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By Electronic Submission

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-Market Notification; Draft Guidance for Industry. Docket No. FDA-2022-D-0281. 87 FR 30843 (May 20, 2022).

The Council for Responsible Nutrition (CRN) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) regarding draft guidance issued on May 20, 2022 titled, "Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-Market Notification; Draft Guidance for Industry" ("draft guidance").[1] CRN is the leading trade association for the dietary supplement industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements.[2]

CRN appreciates FDA's intention to encourage marketers and distributors to submit NDI notifications by exercising enforcement discretion when firms submit notifications within a 180-day grace period for NDIs already on the market but have not had a required notification submitted. There may be a few companies, as FDA indicated in the draft guidance, that are prepared to submit catch-up NDI notifications if given the opportunity. However, much of the industry is awaiting FDA to address major concerns related to the agency's revised NDI draft guidance issued in August 2016. CRN expects only a small number of notifications will be submitted under FDA's proposed enforcement discretion period while these concerns remain, and the August 2016 draft guidance still represents FDA's current thinking on the NDI notification requirement and related issues.

In response to FDA's 2016 revised draft guidance[3], CRN voiced concerns that FDA's narrow interpretations of the Food, Drug, and Cosmetic Act (FDCA) and prescriptive safety data requirements would create significant and unnecessary burdens on the dietary supplement industry without increasing safety for consumers.[4] It has been nearly 30 years since Congress enacted the Dietary Supplement Health and Education Act of 1994 (DSHEA) and industry does not have reasonable guidance from FDA on NDI notification requirements. While industry desires FDA guidance, we remain deeply concerned that parts of the 2016 draft guidance are inconsistent with the intent of DSHEA and therefore request that those parts be withdrawn. Table 1 presents a summary of these concerns.

In addition, FDA has not progressed in developing useful tools that would help companies determine their notification obligations and incentivize participation in the NDI notification process. FDA stated in 2016 it was willing to establish an authoritative list of pre-1994 dietary ingredients that are not subject to the NDI notification requirement. This list would create a safe harbor for newer firms that do not have physical evidence that an ingredient was on the market nearly 30 years ago. Aside from holding a public meeting in 2017,[5] FDA has not engaged in any public activity to develop an authoritative list of pre-DSHEA dietary ingredients. CRN continues to advocate for the creation of such an authoritative list to provide companies with clarity on dietary ingredients that do not require an NDI notification.

The 2016 draft guidance indicates firms have the option of creating a confidential NDI master file, which enables supplement manufacturers to purchase and use NDIs that are already the subject of an NDI notification while protecting the intellectual property of the firm that originally submitted the notification. In effort to assist FDA in implementing NDI master files, industry trade associations suggested a tailored NDI master file framework based on the existing Drug Master File; however, FDA has not indicated willingness to establish an NDI master file system.

Protection of innovation through implementation of the NDI master file helps the agency fulfill its public health goals. It incentivizes the submission of NDI notifications and thereby informs FDA about NDIs that enter the market and facilitates agency actions to protect public safety. Responsible companies in the dietary supplement industry invest in generating the necessary data to establish the safety of their ingredients. A significant concern for these ingredient manufacturers is that they must compete on an uneven playing field with companies that fail to generate and submit safety data specific to their NDIs and claim that their ingredients are identical to NDIs that other firms properly notified. The lack of deterrence of companies that bypass the notification requirement discourages those that follow the rules. The NDI master file is a tool to streamline the collection and protection of data investments made by ingredient manufacturers. It provides a way to keep secured confidential information such as safety data related to an NDI and enables companies to authorize others to properly reference master file data. Without proof of authorization, a company cannot claim to have the same ingredient as another. With use of the NDI master file, FDA would be able to identify and enforce against certain marketers of NDIs that fail to comply with the notification requirement.

While CRN appreciates the intention behind FDA's enforcement discretion, we question whether the proposed action would lead to increased NDI submissions considering many NDI-related issues remain. FDA estimates that 4,600 NDI notifications should have been submitted and acknowledges receiving 1,200 notifications.[6] CRN is concerned that the agency's estimate, based on assumptions that 46,000 products were brought on the market since 1994 and 10 percent of those products required an NDI notification,[7] is not supported by evidence. To avoid misleading the public, FDA should rescind this estimate.

If FDA decides to move forward with the enforcement discretion, CRN recommends the agency extend the catch-up submission period beyond 180 days and commit to responding to notification submitters within 90 days of receipt of an NDI notification. More time is needed for FDA and industry to reach common ground on the unresolved NDI-related issues. Moreover, the law requires FDA to make the existence of an NDI notification public within 90 days of receipt. Submitters should be assured their notification receives an FDA response and an opportunity to respond to FDA comments prior to public

display. FDA's draft guidance states that FDA will prioritize review of catch-up notifications but may not be able to complete review of notifications within 75 days. The uncertainty of when submitters may receive a response from FDA, and whether they may be able to respond to any FDA comments about of their notification prior to public display of the notification's existence, may discourage submitters.

