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June 3, 2024

By Electronic Submission

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

Re: Guidance for Industry: New Dietary Ingredient Notification Procedures and Timeframes - Dietary Supplements. Docket No. FDA-2023-D-5280.

The Council for Responsible Nutrition (CRN)[1] appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA) Guidance for Industry "New Dietary Ingredient Notification Procedures and Timeframes - Dietary Supplements" (Guidance).[2] We recognize that FDA is taking a piecemeal approach to issuing final guidance on New Dietary Ingredient (NDI) Notifications and related issues, and appreciate the initial progress, but urge the agency to expeditiously release final guidance sections that industry has awaited since 2016. At that time, CRN submitted extensive comments on FDA's revised draft guidance[3] offering our interpretation of when an NDI notification (NDIN) is required and recommendations, including the appropriate safety standard for NDIs and information submitted in an NDIN demonstrating that the NDI is reasonably expected to be safe in accordance with 21 U.S.C. 350b(a)(2).[4] CRN voiced concerns that FDA's narrow interpretations of the Food, Drug, and Cosmetic Act

[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] Food and Drug Administration. Guidance for Industry: New Dietary Ingredient Notification Procedures and Timeframes - Dietary Supplements. Last updated 5 March 2024. Accessed 26 April 2024.

[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 3 April 2024. Accessed 26 April 2024.

[4] Council for Responsible Nutrition. Comment from Council for Responsible Nutrition (CRN). https://www.regulations.gov/comment/FDA-2011-D-0376-1994. Accessed 26 April 2024.

(FDCA) and prescriptive safety data requirements would create significant and unnecessary burdens on the dietary supplement industry without increasing safety for consumers.

FDA's recent Guidance signals that FDA is continuing to interpret the statute in a way that would impose the NDIN requirement for dietary supplements when not required by law, and that would apply overly burdensome, unjustified standards for the safety evaluation of NDIs. CRN reiterates our concerns and urges FDA to reconsider this Guidance and to address concerns relevant to other NDIN guidance sections that have yet to be finalized.

I. FDA's recommendations trigger NDINs more than is required by statute.

CRN contends that FDA's Guidance maintains the 2016 draft guidance's overreach by exceeding the NDIN requirements of the FDCA. The agency appears to require two types of premarket notifications related to an NDI: (1) premarket notification of the NDI *and* (2) premarket notification of any dietary supplement containing the NDI. The only exception to the latter is when the prior NDI notification specifically describes the dietary supplement with information covering five elements in Guidance's Section III.E, including identity and levels of other dietary ingredients and non-dietary ingredients, and includes history of use or other evidence of safety for the dietary supplement under its labeled conditions of use. This exception is not expected to be common, as NDI-focused notifications often do not anticipate the dietary supplements that could contain the NDI to the level of detail described in Section III.E, unless the dietary supplement contains only the NDI and no other dietary ingredients. Once again, FDA is suggesting an NDIN should be submitted for nearly *every* dietary supplement that intends to contain an NDI that has already been notified.

Guidance Section III.A states, in part:

> "…notifications from ingredient manufacturers do not eliminate the requirement for a NDIN from the manufacturer or distributor of the dietary supplement in which the NDI will be used unless the prior notification for the NDI included information about the dietary supplement, specifically: (1) a description of the dietary supplement that contains the information required by 21 CFR 190.6(b)(3); and (2) the history of use or other evidence of safety that formed the basis of the notifier's conclusion that the dietary supplement would reasonably be expected to be safe under its labeled conditions of use."

Guidance Section III.E states, in part:

> "**E. How should the NDIN describe the dietary supplement in which the NDI will be used?**
>
> The NDIN should contain a description of the dietary supplement in which the NDI will be used, including: (1) the level of the NDI in the dietary supplement per serving; (2) the identity and level of any other dietary ingredients and non-dietary ingredients (e.g., binders and fillers) in the dietary supplement per serving..."

A. FDA's interpretation is contrary to the plain language of the FDCA.

Section 413(a) of the FDCA, as added by DSHEA, provides that a dietary supplement that contains an NDI is adulterated and cannot lawfully be marketed unless:

(a) (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.

