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March 9, 2023

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

Re: 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, Docket No. FDA-2019-N-2650

Dear Sir or Madam:

The Healthcare Nutrition Council (HNC) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA or agency) regarding the proposed rule that FDA issued on December 9, 2022 that would establish certain exemptions for clinical investigations evaluating a drug use of a product lawfully marketed as a conventional food, dietary supplement, or cosmetic ("Proposed Rule").[1] HNC is an association representing manufacturers[2] of enteral nutrition (EN) formulas and oral nutrition supplements (ONS), including those categorized as medical foods, and parenteral nutrition (PN). Our mission is to improve patient outcomes by advancing nutrition policies and actions that raise awareness and optimize access of essential nutrition support therapies across the continuum of care.

HNC is a proponent of advancing nutrition science and ensuring the agency continues to incentivize clinical investigations of foods to support safety, tolerance, and efficacy. HNC appreciates FDA's efforts to develop the Proposed Rule and the agency's goal of reducing the regulatory burden of conducting clinical investigations evaluating foods, dietary supplements, or cosmetics while maintaining adequate safeguards for human subjects. HNC generally supports the establishment of exemptions from IND requirements for foods, but we are concerned with FDA's failure to clearly define the scope of studies that are subject to IND requirements in the first instance. As discussed further herein, the Proposed Rule creates an exemption for studies that would otherwise be subject to IND requirements because they investigate the "drug use" of an article. However, FDA fails to define this phrase, leaving open the possibility that it will be construed broadly to include any study that evaluates the effect of a food on a disease.

HNC agrees that certain studies evaluating a food or food ingredient's use in treating a disease could trigger IND requirements, such as, for example, a study evaluating a food's effectiveness in treating certain serious and life-threatening diseases. But short of such a study, there is ample room to evaluate the role that food and nutrition play in health without that study triggering IND requirements designed for investigational drugs. This is particularly true for foods that Congress has expressly recognized are lawful for, and intended for, use in managing diseases or conditions, like medical foods and foods for special dietary use (FSDU). The Federal Food, Drug, and Cosmetic Act (FDCA) requires these foods to be marketed for use in managing disease; investigating the role that food and nutrition plays in health, a lawful purpose, therefore is not subject to IND requirements for drugs. Even beyond medical foods and FSDU, however, the same principle applies: not everything administered to or consumed by a person with

[1] 87 Fed. Reg. 75536 (Dec. 9, 2022).
[2] HNC members are Abbott Nutrition, Nestle Health Science, and Nutricia North America.

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a disease or condition is a drug or should be regulated as such. The nutritional effect of food can benefit individuals with disease without being drugs.

HNC therefore asks FDA to make clear in the final rule that a study would only involve a "drug use" that triggers application of IND requirements if that study is intended to evaluate a product's ability to treat, prevent, mitigate, or cure disease, and further, and most critically, that the effect of a food on disease or condition can be studied *without* being a "drug use" that would require an IND. FDA's failure to provide clear guidance on the scope of studies subject to IND requirements—both under its 2013 guidance and under the Proposed Rule—creates significant uncertainty for study sponsors and Institutional Review Boards (IRBs). This uncertainty creates unnecessary delay, cost, and regulatory barriers, which can impact patient access to important nutritional interventions, including those essential to patient health such as tube feedings.

We are also concerned that the Proposed Rule does not provide a sufficiently detailed framework for FDA engagement, when needed, such that the FDA engagement process could become overly burdensome for both FDA and for industry. Our comments below focus on these considerations in particular, and include specific suggestions for the Proposed Rule to ensure equity and clarity.

A. FDA should clarify that studies assessing the intended uses of lawfully marketed medical foods and FSDU, in particular, are not studies of "drug uses" that would trigger an IND obligation.

The Proposed Rule would establish an exemption for certain clinical investigations studying a "drug use" of products that are lawfully marketed as foods for human consumption, when such investigations would otherwise require an IND.[3] A clinical investigation requires an IND if it concerns a product subject to Section 505 of the FDCA, meaning a product that is a drug: an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.[4] Studies on human food for non-drug uses are not subject to IND requirements. FDA does not, in the Proposed Rule, identify any specific criteria that would distinguish a food study for non-drug use from a study for a "drug use," particularly when there is no intent to market the food as a drug.

