

---

# Healthcare Nutrition Council

529 14<sup>th</sup> Street, NW • Suite 750 • Washington, DC 20045

February 5, 2018

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

RE: Docket No. FDA-2017-N-5101 titled “Review of Existing Center for Drug Evaluation and Research Regulatory and Information Collection Requirements”

To Whom It May Concern:

The Healthcare Nutrition Council (HNC)\* appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) regarding to its open docket titled “Review of Existing Center for Drug Evaluation and Research Regulatory and Information Collection Requirements” (Docket No. FDA-2017-N-5101).

HNC applauds the FDA for being open to identifying existing regulations that could be modified, repealed, or replaced, aiming at achieving meaningful burden reduction while allowing the Agency to achieve its public health mission and fulfill its statutory obligations. One important FDA regulatory area HNC will address is the “Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND” and its impact on Medical Foods. Medical Foods play an important role in the dietary management of patients with numerous diseases and conditions. Since the Medical Foods category was defined in 1988 (21 U.S.C. §360ee (b)(3)), several attempts to develop a clearer framework were initiated without necessarily leading to the needed result. HNC strongly believes there is a need for a broad and open dialogue with all concerned stakeholders (i.e., government, patients, manufacturers, academia and health care professionals) followed by firm and decisive actions to enact a comprehensive, efficient and science-based framework for Medical Foods. We think that such reform would reduce regulatory burden in areas where such burdens have not served a public health interest.

To achieve the ultimate goal of improving patient health outcomes, and echoing FDA Commissioner Scott Gottlieb on the FDA’s new policy steps related to stem cell therapies and regenerative medicine, “the FDA must advance an efficient and least burdensome framework as a way to help new products remain compliant with the law through a regulatory structure that does not become a barrier to beneficial new innovation”. FDA’s efforts should maintain high ethical, quality and scientific standards and prevent unscrupulous actors from being able to deceive patients, caregivers and healthcare providers.

We would like to call FDA’s attention on the need to initially review and modify a specific, unduly, and burdensome regulatory requirement that currently impacts Medical Foods, resulting in an ambiguous environment that stifles research and innovation. Focusing on the following interim revision, while a broader modernization of regulations takes place, could alleviate confusion and lead to a more efficient and less burdensome regulatory system:

- Repeal portions of “Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND”, specifically all portions related to foods including section VI(D) which indicates an investigation intended to evaluate the effects of a Medical Food on a disease (including the dietary management of a disease) would require an IND.

The suggestions are framed below in the format requested by the agency:

<b>Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determine Whether Human Research Studies Can Be Conducted Without an IND” (IND Guidance)</b>	
FDA Center	CFSAN, CDER, CBER
Citation	21 CFR part 312
Approved information collection and OMB Control Number (as applicable)	N/A
Brief description of concern	We are concerned with certain sections of IND Guidance that relate to studies involving foods, specifically the fact that FDA would expect an IND for clinical studies evaluating the effects of a Medical Food on disease, including dietary management of disease. An IND is by its very name intended only for an investigational new <i>drug</i> . Requiring an IND for conducting a study that involves nutritional research and food is unprecedented and unsupported by the Federal Food, Drug and Cosmetic Act, particularly for research on the effect of Medical Foods on diseases, as Medical Foods are required by statute to be intended for the dietary management of a disease or condition. Requiring an IND also significantly delays nutrition research timelines by requiring the upfront completion of an IND application from nutrition researchers who likely have no experience with the investigational drug process. This has created unnecessary obstacles for nutrition research in the area of Medical Foods. HNC has several additional concerns that are outlined in detail below.
Available data on cost or economic impact	Available Upon Request
Proposed solution	HNC recommends FDA repeal portions of the IND Guidance, specifically all portions related to foods including section VI(D) which indicates an investigation intended to evaluate the effects of a Medical Food on a disease (including the dietary management of a disease) would require an IND.

