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April 7, 2014

VIA ELECTRONIC SUBMISSION

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

RE: Docket No. FDA-2010-D-0503. Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on Investigational New Drug Applications-Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug Application.

The Council for Responsible Nutrition (CRN) respectfully submits these comments on the Food and Drug Administration's (FDA's) *Final Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards on Investigational New Drug Applications-Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug Application* (Final Guidance). CRN is the leading trade association for the dietary supplement and nutritional products industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements.[1]

CRN appreciates the opportunity to once again submit comments to FDA on this matter.[2] We believe that robust clinical investigations are essential for providing efficacious and safe dietary supplements and ensuring that dietary supplement claims are adequately substantiated. We also recognize the importance of maintaining the distinction between products that are promoted to prevent, treat, cure, or mitigate disease (i.e., drugs) and which clearly require an Investigational

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 100 companies that manufacture dietary ingredients and/or dietary supplements, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

[2] CRN Comments on Docket No. FDA-2010-D-0503, Draft Guidance for Industry on Investigational New Drug Applications--Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug Application (Jan. 11, 2011).

New Drug Application (IND), and those that are intended to be marketed as dietary supplements or foods. However, as we noted in our previous comments, the Final Guidance leaves many important questions unanswered for industry and the research community regarding the legal implications and unintended consequences of the Final Guidance on clinical research and product development. These unanswered questions are particularly troubling in light of the expansive scope of the Final Guidance, which now includes conventional foods, medical foods, infant formula, and cosmetics. It is also unclear how the agency will efficiently carry out the IND process for dietary supplements, and given the well-established safety history of many food components, the rationale for applying the IND regulations to such articles is unclear. Further, the Final Guidance creates uncertainty as to the status of potential New Dietary Ingredients (NDIs) and will ultimately stifle research and product innovation.

Although these comments are primarily focused on dietary supplements, FDA should consider our comments broadly as they apply to research and product development for all foods and food components.

The IND Framework Was Not Designed for and Is Not Suited for the Study of Dietary Supplements and Other Foods

The procedures and requirements for an IND are specific to the study of drugs and applicable to clinical investigations of products that are subject to Section 505 of the Federal Food, Drug, and Cosmetic Act (FD&CA). Section 505(a) of the FD&CA prohibits the introduction into interstate commerce any "new drug."[3] To allow manufacturers to study "new drugs," without violating the section 505 prohibition, Congress enacted section 505(i), which permits the shipment of "new drugs" into interstate commerce for the purpose of conducting clinical investigations. To implement the section 505(i) exemption for "new drugs," FDA promulgated its IND regulations in 21 C.F.R. Part 312. FDA promulgated Part 312 expressly as part of the drug approval process, and not as a way of regulating the clinical study of foods and dietary supplements. The agency made this purpose clear in the preamble to its final rule establishing Part 312, called the IND Rewrite:

> "This action is one part of a larger effort by FDA to improve the agency's drug approval process . . . The objectives of the IND Rewrite final rule are to establish an efficient investigational drug process in order both: (a) To focus FDA's attention during the early phase of clinical research on protecting the safety of human test subjects . . . and (b) to facilitate consultation between FDA and drug sponsors . . . to help ensure that the design of major clinical trials is acceptable and will support marketing approval if the test results

[3] A "new drug" is defined as, among other things, "any drug . . . the composition of which is such that such drug is not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof." 21 U.S.C. § 321(p)(1).

> are favorable. These changes are also intended to encourage innovation and drug development while continuing to assure the safety of test subjects."[4]

It is therefore manifestly clear that at the time FDA promulgated its IND regulations, the agency intended them to apply solely to articles being researched as therapeutic drugs for which new drug applications were contemplated. FDA's position in the Final Guidance that Part 312 covers the clinical study of dietary supplements and other foods is not only untenable, but also is contrary to the agency's own stated purpose in establishing Part 312.

The text of Part 312 further demonstrates the inapplicability of the IND regulations outside of the new drug approval context. For example, Section 312.7 states that the intent of the provision is to "restrict promotional claims of safety or effectiveness for the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution."[5] However, for dietary supplements or other foods that are currently legally marketed for a particular use prior to filing an IND, this section could preclude promotion of a supplement or food for that previously commercialized use if it is now the subject of an IND. The application of this provision, which is intended only for the new drug approval process, will create additional confusion and uncertainty, particularly for those ingredients that are established as Generally Recognized as Safe (GRAS) or otherwise recognized as safe dietary ingredients, and which have long been consumed safely as foods or supplements.