Medical foods are, by definition, intended for use in the dietary management of a disease or condition.[5] An FSDU can be intended to fulfill a special dietary need which may exist as a condition of disease.[6] Providing appropriate nutrition to people living with a disease is not and should not be considered a drug use; accordingly, a clinical investigation evaluating a food for these uses does not require an IND.

We appreciate the proposed pathway for exemption from the IND requirements for certain studies of food that *do* evaluate a drug use. However, we want to emphasize the importance of FDA recognizing that lawfully marketed medical foods or FSDU are not subject to Section 505 and FDA does not have IND authority over clinical studies intended to assess lawful uses of these products. We are concerned that the phrase "drug use" could be interpreted broadly, by FDA or other stakeholders, to include studies of

[3] 21 C.F.R. § 312.2(a).
[4] 21 U.S.C. § 321(g)(1).
[5] The Orphan Drug Act Amendments of 1988 define a "medical food" as a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.
[6] The FDCA defines "special dietary use," in part, to mean "a particular use for which a food purports or is represented to be used, including . . . [s]upplying a special dietary need that exists by reason of a physical, physiological, pathological, or other condition, including but not limited to the condition of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control the intake of sodium."

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medical foods or FSDU for their intended purposes, which inherently would involve an evaluation of the effect of a food on a disease.

As discussed above, we request that, in the final rule, FDA clarify that foods studied for a lawful medical food or FSDU purpose are not subject to IND requirements, even if such studies involve evaluation of impact on disease. We note that the Proposed Rule does not define "drug use" (though uses the phrase "drug use" 35 times in the preamble and twice in the proposed regulatory text); we do not think a regulatory definition of "drug use" is essential, but we do think that FDA should provide clarity around what it means by "drug use" either in the preamble to the final rule or in the final regulatory text. Specifically, FDA should make clear that a clinical study on a "drug use" does not include clinical studies whose primary endpoints evaluate the effect of a food in the dietary management of a disease or condition, and should articulate what aspects of a study trigger IND requirements and application of the exemption pathways.

B. FDA should provide an exemption pathway both for products that are already lawfully marketed in the United States as a food and also for products that could be lawfully marketed in the United States as a food.

FDA's proposed IND exemption would apply to studies on foods that are "lawfully marketed" in the United States as human food. The preamble to the Proposed Rule also indicates the study sponsor must be evaluating the marketed form and dose of the food and provide the label for the marketed food. The Proposed Rule fails to contemplate studies conducted on reformulations of an existing marketed product and/or clinical studies conducted prior to introducing a new food into the market.

We understand that FDA's proposed IND exemption takes a risk-based approach—exempting foods from studies on "drug uses" based on certain health, safety, and welfare criteria. Consistent with this risk-based approach, FDA appears to have concluded that food that is already lawfully on the market has a presumption of safety. In the food context, however, this distinction does not carry significant meaning, as food is not subject to FDA pre-market review; in other words, food that is already marketed has not received any more regulatory scrutiny than food that has not yet been marketed. We do not believe there is a basis for allowing an exemption for food products already marketed in the United States but not allowing the same exemption for food products in development, so long as such products would be lawful if marketed in the United States.

We request that FDA clarify that articles that are and may be lawfully marketed as food—either as a modification to an already-marketed food or as a new food—are eligible for the proposed IND exemption. Without this clarification, the Proposed Rule implies that the industry must either submit an IND in this circumstance or first introduce the food to the market and then conduct the clinical study, neither of which are consistent with FDA's risk-based approach.

C. FDA should clarify that a "serious or life-threatening disease or condition" is not intended to include those diseases or conditions that are managed through nutritional interventions.