Detailed comments to follow:

We appreciated the Agency re-opening the final guidance as described above (hereafter referred to as IND Guidance) for public review and comment in February 2014, given the previous version of the IND Guidance had never before referenced food investigations. This provided the research community with an opportunity to comment and elaborate on important distinctions between food-related research and

drug-related research. Numerous comments submitted to FDA expressed serious concerns about the food-related aspects of the IND Guidance and its implementation. The final version of the IND Guidance represents a fundamental change in FDA's interpretation and application of food regulations (especially the delineation between food and drug definitions) and the investigation of the role of nutrition in health, both of which are now having broad implications on clinical research in the U.S. Specifically, FDA concluded in the IND Guidance that an investigation intended to evaluate the effects of a Medical Food on a disease would require an IND because such an investigation would be evaluating a drug use. However, this conclusion directly conflicts with the statutory purpose of a Medical Food, which is to assist *in the dietary management of a disease or condition*. Investigation of a Medical Food's effects on a disease does not inherently make that Medical Food a drug; rather, it comports with the intended use of Medical Foods set forth by statute.

Although FDA eventually stayed portions of the final IND Guidance in October, 2015, HNC still remains concerned about its intent and effect on clinical investigation of Medical Foods consistent with the statutory definition, especially the new, misplaced burden on Institutional Review Boards (IRBs) and academia. Requiring an IND for conducting a study that involves nutritional research and food is unprecedented and unsupported by the Federal Food, Drug and Cosmetic Act (FD&C Act), particularly for research on the effect of Medical Foods on diseases, as Medical Foods are required by statute to be intended for the dietary management of a disease or condition. Furthermore, it fails to address a legitimate public health need, significantly discourages both research and innovation, and incrementally and unnecessarily increases regulatory burden on industry, academic researchers and FDA. IRBs have long served the purpose of certifying that appropriate procedures are in place to ensure the ethical conduct of clinical research and protect the safety and interests of clinical research subjects. Further, nutrition and food research is distinct from research related to the development of new drugs as there is no intent to market foods as drugs or make drug claims, and the authority under which FDA regulates each is likewise distinguishable: IND requirements pertain to drugs and not foods, and evaluating the effects of a Medical Food on a disease does not inherently cause that Medical Food to be a drug.

Despite FDA's partial stays on certain sections of the IND Guidance that relate to studies involving foods, a key section communicating that FDA would expect an IND for clinical studies evaluating the effects of a Medical Food on disease remains in effect. Because Medical Foods are, by statutory definition, intended for the dietary management of diseases or conditions, this has created unnecessary obstacles for nutrition research in the area of Medical Foods. As IRBs and researchers attempt to comply with the IND Guidance in good faith, the lack of clarity is causing confusion and unnecessarily burdening important clinical research and innovation. Implying or otherwise stating that the IND requirements now apply to food and nutrition research, including research conducted on Medical Foods, results in objectionable consequences. These include but are not limited to:

- **The addition of new regulatory and resource burdens:** The IND process would significantly delay nutrition research timelines by requiring upfront completion of an IND application from nutrition researchers who likely have no experience with the investigational drug process, awaiting FDA approval of an IND application, and ultimately slowing time-to-market for any innovative developments that stem from such nutritional research. FDA's processing and approval of an IND in these cases is also complicated by the fact that although the Center for Drug Evaluation and Research (CDER) routinely processes INDs for clinical studies on drugs, this Center has yet to establish a standard procedure for processing INDs for foods. Likewise, the

Center for Food Safety and Applied Nutrition (CFSAN) is lacking a formal process to receive, review and act upon an IND Application.