In addition to the legal shortcomings in FDA's imposing drug standards on food and dietary supplement research, the IND framework, as a practical matter, is not a suitable model for the study of foods, dietary supplements, and their ingredients. The IND regulations are tailored specifically to research that involves a drug, with little application to food components. The process is designed to investigate molecules for pharmacological activity and acute toxicity potential in animals, in order to test their diagnostic or therapeutic potential in humans. Drugs are often well-characterized synthetic molecules that are stable over time. In contrast, some dietary supplements and food components are derived from natural material that may have inherent batch-to-batch variability, multiple active ingredients, and other variables that make them unique when compared to drugs. To complete an IND for an investigation of this nature would be difficult if not impossible, especially for nutrition researchers not contemplating an investigation based on the drug approval process, highlighting the practical limitations of the Final Guidance.

For example, the IND process would present challenges for a fish oil product with a two-year shelf life intended for use in a five-year clinical trial. If a second lot of fish oil is introduced during the second year of the trial there may be small (but unavoidable) differences in fatty acid composition and ratios in the replacement lot, due to natural seasonal variability in the fatty acid

[4] 52 Fed. Reg. 8798, 8799 (Mar. 19, 1987).
[5] 21 C.F.R. § 312.7 ("Promotion of investigational drugs").

composition of fish used to produce fish oil. IND application reviewers, presumably without dietary supplement expertise, may struggle to understand these practical differences between dietary supplements/food components and drugs, thus making it challenging for FDA to permit the study to proceed under an IND.

Similar examples are well documented in a manuscript generated from a New York Academy of Sciences Symposium, *Probiotics: From Bench to Market*.[6] During the symposium, researchers shared their experiences and concerns with the burden and delays associated with preparing and submitting INDs to FDA. Despite the researchers following Consolidated Standards of Reporting Trials (CONSORT) guidelines, receiving Institutional Review Board (IRB) approvals, convening data and safety monitoring boards, and registering their trials on ClinicalTrials.gov, FDA still found reason to place their clinical trials on hold. CRN strongly encourages FDA to review the *Probiotics: From Bench to Market* manuscript because it provides extensive examples of how the Final Guidance's requirement to obtain an IND for a dietary supplement or food component clinical trial serves as a significant obstacle to advancing science, without necessarily improving the safety or rigor of a study.

Additional examples are found in academia, especially for post-doctoral and graduate students engaged in complementary and alternative medicine (CAM) research. Using the example in the Final Guidance regarding the role of broccoli sprouts in cancer prevention,[7] the Final Guidance would require an academic researcher conducting such a study to dedicate a significant amount of time to filling out the IND application; conducting or paying for analytical testing to determine the characteristics, potency, purity, and stability, as well as safety, of the broccoli sprout test agent (assuming these characteristics are even determinable); and, likely engaging other professionals experienced with the IND process – all in addition to meeting the research institution's requirements. Further, even if the broccoli sprout preparation is already sold as a food or dietary supplement, he/she would need to partner with the manufacturer to obtain information for the chemistry, manufacturing, and controls (CMC) section of the IND application or ask the manufacturer to dedicate its own resources to establishing a product master file that can be reviewed by FDA. As evidenced by the experienced researchers' testimonies published in *Probiotics: From Bench to Market*, completing an IND requires numerous hours and regulatory expertise that academic researchers typically do not possess. Although this type of expertise is common among those in the drug industry, that is not the case for academic researchers wishing to explore the benefits of commonly consumed foods and dietary supplements, who might as a result, be significantly delayed or unable to complete their research.

The Final Guidance also does not address how CDER or CBER will adapt its current drug-level approach to food and dietary supplement research, nor does it address how these centers will

[6] Probiotics: from Bench to Market. Annals of the New York Academy of Sciences. 2010; Vol.1212.S1:E4 – E14, available at http://onlinelibrary.wiley.com/doi/10.1111/nyas.2010.1212.issue-s1/issuetoc.
[7] Final Guidance at 16.

work with CFSAN to address the complexities of food research. The current IND regulations neither provide legal authority for CFSAN to review INDs nor do they establish a role for CFSAN at any stage of the IND process. Although we understand these centers could consult with CFSAN, the Final Guidance does not describe how such a process would work and the current IND regulations and make no reference to CFSAN in this regard or otherwise. It is also unclear whether CBER and CDER would harmonize their approaches to reviewing food, food component, and dietary supplement INDs, and how FDA would ensure the centers apply consistent approaches to reviewing such studies.