The self-determined IND exemption option is only open to investigations where the subjects do not have compromised immune systems or a "serious or life-threatening disease or condition." In the Proposed Rule, FDA defines a "serious" disease or condition as "one that is associated with persistent or recurrent morbidity (a diseased condition or state) that has substantial impact on day-to-day functioning." FDA explains that the "morbidity need not be irreversible to be 'serious' if it is persistent or recurrent." This definition is derived from FDA's regulations for expanded access to investigational drugs for treatment.

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FDA further defines a "life-threatening" condition to be one where "(1) the likelihood of death is high unless the course of the disease is interrupted or (2) the disease or condition has a potentially fatal outcome." This definition comes from the regulations on IND requirements studied for use in "life-threatening or severely-debilitating diseases."

We are concerned that these definitions would have a disproportionate impact on studies involving medical foods and FSDU, including those designed for inborn errors of metabolism, as has been established in the Orphan Drug Act definition of medical foods.[7] For example, individuals with PKU cannot break down the amino acid phenylalanine and without a special diet, can experience severe brain damage. But with a special diet, the disease is easily managed and does not necessarily have a "substantial impact on day-to-day functioning." We do not think patients with inborn errors of metabolism that are readily controlled by diet should fall within the scope of "serious or life-threatening disease or condition" for purposes of the Proposed Rule, and we do not think the definitions, as drafted, would clearly exclude such conditions. In individuals with PKU, the likelihood of death is high unless the course of the disease is interrupted through dietary intervention, and the disease has a potentially fatal outcome. However, PKU is readily controlled through dietary intervention and does not require other medical treatment to prevent bad outcomes.

We request that FDA clarify that whether a disease is considered serious or life-threatening should be determined after the application of nutritional and dietary modifications specific to and appropriate for that disease.

D. FDA should establish a more precise framework for its review of exemption requests.

1. Label Review

Under the FDA-determined pathway, the study sponsor is required to provide a copy of the lawfully marketed product's labeling. The Proposed Rule does not explain how FDA will use submitted labels in evaluating an FDA-determined exemption request. However, the Proposed Rule only explains that labeling will be used to review ingredients, as the sponsor is required to provide a separate description of the product composition if labeling does not identify ingredients, and to evaluate the conditions of use if the product is being used consistent with its labeled conditions for use. If these are the only purposes for requesting labeling, then we think the requirement to submit a copy of the product labeling is too broad.

We request that FDA clarify the scope of the labeling review that it will conduct under this pathway. Specifically, we think that FDA should limit its label review to information about composition and instructions for use, and allow for submission of label or labeling only necessary to convey this information. Alternatively, FDA could require sponsors to provide a list of ingredients and the instructions for use instead of providing a complete label or labeling.

2. IRB Role

We understand that IRBs have experienced confusion with the existing IND guidance as it pertains to food studies given FDA's failure to clearly define what it means to investigate a "drug use," resulting in IRBs requesting INDs when the sponsor believes they are not required. We are concerned that IRBs could take a similarly active role in attempting to police whether a sponsor's self-determined exemption is valid. On this point, FDA said in the Proposed Rule that the agency can issue a warning or untitled letter if

[7] Medical food as defined in section 5(b)(3) of the Orphan Drug Act, 21 USC 360ee(b)(3); and as defined in 21 CFR 101.9(j)(8).

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it "becomes aware (such as during an IRB inspection or through communications from the sponsor, an investigator, a subject, or the IRB) that a study conducted without an IND in reliance on the self-determined exemption is ineligible." This suggests that IRBs could play some role in sponsors' eligibility for self-determined exemptions, including by potentially sharing information with FDA. It is unclear whether IRBs would feel sufficiently comfortable with a sponsor's self-determined exemption to provide approval of an IRB request, or whether they would insist on receiving some kind of confirmation from FDA that the self-determined exemption is valid.

Because the Proposed Rule is intended, in part, to ease the burden of IND requests on the agency, we think an outcome where IRBs may request FDA's confirmation of a self-determined exemption before allowing an investigation to proceed would be counter-productive, and it would also render the term "self-determined" meaningless. We request that FDA clarify that FDA does not intend for IRBs to, as a matter of course, inquire into the adequacy of a self-determined exemption, and that FDA is not providing a mechanism for sponsors to obtain confirmation from FDA that a self-determined exemption is valid. Consistent with our comments in this document, we reiterate that clarity around the definitions of "drug use" and the health, safety, and welfare criteria will be critically important to facilitate efficient review by IRBs.