- **FDA Overstepping of Statutory Authority:** There is a lack of consistency between the IND Guidance and the FD&C Act’s statutory definition of food, as there is no basis in FDA’s statutory authority for requiring an IND application for food and nutritional research. The definitions in the FD&C Act establish a clear distinction between drugs and foods. Congress did not grant FDA the authority to require an IND for foods in the FD&C Act. A food that is contemplated to be tested in a clinical trial to assess whether it affects the structure or any function of the body of man remains a “food” under the FD&C Act. This remains true for Medical Foods, which are expressly intended for the dietary management of a specific disease or condition; clinical evaluation of a Medical Food’s use in the dietary management of disease or condition is *not* evaluation of a drug use, but rather evaluation of a Medical Food use. The intended use of a Medical Food is not to treat, cure, mitigate, diagnose or prevent a disease and Medical Foods cannot be marketed as such. Further, requiring an IND for the clinical research of Medical Foods directly contradicts Congressional intent of the Orphan Drug Act in removing Medical Foods from the drug category (21 U.S.C. §360ee).
- **Failure to Address a Legitimate Public Health Need:** Force-fitting applicable IND rules onto food and nutrition research, the IND Guidance significantly increases regulatory complexity to multiple stakeholders in this field and, at the same time, does not address any identified public health problem. Identifying such a public health need is ordinarily a prerequisite for a new rule or substantive change in policy. If FDA is concerned with violative disease claims, the Agency can take other more appropriate enforcement actions instead of unnecessarily constraining clinical research. Even after the partial, temporary stays this IND Guidance may continue to negatively impact the quality and quantity of scientific evidence necessary to adequately inform the development of new and innovative Medical Foods. The impact may not be isolated to food manufacturers and marketers, but could also create hurdles for individual academic research and the conduct of clinical research necessary to develop, update and refine health claims, dietary guidelines and nutrient requirements, which inform public health policy. Furthermore, requiring an IND for new research does nothing to attenuate violative Medical Foods currently in the marketplace.
- **The Conflict With and Violation of the FD&C Act:** The FD&C Act defines drugs, in part, according to the article’s “intended use” and distinguishes such articles from those that are otherwise classified as foods. More specifically:
  - Section 201 of the FD&C Act (21 U.S.C. §321) defines “food” and “drug” in relevant part as follows:
    - (f) The term “food” means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.
    - (g)(1) The term “drug” means ... (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (**other than food**) intended to affect the structure or any function of the body of man or other animals.... (**emphasis added**).

The parenthetical phrase “(other than food)” in the definition of drug draws a clear line with respect to a food being studied for its potential to affect the structure or any function of the body of man. Any such food is not a “drug,” but remains a “food” for all relevant purposes under the FD&C Act. The IND Guidance, however, conflates these two different statutory classifications. HNC recognizes that the IND Guidance carved out studies evaluating the intended structure or function effect when such effect is derived from the nutritive value of the food (either taste, aroma, or nutritive value) and also recognizes that FDA later stayed the portion of the IND Guidance which implicated studies evaluating the intended structure or function effect when such effect is *not* derived from taste, aroma, or nutritive value. However, the IND Guidance appears to narrowly interpret structure or function derived from nutritive value to studies which essentially quantify serum nutrient levels (example given is a study of the effect of iron consumed through food on hemoglobin levels) but considers studies evaluating a food or food component’s physiological effect as intended drug research (example given is a study of the effect of soy isoflavones on bone metabolism). This is entirely inconsistent with the historical interpretation industry has come to understand regarding a food’s role on the structure or function of the body. Further, it’s inconsistent with the well-understood connection of food and health and would unduly limit the advancement of nutrition science through research. Although this portion is stayed, it continues to promulgate confusion in the nutrition arena, including research involving Medical Foods when the endpoint is physiological in nature.

Further, FDA’s attempt to broaden the scope of the IND requirements to cover studies being conducted on foods (including Medical Foods) lacks credibility when these products can legally be commercially distributed. Section 505 of the FD&C Act, 21 U.S.C. §355, “New Drugs,” generally prohibits new drugs from being introduced into interstate commerce without an approval from FDA. In order to put an unapproved drug in interstate commerce for clinical testing purposes, new drugs are subject to Section 505(i) of the FD&C Act. This Section contains the statutory language requiring FDA to promulgate regulations to establish procedures for filing, and FDA approval of, IND Applications.

(i)(1) The Secretary shall promulgate regulations for exempting from the operation of the [new drug application requirements] drugs intended solely for investigational use by experts qualified by scientific training and expertise to investigate the safety and effectiveness of drugs

The corresponding regulation promulgated by FDA, 21 C.F.R. Part 312, entitled “Investigational New Drug Application” has a “Scope” and “Applicability” section that limits the coverage of the regulations to “drugs”:

312.1 Scope. (a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND’s).

312.2 (a) Applicability. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug and Cosmetic Act...

