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By Electronic Submission

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

Re: Proposed Rule: Investigational New Drug Applications; Exemptions for Clinical Investigations To Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic. Docket No. FDA-2019-N-2650.

The Council for Responsible Nutrition (CRN)[1] appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA) Proposed Rule "**Investigational New Drug Applications; Exemptions for Clinical Investigations To Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic**" (Proposed Rule).

As stated previously, we believe that robust clinical investigations are essential for providing efficacious and safe dietary supplements and ensuring that dietary supplement claims are adequately substantiated.[2] 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 New Drug Application (IND), and those that are intended to be marketed as dietary supplements or foods. We support FDA's proposal to formally exempt clinical studies conducted on food and dietary supplements from IND requirements if they are not intended to support marketing of the products as a drug. The proposal comes after several years of uncertainty following FDA's issuance of final guidance in 2013, "Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards (IRBs) on Investigational New Drug Applications—Determining Whether Human Research Studies Can Be

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food 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 200 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 in response to final guidance (2013), *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*
https://www.crnusa.org/sites/default/files/CRN%20Comments_IND%20Final%20Guidance_4.7.2014.pdf

Conducted Without an IND," (final guidance) followed by a notice of administrative stay of action staying parts of the final guidance in 2015.

CRN appreciates FDA's efforts to provide clarity and facilitate scientific research on food and dietary supplements in the U.S. We believe that modifications and clarification of several points in the Proposed Rule are needed, however, to help achieve FDA's goal of reducing unnecessary burden on the agency and investigators.

IND regulations may be viewed by researchers as a costly and time-consuming regulatory barrier for nutrition research. As written, the Proposed Rule may discourage U.S. researchers from performing important research, which is needed to inform nutrition recommendations and policies, including the Dietary Reference Intakes and Dietary Guidelines for Americans, as well as drive innovation. Research on the effects of nutrition on health outcomes, including disease risk reduction, is necessary to develop and expand access to "food is medicine" interventions, a priority of the White House National Strategy on Hunger, Nutrition, and Health.[3] The barriers to research that would be imposed by the Proposed Rule appear to contradict the national strategy.

Another consequence of the Proposed Rule is the risk that researchers may choose to conduct clinical investigations outside of the U.S. to avoid the IND process. As a result, the U.S. may fall behind the rest of the world in nutrition clinical research due to the challenges associated with submitting INDs.

For food and dietary supplements that are not intended to be marketed as drugs, an IND is not necessary to ensure the safety of study participants. Several procedures are already in place to support clinical trial safety and data transparency, including the CONSORT guidelines, FDA's IRB and Protection of Human Subject requirements, and the data and safety monitoring boards and registration of trials on ClinicalTrials.gov. Therefore, the public health benefit of subjecting clinical investigations on food and dietary supplements not intended for marketing as drugs to IND requirements is unclear.

The Proposed Rule provides two exemptions: a self-determined exemption and an FDA-determined exemption. CRN is concerned that without clear delineation between the two proposed exemptions using well-defined terminology and distinct criteria based on safety, IRBs may unnecessarily demand FDA-determined exemptions for clinical investigations on food and dietary supplements not intended for marketing as drugs. The overuse of the FDA-determined exemption pathway will further burden an agency that is already under resourced.

CRN offers the comments below in response to the Proposed Rule. 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 term "drug use" in the Proposed Rule is not clearly defined and may be subject to misinterpretation

The term "drug use" to describe food uses in the Proposed Rule is not clearly defined. The FD&CA excludes a dietary supplement from the statutory definition of "drug" if it is intended to affect the

[3] https://www.whitehouse.gov/wp-content/uploads/2022/09/White-House-National-Strategy-on-Hunger-Nutrition-and-Health-FINAL.pdf

structure or function of the body and if it does not claim to diagnose, cure, mitigate, treat, or prevent disease.[4] 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,[5] which is also supported by past agency statements.[6] In the Proposed Rule, FDA continues to expand the definition of "drug" to include the intent of the clinical investigation, as the agency did with the final guidance, even if the study will not be used in the development or promotion of new drugs, but rather will be used only to support lawful structure/function claims.