The Final Guidance Expands the Definition of "Drug", Creating Uncertainty as to the Regulatory Status of Dietary Supplements

The FD&CA excludes a dietary supplement from the statutory definition of "drug" if it is intended to affect the structure or function of the body and if it does not claim to diagnose, cure, mitigate, treat, or prevent disease.[8] However, by subjecting dietary supplements to Part 312, the Final Guidance now categorizes these products as investigational new drugs, even if the studies subject to the IND requirements will not be used in the development or promotion of new drugs, but rather will be used only to support lawful structure/function claims.

Historically, FDA has regulated products based on intended use, which is determined by the manufacturer's marketing representations and labeling of a product. Courts have consistently upheld this approach,[9] which is also supported by past agency statements.[10] FDA offers no explanation for why the agency has now chosen to focus on the intent of the *clinical investigation* to evaluate a product's intended use, and we question the rationale and legal basis for this departure from past agency practice.

We agree with FDA that a dietary supplement should not bear claims that would cause the product to be an unapproved new drug under the FD&CA. Contrary to the agency's position, however, CRN believes that if the supplement under investigation is fully compliant with IRB procedures and not represented as a drug through marketing statements, and any claims made for the supplement are lawful dietary supplement claims, then FDA should not regulate the product as a drug by applying its Part 312 procedures. Supplement manufacturers who are complying with the law and marketing products in accordance with FDA guidance related to substantiation

[8] 21 U.S.C. § 321(g)(1), further noting that such product must also meet the requirements of 21 U.S.C. § 343(r).
[9] *See, e.g., Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (citing *Coyne Beahm Inc. v. FDA*, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997), *aff'd* 529 U.S. 120 (2000)); *Nat'l Nutritional Foods Assoc. v. Matthews*, 557 F.2d 325, 333 (2d Cir. 1977) (The "vendor's intent in selling the product to the public is the key element" in the FDCA drug definition.).
[10] *See* Letter from FDA Chief Counsel Daniel E. Troy, to Jeffrey N. Gibbs (Oct. 17, 2002), at 3.

of structure/function claims should not be subject to a process which places the regulatory status of the product in question.[11]

For example, a dietary supplement may lawfully claim to support blood pressure levels already within the normal range. However, to substantiate this lawful structure/function claim, a manufacturer often must design a clinical trial to study subjects with elevated blood pressure levels – levels which may not signify a disease state (i.e., hypertension) but are at the high end of the normal range. Because FDA characterizes this endpoint as a disease endpoint, the study must be conducted under an IND in accordance with the Final Guidance, even though the study is intended to support a permissible structure/function claim and not a drug claim. This result is particularly problematic for dietary supplements because there are generally no validated biomarkers that could serve as surrogate endpoints for supporting claims related to "health promotion", "wellness", or "supporting normal structure and function". Instead, investigators need to assess effects such as lowering of blood pressure or serum cholesterol levels, or similar effects on other established surrogates, to adequately substantiate lawful structure/function claims. However, FDA views these effects as therapeutic effects and thus, disease endpoints. In turn, the agency will require the supplement or food component to be studied as an investigational new drug, which may limit how these products are marketed and regulated in the future.

This example also illustrates the potential for a dietary supplement to have a dual definition, which is likely to lead to confusion in the research community. In fact, a significant portion of clinical research conducted using dietary supplements or food components involves assessing the supplements' or food components' therapeutic (disease-related) effects. Some of this research is conducted by independent investigators who are unaware of a product's regulatory category and therefore design studies that are appropriate to their research questions – rather than conforming to the appropriate regulatory terminology and categories. As a result, many of these investigations will lead to the product's classification as an investigational new drug, even if the product will not be marketed or represented as a drug.

