conduct, especially in view of the concern that IRBs are likely to err on the side of requiring INDs.

Due to the new research and marketing barriers the IND guidance imposes, the food and dietary supplement industries are discouraged from conducting nutrition research. The guidance may lead the food and dietary supplement industries to conduct certain human nutrition research studies outside of the U.S., thus harming the U.S. research enterprise and economies. Nutrient needs and populations vary and research conducted outside of the U.S. may not reflect the U.S. population's dietary needs, thus harming research to support the *Dietary Guidelines for Americans*, Dietary Reference Intakes, and other dietary recommendations and policies. The guidance may also unintentionally result in certain dietary supplements and/or food components being marketed without the benefit of substantial human research on their physiological effects.

**ASN Recommendations**

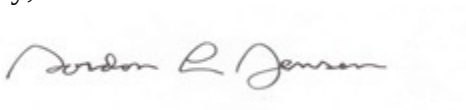
The guidance narrows food and nutrition research endpoints to solely include taste, aroma, or nutritive value and does not allow U.S. researchers to determine the strength of relationships between food components and the important functional endpoints they provide for the general population, excepting with an IND. It is inappropriate that research on nutritive and physiologic effects in a general population (such as the reduction of risk of disease and structure/function endpoints) be required to be conducted under an IND.

ASN recommends that FDA reexamine the definition of nutritive value, which has been narrowed excessively in recent years in direct contrast to the wealth of nutrition research data that are utilized by many government agencies, academic institutions, and non-profit scientific and medical organizations to promote the American public health. FDA should broaden the definition of nutritive value, at a minimum for interpretation in this guidance, to include the many nutritive, functional effects that food components provide beyond taste and aroma, including reduction of disease risk and structure/function endpoints.

ASN strongly recommends that the Center for Food Safety and Applied Nutrition (CFSAN) be the *lead* FDA Center to review the need for an IND when food- or dietary supplement-related research is involved. Center for Biologics Evaluation and Research (CBER) or Center for Drug Evaluation and Research (CDER) oversight is not appropriate for food- and dietary supplement-related research. Likewise, the current IND application and review processes are not appropriate for human research on foods, nutrients and dietary supplements since a drug development model cannot accurately be applied to food components.

Thank you for your attention to this important research issue. ASN appreciates the opportunity to comment on the Guidance since it has such a significant potential impact on food and nutrition research. Please contact Sarah Ohlhorst, MS, RD, ASN Director of Government Relations, at sohlhorst@nutrition.org or 301.634.7281 should you have any questions or need additional information. ASN staff are available to discuss these recommendations in greater detail with FDA at any point.

Sincerely,



Gordon L. Jensen, M.D., Ph.D.
ASN President, 2013-2014