While the proposal would allow for a self-determined exemption or written exemption from FDA for a clinical investigation on a dietary supplement that is not intended to support a drug development plan, CRN is concerned that without a definition, the term "drug use" may lead to confusion and misinterpretation. For example, IRBs may apply the term "drug use" too broadly and err on the side of caution, requiring an IND when it would not be required. To avoid misinterpretation and the resulting additional burden on researchers and FDA staff who would have to address the influx of IND exemption requests, CRN recommends FDA limit the term "drug use" to investigations that will be used to support marketing of the product with an intended use to diagnose, cure, mitigate, treat, or prevent disease. Additionally, FDA should make clear that a clinical study intended to evaluate the safety of a dietary ingredient does not require an IND, as was done for food ingredients in the final guidance.[7]

The proposal to limit IND exemptions to products that are "lawfully marketed in the United States" creates uncertainty as to when a product would be subject to an IND

Proposed (b)(4) specifies IND exemptions for food and dietary supplements that are "lawfully marketed in the United States." The preamble to the proposed rule states, "'lawfully marketed' means the product is marketed in the United States as a food or cosmetic consistent with the FD&C Act and any applicable FDA regulations."[8] As written, the proposal creates significant uncertainty as to what food and dietary supplement ingredients are subject to the exemption and could limit innovation on ingredients under development.

With regard to the term, "lawfully", determining what FDA would consider to be "lawful" is not clear in many situations. This task has become harder in recent years due to inconsistent FDA applications of the FD&C Act and FDA regulations and the lack of finalized guidance around important dietary supplement requirements.

For example, companies have marketed n-acetyl-L-cysteine (NAC) as a dietary supplement in the U.S. for decades under the assumption that FDA considered the marketing to be legal. In 2020, however, FDA issued warning letters suggesting that NAC was not a legal dietary ingredient due to the alleged timing

[4] 21 U.S.C. § 321(g)(1), further noting that such product must also meet the requirements of 21 U.S.C. § 343(r).
[5] *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.).
[6] *See* Letter from FDA Chief Counsel Daniel E. Troy, to Jeffrey N. Gibbs (Oct. 17, 2002), at 3.
[7] Final guidance p.13.
[8] 87 Fed. Reg. 75536, 75542 (Dec. 9, 2022).

of NAC drug approval and NAC's first use in a dietary supplement (i.e., "drug preclusion").[9] Drug preclusion refers to a section of the FD&C Act that prevents an ingredient's use in food or supplements if the ingredient was approved as a drug or subject to an IND authorization and had undergone substantial, public clinical investigations before the ingredient is used in a supplement or food.[10] Prior to 2020, FDA had not objected to NAC's use and even noted in one public document that the agency considered it to be an appropriate dietary ingredient. FDA has created similar confusion with another ingredient – nicotinamide mononucleotide (NMN) – when it recently permitted new dietary ingredient notifications (NDIN) to move forward based on an FDA determination that NMN is an appropriate dietary ingredient. The agency later revoked this determination citing drug preclusion and the existence of IND authorization and clinical studies that purportedly predated the date of NMN's use in supplements.[11]

Other aspects of food and dietary supplement law, that are key to understanding when an ingredient is "lawful", also remain unsettled, such as when an ingredient is considered a new dietary ingredient (NDI) and subject to a NDIN. Final guidance on this issue has not been provided, creating further challenges with interpreting what is "lawful." Rather than putting the burden on entities seeking to use the IND exemption, the determination of legality should be tied to clear FDA action. We provide suggested language below.

CRN also has concerns with tying the exemption to whether a product has been "marketed." This term is not defined in the proposed rule and, even if defined, could stifle innovation by limiting research for new product development. A food or dietary supplement product could be eligible to be offered in a manner that is consistent with FD&C laws and FDA regulations, but a company has not yet sold the product or advertised it to consumers. There are a number of reasons why an ingredient that is "lawful" in the U.S. may not have been advertised and made available to consumers, such as that a company may not have identified the right sales channels or the company is still conducting research to support potential claims. The "marketing" requirement may also create an unnecessary burden for investigators intending to study a product containing a combination of existing ingredients. For example, would a clinical investigation on a product containing a protein and a fat, neither of which are new ingredients but have not been marketed in that specific combination, require an IND?

Given both the concerns with the term "lawfully" and "marketed", CRN suggests that the rule make clear that the exemption applies to products that could be offered as food or dietary supplements in the U.S., unless FDA has declared the product unlawful for food and/or dietary supplement use in accordance with a final agency action and the product is not subject to (1) court precedent reversing the determination made through final agency action; or (2) agency enforcement discretion guidance.