Table 1. Concerns raised by CRN in response to FDA's 2016 revised draft guidance

NDI Related Issue	CRN Concern
Definition of "dietary ingredient"	FDA's narrow interpretation of FDCA section 201(ff)(1): • Limits the "dietary substance" category in 201(ff)(1)(E) to substances that have a history of common use as food or drink. CRN believes Congress did not impose the "common use" requirements and that the definition permits substances without history of common use in food or drink as long as they are intended to serve a dietary function in supplementing the diet. • Disqualifies a synthetic copy of an herb or other botanical as a dietary ingredient, unless it first becomes a lawfully marketed ingredient in the conventional food supply therefore qualifying as a "dietary substance" under 201(ff)(1)(E). CRN believes there are no legally or scientifically justifiable grounds for treating synthetic copies of botanical constituents differently where they are chemically equivalent to their naturally occurring counterpart, just as synthetic vitamins are equivalent to naturally occurring vitamins and qualify as dietary ingredients under 201(ff)(1)(A). • Limits synthetically produced dietary ingredients that are "metabolites" to those whose starting material is a dietary ingredient and the production process mimics the metabolic process in the body following ingestion. CRN believes the chemical identity of the end product (the metabolite) should be considered, not the starting material or how the metabolite was synthetically produced. • Limits the category of "amino acids" to alpha-amino carboxylic acid. CRN believes Congress did not limit or narrow this category.
Consideration of "chemically altered"	• FDA's interpretation that extraction with a filtration step and/or extraction with a solvent other than water or aqueous ethanol are processes that cause chemical alteration.
Consideration of "food supply"	• FDA's interpretation of "food supply" excludes dietary supplements so that prior use in dietary supplements does not constitute presence in the food supply.
Changes applied to the manufacture of a pre-DSHEA ingredient that would create an NDI	• FDA's interpretation of manufacturing changes related to pre-DSHEA dietary ingredients that would create an NDI is impractical e.g., FDA states that changing solvent to prepare an extract from a pre-DSHEA dietary ingredient and using a different starting material would create an NDI. CRN believes the focus should be on identity and safety.
Supplement-focused NDI notifications	• FDA's interpretation of when an NDI notification is required to be submitted is impractical. CRN believes the statute does not authorize

	FDA to require a separate NDI notification for each finished product using that NDI unless the finished supplement utilizes the ingredient in a manner that is inconsistent with the serving size range or restrictions on use indicated in the earlier notification, or in combination with other dietary ingredients that may adversely affect the safety profile of the finished supplement. Firms should self-determine if a notification is needed based on an evaluation of the safety of the supplement.
Safety data requirements	• FDA's guidance is prescriptive in describing safety data needed, including a supplement safety narrative that describes the NOAEL and ADI for each ingredient, toxicity data or adverse events that were the basis for determining the NOAEL, the basis for the margin of safety for each ingredient, and possible synergy or interaction among any or all ingredients that could affect the safety of the dietary supplement. • CRN maintains that firms should self-determine if a notification is needed based on an appropriate evaluation of the safety of the supplement. The supplement manufacturer should have the flexibility to determine the appropriate evidence needed to satisfy the requirement that all dietary ingredients, including the NDI, are safe for use in a dietary supplement.

Thank you for considering our comments.

Sincerely,

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[1] Food and Drug Administration. Draft Guidance for Industry: Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-market Notification. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-policy-regarding-certain-new-dietary-ingredients-and-dietary-supplements. Last updated 19 May 2022. Accessed 9 June 2022.

[2] The Council for Responsible Nutrition (CRN), founded in 1973, is a Washington, D.C.-based trade association representing 150+ dietary supplement and functional food manufacturers, ingredient suppliers, and companies providing services to those manufacturers and suppliers. In addition to complying with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety, our manufacturer and supplier members 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.

[3] Food and Drug Administration. Draft Guidance for Industry: New Dietary Ingredient Notifications and Related Issues. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues. Last updated 4 October 2016. Accessed 17 May 2022.

[4] Council for Responsible Nutrition. Comment from Council for Responsible Nutrition (CRN). https://www.regulations.gov/comment/FDA-2011-D-0376-1994. Accessed 17 May 2022.

[5] Food and Drug Administration. Public Meeting to Discuss the Development of a List of Pre-DSHEA Dietary Ingredients. https://www.fda.gov/food/workshops-meetings-webinars-food-and-dietary-supplements/public-meeting-discuss-development-list-pre-dshea-dietary-ingredients. Last updated 29 December 2017. Accessed 9 June 2022.

[6] Food and Drug Administration. Draft Guidance for Industry: Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Pre-market Notification. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-policy-regarding-certain-new-dietary-ingredients-and-dietary-supplements. Last updated 19 May 2022. Accessed 9 June 2022.

[7] Tave S. Public meeting: Responsible Innovation in Dietary Supplements. https://www.fda.gov/media/127746/download. Last updated 6 June 2019. Accessed 6 July 2022.