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

RE: 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 Draft Guidance for Industry on Investigational New Drug Applications-Determining Whether Human Research Studies Can Be Conducted Without an Investigational New Drug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.

The Council for Responsible Nutrition (CRN)[1] is a Washington, DC-based trade association representing the dietary supplement industry. Our members include some of the largest and most well known ingredient suppliers, manufacturers, direct sellers and retailers of dietary supplements and dietary ingredients. CRN applauds the Food and Drug Administration (FDA) for developing the recently issued Draft Guidance[2]. CRN is aware that the purpose of this guidance document is to provide the industry with clarity around FDA's thinking on this particular regulatory issue. The Draft Guidance does provide clarity in some areas, including the important distinction that the clinical investigation of a dietary supplement for a structure/function endpoint does not require an Investigational New Drug Application (IND). However, CRN has identified several areas where the Draft Guidance leaves important questions unanswered for industry and the research community.

While CRN appreciates that the intent of the IND is to provide the agency with an opportunity to review a study proposal and product for safety to assure that research subjects will not be subjected to unreasonable risk, CRN has concerns that the position reflected in the Draft Guidance may result in unintended consequences for dietary supplement research. The IND is

[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 store and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. In addition to complying with a host of federal and state regulations governing dietary supplements, our 70+ manufacturer and supplier members also agree to adhere to voluntary guidelines for manufacturing, marketing and CRN's Code of Ethics. Learn more about us at www.crnusa.org.

[2] 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.

specifically designed to support companies that have screened a novel molecule for pharmacological activity and acute toxicity potential in animals and wish to test its diagnostic or therapeutic potential in humans. This framework is applicable to the drug development process, but may not be a suitable framework for research on dietary supplements and food components that are already safely consumed by millions of Americans. CRN's comments will explore the areas of the Draft Guidance that need clarity and/or may result in unnecessary delays and obstacles to initiating dietary supplement research without improving patient/subject safety.

CRN is aware that in addition to dietary supplements the Draft Guidance affects clinical research involving food and food components. CRN's comments on the Draft Guidance are directed toward dietary supplement research, but we would like FDA to consider our comments broadly as they apply to all food and food components.

While CRN agrees that a product's intended use should dictate its regulatory category, we question the rationale for allowing a product's regulatory category to drive scientific inquiry. CRN agrees that the safety of subjects enrolled in human clinical trials is always a first priority. However, other checks and balances, such as following Consolidated Standards of Reporting Trials (CONSORT) guidelines[3], using an Institutional Review Board (IRB), convening data and safety monitoring boards and registering trials on ClinicalTrials.gov, are already in place to support clinical trial safety and data transparency. CRN opines that some aspects of the Draft Guidance may have the unintended consequence of acting in opposition to the spirit of the Dietary Supplement Health and Education Act of 1994 (Public Law 103-417, DSHEA) and may create unnecessary obstacles to the continued scientific study of dietary supplements. DSHEA authorized the establishment of the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH). DSHEA defined the purpose and responsibilities of ODS to include promoting scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions[4]. Thus, DSHEA mandates ODS to support and promote the scientific study of dietary supplements as both "dietary supplements" and as "drugs." The potential for a dietary supplement to have a dual definition, which is dependent on its intended use, has resulted in much confusion amongst the research community.

[3] 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/

[4] The Office of Dietary Supplements (ODS). National Institutes of Health (NIH). Mission, Origin, and Mandate. http://ods.od.nih.gov/About/MissionOriginMandate.aspx

According to the Draft Guidance, an IND may be required to study a dietary supplement that is currently safely consumed by millions of Americans or a food ingredient that has Generally Recognized as Safe (GRAS) status for a given use, even when the research is conducted on a healthy population. This is true even when the investigator has no involvement or interest in the commercial aspects of a product. For example, an investigator interested in evaluating a yogurt product from the grocery store that contains beneficial bacteria for its ability to prevent constipation in a healthy population would be required to file an IND. This seems incongruent with the intent of the IND which is for companies that have screened a new molecule for pharmacological activity and acute toxicity potential in animals and wish to test its diagnostic or therapeutic potential in humans. The differences in these two scenarios highlight practical limitations of the Draft Guidance and the need for additional clarity from FDA.

1) Dietary supplement and ingredient research is often not industry-initiated.