Another example provided in the Final Guidance further illustrates this point. In the Final Guidance, FDA states that an IND would be required for a study intended to evaluate a dietary supplement's ability to prevent osteoporosis.[12] If the same dietary supplement is being evaluated for its influence on bone mass, however, an IND would not be required. The Final Guidance therefore suggests that different regulatory requirements may apply when a dietary supplement, already available to millions of consumers, is the subject of a study using healthy volunteers

[11] 21 U.S.C. § 343(r)(6); 21 C.F.R, § 101.93(f)-(g); FDA, Guidance for Industry: Structure/Function Claims, Small Entity Compliance Guide, January 9, 2002. We also note that 21 CFR 101.93(g), which describes the criteria used by FDA to determine whether a claim is disease claim, thereby rendering the product a drug, makes no reference to the intent of the clinical investigation used to substantiate the claim.
[12] Final Guidance at 12.

intending to evaluate impact on bone mass, or when evaluated to reduce the risk of osteoporosis. This example demonstrates how determining if an IND is necessary becomes an exercise in regulatory language manipulation, rather than focusing on designing a quality study that results in the most beneficial product for consumers, where the safety of the product is already well-established.

The Status of New Dietary Ingredients

CRN also has concerns related to the study of potential NDIs and their ability to be marketed as dietary supplements. The FD&CA states that a dietary supplement may not include "an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public", unless the article was marketed as a supplement or food before the IND became effective.[13] Under the Final Guidance, however, many potential NDIs might no longer qualify as lawful NDIs because many NDI studies will now be required to be conducted under an IND. Once the existence of these newly required INDs for these potential NDIs becomes public, the article will no longer be a lawful NDI, notwithstanding the fact that the NDI would not be marketed for any drug purpose.

Requiring INDs for NDI research is also particularly problematic because a significant amount of dietary supplement and food component research is conducted independently and is not industry-initiated. As a result, a supplement company that is collecting data to submit an NDI notification to FDA may be unaware that independent studies are concurrently being conducted under an IND. If the independent investigator makes his or her study public before the product that would contain the NDI under investigation is marketed as a dietary supplement, however, then the product or ingredient being studied under the IND can no longer be marketed as a dietary supplement, or any food product. This is true even if the investigator conducted the IND with no commercial intent, as the Final Guidance makes clear that "[w]hether the IND regulations apply to a planned investigation does not depend on whether the intent of the clinical investigation is commercial or noncommercial."[14] Instead, the NDI or a product containing the NDI previously studied under the IND would require FDA drug approval before it may be legally marketed.

CRN believes that the above-mentioned scenario is a significant disincentive to conducting NDI-related clinical research and creates an additional legal grey area, as well as an obstacle to ingredient innovation for the dietary supplement industry. Given the existing uncertainties surrounding the NDI notification process, CRN encourages the agency to further consider how

[13] 21 U.S.C. § 321(ff)(3)(B)(ii). Likewise, 21 U.S.C. § 331(ll) prohibits the addition to food of an approved drug, a licensed biological product, or a drug or biological product for which substantial clinical investigations have been instituted and their existence made public.
[14] Final Guidance at 14.

the Final Guidance will affect NDI research and the ability to market NDIs. At a minimum, FDA should clarify under what circumstances, if any, an NDI also being studied under an IND (where the existence of the IND has been made public) may be still allowed to go to market as a dietary supplement, once the NDI review process is complete and the NDI's safety is established.

Effect on Nutrition Research and Innovation

The uncertainty as to how the IND requirements would apply to supplement and food research will likely result in delays and confusion in initiating such research, which is problematic given the need for this type of research. Researchers, particularly those in academia or conducting studies independent of industry, may be unaware that the intent of their investigation drives the need for an IND and may not understand the regulatory distinctions between drugs, supplements, and their respective intended uses. Thus, these researchers may be unable to appropriately design a study protocol that avoids designation as an investigational new drug and may choose to forgo the research, rather than rewrite their protocols or hire a regulatory attorney to do so.

As noted above, because of the difficulties in designing studies that measure disease-risk reduction and health promotion for purposes of supporting a lawful structure/function claim, a large number of supplements and food components are then likely to be categorized as investigational new drugs as a result of the Final Guidance, creating a *de facto* IND requirement for a significant portion of dietary supplement research studies and essentially limiting the types of nutritional endpoints that can be studied without an IND. In addition, IRBs will likely have difficulty discerning when an IND is or is not required; erring on the side of caution, however, IRBs will interpret the Final Guidance as requiring an IND for the majority of clinical studies, even if an IND is not needed. CRN is further concerned that such a large volume of IND applications would create obstacles to conducting clinical research as investigators struggle to provide the necessary information, as noted in the examples above, in addition to the increased workload for an agency with already limited resources. And although the IND regulations provide a process for a sponsor to request a waiver from FDA, this request must be submitted to the agency either in an IND or in an information amendment to an IND.[15]