3. Timeline for FDA Review

The Proposed Rule does not include any timeline by which FDA must respond to FDA-determined exemption requests. Because FDA is not bound to a review timeline, and is otherwise resource constrained, we are concerned that FDA could be delayed in acting upon FDA-determined exemption requests. We think it's particularly relevant that, for IND submissions themselves, sponsors need only wait 30 days before initiating any clinical trials. During this period, FDA has an opportunity to review the IND and raise any objections.

We do not think there is a basis for imposing a potentially indefinite waiting period on sponsors seeking FDA's determination of an exemption, when there is an established, finite waiting period for sponsors seeking to initiate a clinical investigation under an IND. Instead, we propose a similar model for FDA-determined exemption requests, where sponsors can move forward if FDA does not object within 30 days of receiving the request. This would help mitigate the bottleneck of FDA review and ensure consistency across the IND framework.

4. Inter-agency review responsibilities and collaboration

Under the Proposed Rule, a sponsor seeking an FDA-determined exemption would have to submit a written request to CBER or CDER, but FDA does not provide further guidance on how to determine the appropriate Center. FDA notes that sponsors can seek guidance in determining the appropriate Center to which an exemption request should be submitted, but provides no other information to assist sponsors. Without further guidance, FDA will continue to receive burdensome requests that, in part, motivated this Proposed Rule, and sponsors will experience unnecessary delays. Further, we are concerned that CBER and CDER do not have the expertise to assess whether a particular product is lawfully marketed as a food or not, and the Proposed Rule does not require any collaboration across Centers to ensure that the appropriate analysis is conducted.

To address this, we ask FDA to provide guiding principles in the preamble to the final rule that will help sponsors determine the appropriate Center for review of FDA-determined requests. We request that the final rule require engagement with food subject matter experts within CFSAN or the re-organized Human Foods program as appropriate in evaluating exemption submissions.

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5. Current guidance while rulemaking process continues

HNC respectfully recommends FDA stay or withdraw Part VI Section D of the existing (2013) IND guidance, which sets forth FDA's guidance on the application of IND requirements to studies on foods. After this guidance was issued, FDA received comments raising significant questions about FDA's positions, and FDA subsequently stayed parts of the final guidance for further consideration. Almost eight years later, the guidance has not been revised and continues to create significant confusion regarding the critical threshold question regarding the application of IND's framework to food studies. While FDA notes that it "anticipate[s] taking action to resolve . . . issues in the final guidance, including the stayed portions of the guidance" at the completion of the rulemaking at issue, this process could take years, and it could be years more before revised guidance is issued. HNC therefore asks FDA to stay Part VI Section D entirely while the current rulemaking process continues in order to help alleviate the significant confusion this guidance causes for both study sponsors and IRBs. Doing so will help reduce barriers to patient access of important medical foods and FSDU, as confusion regarding the application of IND requirements can delay or complicate studies on such products.

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HNC appreciates the opportunity to provide our thoughts on FDA's Proposed Rule and would be pleased to provide FDA with any additional information that might be helpful to the agency as it develops its final rule. HNC supports FDA's efforts to establish an exemption from the IND requirements for certain clinical studies of food. We feel strongly that FDA needs to make clear in the final rule that a study would only involve a "drug use" that triggers application of IND requirements if that study is intended to evaluate a product's ability to treat, prevent, mitigate, or cure disease, and further, and most critically, that the effect of a food on disease or condition can be studied *without* being a "drug use" that would require an IND. Clarifying this important distinction is critical to easing the significant barriers study sponsors face when investigating medical foods and FSDU, which creates unnecessary burdens on product innovation and patient access. We also recommend that FDA consider hosting a public workshop with scientific stakeholders and potential study sponsors to evaluate the logistics of the exemption proposal, including real world examples.

Sincerely,

Robert Rankin

Robert Rankin
Executive Director

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