Unlike pharmaceutical research, the majority of dietary supplement and ingredient research is not driven by industry. For a variety of reasons, including limited intellectual property protection, the majority of supplement research is supported by government grants and performed by academic researchers that are independent of industry. Because FDA guidance is aimed at industry and not academia, CRN is concerned that the Draft Guidance will go unnoticed by the academic nutrition and complementary and alternative medicine (CAM) research communities that are focused on expanding scientific knowledge and pay little attention to the complex linguistic nuances encompassed within regulatory definitions. The Draft Guidance does not make it clear how FDA intends to alert academic researchers planning clinical studies independent of industry about the provisions in the Draft Guidance. These researchers will likely be unaware that the intent of the investigation drives the need for an IND. Furthermore, they may not understand the regulatory distinctions between drugs, supplements and their intended use, and thus may be unable to appropriately design a study protocol to accurately reflect the intent of the investigation.

Independent investigators who happen to become aware of the IND requirements and attempt to file an IND application will require cooperation from the manufacturer of the dietary supplement or ingredient to complete the IND. The IND requires significant amounts of detailed and often proprietary manufacturing information. Further, the IND filing process is time and resource intensive. Due to business decisions, a company may choose not to support a particular study or may be reluctant to release confidential and proprietary manufacturing information to an investigator. The option of providing this information directly to FDA in lieu of the researcher may not placate firms' concerns about confidentiality. The net effect is that research cannot be conducted even though in many cases the investigator and millions of consumers can already purchase the product from a store shelf. This example highlights how

the Draft Guidance can become an obstacle to gaining a better scientific understanding of potentially health-promoting products already available to consumers. CRN is aware that the Center for Drug Evaluation and Research (CDER) has available an investigator-initiated IND that may alleviate some of these concerns. However, it is our understanding that the Center for Biologics Evaluation and Research (CBER) does not have such a program available and the Center for Food Safety and Applied Nutrition (CFSAN) has no IND process whatsoever. CRN recommends that FDA develop a consistent IND process across all the relevant regulatory categories and consider how academic researchers will be made aware of and comply with the provisions in the Draft Guidance.

2) If all companies and independent investigators conducting clinical research on dietary supplements with the intent of studying them as drugs followed the Draft Guidance, FDA would likely not have the resources to review and process the massive numbers of INDs that would be submitted.

The Draft Guidance categorizes a dietary supplement or food component as an Investigational New Drug when it is being researched for the diagnosis, cure, mitigation, treatment, or prevention of disease, i.e. as a drug. A significant portion of clinical research conducted using dietary supplements or food components involve assessing the supplements' or food components' therapeutic (disease-related) effects. Some of this research is conducted by independent investigators that are unaware of a product's regulatory category and therefore design studies that are appropriate to their research questions. On the other hand, dietary supplement companies intending to support structure-function claims may desire to study dietary supplements with a focus on health promotion or disease risk reduction. Designing a clinical trial to demonstrate health promotion or disease risk reduction has tremendous implications on cost and feasibility. Currently, there are no validated biomarkers as surrogate endpoints for "health promotion,""wellness," or "supporting normal structure and function" and therefore investigators by default will choose to assess effects such as lowering of blood pressure or serum cholesterol levels, or similar effects on other established surrogates, many of which may also be viewed as therapeutic effects. This, in turn, would necessitate an IND.

The combination of the aforementioned scenarios, verified by a search of ClinicalTrials.gov[5], demonstrates the large number of clinical studies examining therapeutic effects of dietary supplements. By association, this indicates how the Draft Guidance creates a de facto IND requirement for a significant portion of dietary supplement research studies. CRN is concerned that such a large volume of IND applications would create obstacles and delays to conducting

[5] A search of "dietary supplement" and "disease" revealed 2762 clinical studies in various stages. This is likely an underestimate as search terms "vitamins," "minerals," "antioxidants" and "botanicals" would likely yield additional studies. www.clinicaltrials.gov. Accessed January 4, 2011.

clinical research as investigators struggle to provide the necessary information and FDA struggles to manage the increased workload.

3) Naturally occurring materials have inherent variability that may not fit the IND model.

The IND filing process is designed for pharmaceutical drugs. Drugs are typically well-characterized synthetic molecules that are stable over time. Some dietary supplements and food components are derived from natural material that may have inherent batch-to-batch variability and be less stable over time when compared to drugs. For example, there can be challenges in obtaining an IND for a fish body oil product that has 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. This is due to natural seasonal variability in the fatty acid composition of fish used to produce fish oil. Historically, IND application reviewers, presumably without dietary supplement expertise, have struggled to understand these practical differences between dietary supplements/food components and drugs.