In fact, upon publication of the Final Guidance, several heads of university departments of nutrition and food science who are affected by the guidance subsequently contacted FDA to express concerns about its impact on a wide range of clinical research.[16] They state that applying the IND requirements to the research of supplements and foods "would have a paralyzing effect on research in the U.S. and stifle innovation and product development." They also highlight the "confusing and contradictory" nature of the Final Guidance. A consortium of organizations

[15] 21 C.F.R. Part 312.10. Only in the case of an emergency could a request by telephone or other form or communication be used to submit the waiver request.
[16] Letter from Connie M. Weaver et al., to Janet Woodcock, Director, CDER (Nov. 13, 2013), accessed April7, 2014 from http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0503-0019.

representing the nutrition, medical, and science communities expressed similar concerns to FDA regarding the Final Guidance and its implications for nutrition research.[17]

Finally, CRN also notes that the requirement for an IND may be viewed by researchers and industry as a costly regulatory barrier. Because the food industry (inclusive of supplement research) is such a large part of the U.S. economy, there is a real risk that researchers may choose to conduct this research outside of the U.S. During the probiotics symposium discussed above, the researchers addressed the large number of clinical trials being conducted on probiotics and noted that many trials are conducted outside of the U.S. to avoid the IND process. The researchers expressed further concern that the U.S. will fall behind the rest of the world in probiotic clinical research due to the challenges associated with submitting INDs, which may hold true for other areas of nutrition and dietary supplement research as well. As HHS and USDA prepare future Dietary Guidelines, the need for additional studies performed on U.S. subjects will only increase. The Final Guidance may discourage U.S. researchers from performing this research, and other research in emerging areas that would similarly benefit the U.S. population.

Public Health Benefit Unclear

To the extent that FDA's goal in the Final Guidance is to assure that research subjects enrolled in human clinical trials will not be subject to unreasonable risk, CRN agrees with FDA that the safety of subjects is always a first priority. The application of Part 312 to the clinical study of dietary supplements and foods, however, is not necessary to ensure the safety of these subjects. There are several procedures already in place to support clinical trial safety and data transparency, including the CONSORT guidelines,[18] FDA's IRB and Protection of Human Subject requirements,[19] and the data and safety monitoring boards and registration of trials on ClinicalTrials.gov. To date, FDA has not cited any deficiency with these procedures as they relate to the study of foods and dietary supplements, so it is unclear to CRN why the scope of the IND regulations should be expanded to incorporate investigations of these products for non-drug uses.

Moreover, the Final Guidance may act as a disincentive to pursuing the type of robust research needed to substantiate claims, and therefore discourage investment in research and the scientific study of dietary supplements. And by requiring an IND for supplements that are not intended to be marketed as drugs, the Final Guidance acts in opposition to the spirit of the Dietary

[17] Letter from American Society of Nutrition et al., to Janet Woodcock, Director, CDER (Nov. 26, 2013), accessed April 7, 2014 from http://www.isapp.net/Portals/0/docs/Letter_to_FDA_re_IND_Guidance_ASN_ISAPP_signatory.pdf.
[18] Consolidated Standards of Reporting Trials encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials (RCTs). http://www.consort-statement.org/home/.
[19] 21 C.F.R. Part 56; 21 C.F.R. Part 50.

Supplement Health and Education Act of 1994 (DSHEA).[20] DSHEA notes the "benefits of dietary supplements to health promotion and disease prevention" and the use of supplements to "limit the incidence of chronic diseases, and reduce long-term health care expenditures."[21] DSHEA also mandates that "the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers."[22] However, the Final Guidance will require an IND to study many types of dietary supplements that have been safely consumed by millions of Americans for years as well as many food ingredients that have GRAS status, even when the research is conducted on a healthy population and is already subject to existing requirements for clinical trial safety. Thus, instead of advancing the public health, which is an integral part of FDA's mission, the Final Guidance instead threatens future research opportunities, discourages investment in health promotion studies, and impedes the development of and access to safe and lawful supplements.

Conclusion

For the reasons set forth above, CRN requests that FDA remove Section VI, Part D of the Final Guidance and reissue the document without this section, so that the agency can address the significant legal and practical uncertainties surrounding the implementation of the Final Guidance in its current form.

Again, thank you for the opportunity to submit these comments.

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[20] Pub. L. No. 103-417, 108 Stat. 4325 (1994).
[21] Pub. L. No. 103-417 § 2.
[22] *Id*.