[9] *See e.g.,* FDA Warning Letter to Les Labs, July 23, 2020.
[10] 21 U.S.C. § 321(ff)(3)(B) [Section 201(ff)(3)(B) of the FD&C Act].
[11] *See e.g.,* Nov. 4, 2022 Letter from P. Yeager, FDA, to SyncoZymes (Shanghai) Co., Ltd.

The proposed self-determined exemption criteria for "conditions of use" are too narrow, creating a requirement for FDA-determined exemptions for changes in conditions of use that do not impact safety

Under proposed 312.2(b)(4), FDA states, among other things, that in order for an investigation to be exempt from the IND requirements using self-determined exemption, the product should be used "in the investigation consistent with its labeled conditions of use or, in the absence of labeled conditions of use, consistent with its ordinary conditions of use (e.g., same dose range and total daily intake, same formulation, same duration of use). CRN believes that the examples provided by FDA of "(e.g., same dose range and total daily intake, same formulation, same duration of use)" are too restrictive. These examples should be removed from the rule. Investigations using the self-determined exemption should be permissible in situations where the Sponsor has made low-risk modifications to the formulation that do not impact safety (e.g., remove a flavor or color). Additionally, Sponsors should be able to design investigations that evaluate products at different dose range, total daily intake, and duration of use so long as the changes do not increase the risk to subjects. CRN recommends that the IRB for the proposed self-determined IND exemption investigation be empowered to determine if the low-risk modifications to the formulation or proposed differences to ordinary conditions of use would impact safety and necessitate an FDA-determined exemption.

The IND exemption should not preclude the use of study results to support a future IND

Proposed section (b)(4)(i)(A) exempts clinical investigations from IND requirements if the investigation is not intended to support a "drug development plan for the product, including a future IND or application for marketing approval (an application under section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act)." At the time a Sponsor makes a self-determined exemption under proposed 312.2(b)(4) for a clinical investigation, they may not intend that the results of such investigation be used to support a future IND or development plan for a drug product. However, should the results uncover an unexpected or hypothesis-generating discovery that the Sponsor wishes to evaluate further under an IND, CRN believes that such investigation should be acceptable in support of such IND or development plan. While the self-determined exemption should not be used by Sponsors to bypass the IND requirement for investigations specifically intended to support drug development plans, restrictions on the use of data from investigations conducted under the self-determined exemption may discourage use of this pathway and could lead Sponsors to conduct such research outside of the U.S.

The exemption for investigations that do not restrict subjects from continuing with treatments or therapies should apply to treatments or therapies prescribed or deemed medically necessary by a healthcare provider

Proposed section (b)(4)(v)(C) exempts clinical investigations from IND requirements if the investigation "does not restrict subjects from continuing with treatments or therapies prescribed or recommended by a healthcare provider." Since the term "recommended" may be interpreted broadly, CRN suggests

replacing "prescribed or recommended by a healthcare provider" with "prescribed or deemed medically necessary by a healthcare provider."

The FDA-determined exemption process should be streamlined and led by the Proposed Human Foods Program

The preamble to the Proposed Rule indicates that requests for an FDA-determined exemption should be submitted to CBER or CDER. Given the complexities of nutrition research, CRN believes that the recently announced proposed Human Foods Program would be better positioned to review exemption requests than CBER or CDER. Staff within this program will have the experience and expertise to address the nuances of research on food and dietary supplements.

The proposal does not provide information on the process or timeline for the FDA-determined exemption process. To ensure that research studies are not unnecessarily delayed, FDA should streamline the review process and provide a timeline for a response to the request. CRN recommends that, similar to the timeline for IND applications, the Agency should respond to FDA-determined exemption requests within 30 days after FDA receives the request.

FDA should withdraw all parts of the final guidance related to food and dietary supplements until rulemaking is completed

In the preamble to the Proposed Rule, FDA states, "(a)t the completion of this rulemaking, we anticipate taking action to resolve related issues in the final guidance, including the stayed portions of the guidance." Given the inconsistencies between the final guidance and the Proposed Rule, CRN recommends FDA withdraw all parts of the final guidance related to food and dietary supplements until rulemaking is completed. CRN also suggests that FDA hold a workshop to discuss the Proposed Rule with stakeholders before finalization.

Thank you for considering our comments.

Sincerely,

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