The above mentioned examples are derived from real world scenarios. 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, Dr. Dan Merenstein, Georgetown University, and Dr. Patricia Hibberd, Massachusetts General Hospital, both shared their experiences and expressed their concerns with the burden and delays associated with preparing and submitting INDs to FDA. Despite the researchers following CONSORT guidelines, receiving 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. In fact, both researchers addressed the large number of clinical trials being conducted on probiotics and the fact that the majority of these are conducted outside of the U.S. to avoid these delays. The researchers expressed the concern that the U.S. will fall behind the rest of the world in probiotic clinical research due to the challenges and delays associated with submitting INDs. This may hold true for other areas of nutrition and dietary supplement research as well. CRN strongly encourages FDA to review the *Probiotics: From Bench to Market* manuscript because it provides extensive examples of how the current requirement to obtain an IND for a dietary supplement or food component does not necessarily improve safety or rigor of a study, but instead serves as a significant obstacle to advancing science.

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

Copious amounts of nutrition and dietary supplement clinical research are conducted by academic researchers that desire to advance the science underpinning nutrition and other CAM therapies. These researchers, many of whom are young post-doctoral and graduate students, may be interested in a research question not too dissimilar to example six on page 12 of the Draft Guidance[7]. In this example, FDA identifies that an IND would be required to perform a study on broccoli sprouts' ability to prevent cancer. This example can be used to explore how an investigator is impacted by the Draft Guidance.

In addition to meeting the research institution's requirements, the Draft Guidance would require an investigator to dedicate a significant amount of time to filling out the IND application, conduct or pay for analytical testing to determine the characteristics, potency, purity, and stability, as well as safety, of the broccoli sprout test agent, and likely engage other professionals experienced with the IND process. If the researcher chooses to use a broccoli sprout preparation that 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, but not the investigator. As evidenced by the experienced researchers' testimonies published in *Probiotics: From Bench to Market*, an IND requires numerous hours and regulatory expertise. This type of expertise is common amongst pharmaceutical and vaccine company staff, but may be too onerous a requirement for academic researchers wishing to explore the benefits of commonly consumed foods and dietary supplements.

4) The Draft Guidance does not address several important legal questions

Current federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because companies developing pharmaceutical drugs usually ship the investigational new drug to clinical investigators in many states, they must seek an exemption from that legal requirement and the IND is the means through which the sponsor technically obtains this exemption from FDA[8].

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[7] *If a complementary or alternative medicine that was derived from organic materials from a botanical source (e.g., broccoli, sprouts) is administered to subjects to study cancer prevention, is an IND required?* A clinical investigation of a complementary or alternative medicine derived from organic materials that is intended to evaluate the medicine's ability to diagnose, cure, mitigate, treat, or prevent disease requires an IND under part 312. 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.

[8] FDA Investigational New Drug Application. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

It is already legal to ship dietary supplements and food components across state lines. Therefore, there may be a legal basis for proceeding with a clinical study on a dietary supplement or food component for a therapeutic use, especially if the sponsor is exploring the use of the product as a medical food or seeking to generate data for a health claim petition. Further, there may be situations where the product does not cross state lines. To be congruent with FDA's Transparency Initiative[9], the Draft Guidance should clarify the legal basis that FDA uses to require an IND for a product that can already be shipped legally across state lines.

CRN has an additional legal/regulatory concern related to New Dietary Ingredients (NDI)[10]. DSHEA defines a dietary supplement, in part, as a "product that does not contain an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which existence of such investigations has been made public[11]."

If a company is collecting data to submit an NDI notification to FDA and studies are conducted under IND Draft Guidance and the study results are published before the product is marketed as a food or dietary supplement, then it can no longer be marketed as a food or dietary supplement. The product would then require FDA drug approval before being legally marketed. In this example the company may impose a particular study design or use of therapeutic endpoints in a clinical study involving a healthy population to explore the possibility of obtaining data for a health claim petition (disease risk reduction) or marketing the product as a medical food with no intentions of marketing the product as a drug. CRN believes that the above mentioned scenario is a significant disincentive to conducting NDI-related clinical research under IND Draft Guidance and creates an additional legal grey area as well as an obstacle to ingredient innovation for the dietary supplement industry[12].

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[9] In June 2009, Food and Drug Administration (FDA) Commissioner Dr. Margaret Hamburg launched FDA's Transparency Initiative and formed an internal task force to develop recommendations for making useful and understandable information about FDA activities and decision-making more readily available to the public. http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm

[10] New Dietary Ingredients in Dietary Supplements. Background for Industry. http://www.fda.gov/Food/DietarySupplements/ucm109764.htm

[11] Dietary Supplement Health and Education Act of 1994 provided a formal definition for dietary supplement, including that a dietary supplement is a product that that does not contain an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which existence of such investigations has been made public.