Section 505 of the FD&C Act does not prohibit the shipment of foods (including Medical Foods) in interstate commerce, and, as discussed above, the investigation of a Medical Food as part of the dietary management of a disease or condition does not make that Medical Food a drug. Therefore, an exemption from the New Drug provisions of the FD&C Act pursuant to an Investigational New Drug Application for such articles is not supported within the scope of this regulation.

- **Failure to Comply With Both the Administrative Procedures Act and the Congressional Review Act:** FDA must comply with the Administrative Procedures Act (APA) when it seeks to change its practices and established policies on which products are subject to the IND requirements. The issuance of the IND Guidance marked the first time FDA expressly stated that foods are subject to the IND regulations. FDA may not depart from a precedent without providing reasoned explanation for the change. (*Greyhound Corp. v. ICC*, 551 F.2d 414, 416 (D.C. Cir. 1977)). The APA requires notice-and-comment rulemaking whenever a federal agency wants to act in a way that materially changes established burdens and benefits, “by which rights or obligations have been determined, or from which legal consequences will flow.” (*Bennett v. Spear*, 520 U.S. 154, 178 (1997)). FDA was acting to substantively change the “rights and obligations” of food manufacturers and nutritional researchers by extending the IND requirements to articles of food, including Medical Foods when being investigated for use in the dietary management of a disease (which does not make such products “drugs”). Additionally, FDA must comply with the Congressional Review Act when it issues any statement – even in the form of a Guidance Document – of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency” (5 U.S.C. § 551(4)). Despite FDA’s classification of the IND Guidance as final, before it can become effective, FDA must submit a report to both Houses of Congress and to the Comptroller General.

Requiring an IND to study the effects of Medical Foods on the dietary management of disease, when these products can legally be commercially distributed as foods makes little sense and does not seem to offer any benefit to the study subjects, IRBs, investigators, FDA, public health, or safety of the food supply. Therefore, HNC recommends FDA repeal portions of the IND Guidance, including section VI(D), which indicates an investigation intended to evaluate the effects of a Medical Food on the dietary management of a disease would require an IND, even though Medical Foods must, by statute, be intended for the dietary management of a disease or condition.

In summary, HNC appreciates FDA’s interest in pursuing meaningful reductions in regulatory burdens while continuing to fulfil its public health obligations. The above revision/recommendation is just the start of a broader dialogue HNC looks forward to having with FDA and all relevant stakeholders. As significant progress is being made on science-based, evidence-driven approaches to develop nutritional products, like Medical Foods, to help patients with the dietary management of certain diseases and conditions, the regulatory framework needs to provide a clear, consistent and scientifically sound path for these products to reach the patients who need them the most. It is critical that the FDA, its inter-agency offices and related Agencies continue focusing on ways to reduce, modify and/or repeal regulations that inhibit innovation while maintaining high ethical, quality, and scientific standards. Implementing the above recommended repeal is the first step towards an efficient, less burdensome and

innovative regulatory system. We respectfully request that the above recommendation be taken into consideration as FDA works to achieve its goals. Please do not hesitate to contact me at 202-207-1122 or mjurch@kellencompany.com if you have any questions regarding these comments or if any additional information may be helpful.

Sincerely,

/s/

Madeline Jurch, Government Affairs Manager

**\*About HNC:** The Healthcare Nutrition Council (HNC) is an organization representing the manufacturers of enteral nutrition formulas, parenteral nutrition solutions, supplies and equipment. HNC member companies are Abbott Nutrition, B. Braun Medical, Nestlé Health Science and Nutricia North America. We are committed to improving health by advancing policies that address and raise awareness of nutrition and its impact on patient outcomes and healthcare costs. This includes promoting nutritional screenings, diagnoses, assessments and appropriate and timely nutrition clinical interventions while protecting patients' access to specialized nutrition support products and services throughout the continuum of care. For more information on HNC, please visit <https://healthcarenutrition.org>.