[12] FDA is also in the process of rulemaking regarding the implications of Section 912 of the FDA Amendments Act of 2007 (amends the Food, Drug and Cosmetic Act), which suggests that a firm loses access to the supplement market for products containing ingredients tested in clinical trials and prohibits the sale of foods with an added approved drug, licensed biological or a substance that underwent publicly disclosed substantial clinical investigation. Stakeholders, including the food and supplement industries and some Members of Congress are pushing FDA to

FDA should also provide additional clarification related to IND requirements for clinical studies designed to assess the ability of a supplement or food component to *reduce the risk of* versus *prevent* disease. According to FDA's Guidance for Industry and FDA: Dear Manufacturer Letter Regarding Food Labeling,[13] *"A health claim is a claim that describes the relationship between a substance (food or food component) and a disease or health-related condition (21 CFR 101.14(a)(1)). Health claims are limited to claims about disease risk reduction and cannot be claims about the cure, mitigation, treatment or prevention of disease. The latter claims are drug claims under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act)."* This indicates that FDA views "disease risk-reduction" to be distinct from "prevention."

The Draft Guidance provides the example in Section VI (C)[14] that an IND is required for a study intended to evaluate a dietary supplement's ability to prevent osteoporosis, but is not required when the same dietary supplement is being evaluated for its influence on bone mass. Further clarity is needed from the agency to determine if an IND is required to investigate the same dietary supplement's ability to "reduce the risk" of osteoporosis either via measurement of the disease endpoint itself or a surrogate endpoint (e.g. fracture risk). It is noteworthy that the Draft Guidance 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 intending to evaluate (a) impact on bone mass, (b) prevention of osteoporosis, or (c) reduction of the risk of osteoporosis. CRN is supportive of using the IND process to improve patient safety, however; this example demonstrates how resolving issues surrounding whether an IND is necessary becomes an exercise in regulatory language manipulation with little impact on parameters of safety. In this example a researcher could either hire a regulatory attorney to re-write the study protocol using language that would not necessitate an IND, or commit necessary resources and expertise needed to complete the IND. Both solutions require researchers to commit time and resources while adding little to already existing requirements that support patient safety and data transparency.

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complete rulemaking for the provision, with some arguing the rule should not discourage firms from conducting clinical trials with supplement ingredients.

[13] Guidance for Industry and FDA: Dear Manufacturer Letter Regarding Food Labeling. http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm053425.htm

[14] 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.

CRN has several additional recommendations for the Draft Guidance.

1) To account for physical and biochemical differences between drugs and dietary supplements/food components, dietary supplement INDs, when required, should be reviewed by individuals with expertise in dietary supplements and food components, nutrition research, and/or the application of complementary and alternative (CAM) therapies. In addition to CBER and CDER, FDA should consider including CFSAN in the process of reviewing and/or approving INDs related to dietary supplements and food components, at a minimum for the CMC section of the IND. Further, CBER and CDER should harmonize their approaches to reviewing food, food component and dietary supplement INDs.
2) FDA should provide a broader list of IND exemptions for dietary supplements and food components. Greater consideration should be given to allow for exemption of products that have a history of safe use, or are currently safely consumed as a food by millions of Americans (e.g. broccoli sprouts, yogurt, etc.). Furthermore, the final guidance should provide clarification on IND requirements for studies conducted on a dietary supplement for targeted endpoints associated with an approved health claim or a qualified heath claim.
3) FDA should consider other clinical trial safety and integrity guidelines and programs, such as CONSORT guidelines, IRB approvals, and data and safety monitoring boards, as possible criteria to allow for exemption from the IND process for clinical studies intending to investigate dietary supplements and foods already available in the marketplace.
4) FDA should include in the final guidance a reference to the penalties associated with the conduct of a clinical trial without a requisite IND and also the responsibilities of a company whose product is being studied by an investigator for research without an IND and without the company's involvement or consent. In addition, FDA should consider how academic researchers will be made aware of and comply with the provisions in the guidance.
5) FDA should clarify the circumstances under which NDIs studied under IND Draft Guidance where the results of the research have been made public may be still allowed to go to market as a dietary supplement product, once the NDI review process is complete.
6) FDA should clarify the legal basis the agency uses to require an IND for a product that can already be legally shipped across state lines.
7) FDA should provide additional clarification related to IND requirements for clinical studies designed to assess "disease risk reduction" versus "prevention."

Thank you.

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