[or]

(2) There is a history of use or other evidence of safety establishing that the ***dietary ingredient*** when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, ***the manufacturer or distributor of the dietary ingredient or dietary supplement*** provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.[5]

We continue to assert that, "the plain language of DSHEA clearly contemplates ingredient-focused notifications. The sole requirement is that FDA receive adequate information on which any party may rely to conclude that its NDI-containing dietary supplement is reasonably expected to be safe."[6] Once a notification for an NDI has been submitted and acknowledged, 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."[4]

CRN continues to recommend that FDA permit ingredient manufacturers or distributors to submit NDINs that serve as the basis for establishing the safety of an NDI in a range of dietary supplements, by describing the range of daily intake levels for the NDI and any use restrictions. The notification for the NDI may identify other dietary ingredients that can be combined with the NDI, however, CRN maintains that "[i]n cases where an NDI will be combined with other ingredients not specifically contemplated in a prior NDI notification, but that empirically will not alter the safety profile of the finished product, a separate notification is not necessary."[6]

This approach satisfies the statutory requirement because "at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor ***of the dietary ingredient***…provide[d] the Secretary with information…which [was] the basis on which the manufacturer or distributor has concluded that ***a dietary supplement containing such dietary ingredient*** will reasonably be expected to be safe."[7]

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[5] FDCA § 413(a) (emphasis added).
[6] CRN Comments on 2011 Draft Guidance. https://www.crnusa.org/sites/default/files/pdfs/CRN_CHPA%20Comments_NDI%20Notification%20Draft%20Guidance_Final_12_2_2011.pdf. Accessed 26 April 2024.
[7] FDCA § 413(a)(2) (emphasis added).

II. FDA's Guidance conflicts with itself regarding who is responsible for NDINs.

Guidance Section III.R states, "FDA regulations require an NDIN to be signed by the person designated by the manufacturer or distributor of the dietary supplement that contains the NDI (see 21 CFR 190.6(b)(5))." CRN disagrees with FDA's view that NDINs are required to be signed only by the person designated by the manufacturer or distributor of the dietary supplement that contains the NDI. There are instances where the NDI manufacturer or distributor is not the same as the dietary supplement manufacturer or distributor. The statute also allows for the NDIN to be submitted by the manufacturer or distributor of the NDI; therefore, it is permissible for the NDIN to be signed by the person designated by the manufacturer or distributor of the NDI.

Further, Section III.R is inconsistent with the Guidance Section III.A, which states, in part:

> "**A. Who must submit an NDIN?**
>
> Either the manufacturer or distributor of a dietary supplement that contains an NDI, or the manufacturer or distributor of the NDI, must notify FDA at least 75 days before marketing the article in the United States…"

Section III.A makes clear that the manufacturer or distributor of the NDI can also satisfy the notification requirement. Moreover, the NDI manufacturer or distributor would be the appropriate entity to submit the NDI notification when safety information for the NDI resides with the NDI manufacturer or distributor. An NDI manufacturer or distributor should also be able to submit an NDIN referencing an NDI master file. Since it would be expected that the notification submitter is the same as the party designating a person to sign the notification, it follows that the NDI manufacturer or distributor who submits the NDIN should also be allowed to designate a person to sign the NDIN.

III. FDA maintains recommendations for unnecessary information in NDINs.

The recommendation in Section III.E remains the same as that in the 2016 draft guidance and indicates that FDA is maintaining that detailed information about other dietary ingredients and non-dietary ingredients should be included in the NDIN for dietary supplements. We repeat that the statute does not require a separate NDIN for each dietary supplement containing an NDI unless the supplement utilizes the NDI in a manner that is inconsistent with the serving size range or restrictions on use indicated in the prior NDIN, or in combination with other dietary ingredients that may adversely affect the safety profile of the finished supplement. In keeping with this position, the NDINs for dietary supplements do not need to (1) identify other dietary ingredients and non-dietary ingredient in the supplement containing the NDI and (2) include the level of other dietary ingredients and non-dietary ingredients.

Although FDA's Guidance does not address the information in the safety narrative, the fact that Section III.E. remains mostly unchanged from its 2016 version is an indication that FDA may continue to recommend additional information that is not necessary to demonstrate the safety of the dietary supplement containing the NDI. CRN reiterates that we disagree with FDA's 2016 draft guidance Section VI.C.3 that if a supplement contains dietary ingredients other than the NDI, the notification should include the no-observed-adverse-effect level (NOAEL) and acceptable daily intake for each ingredient, describe the toxicity data or adverse events that were the basis for determining the NOAEL, state the

basis for the margin of safety for each ingredient, and discuss whether there is any possible synergy or interaction among any or all ingredients that could affect the safety of the dietary supplement.

The NDIN does not need detailed information about other dietary ingredients because the adulteration provision prohibits dietary supplements and dietary ingredients that present a "significant or unreasonable risk of illness or injury."[8] Further, an analysis of the possible synergy or interaction among the ingredients should be provided only when the combination of the NDI with other dietary ingredients in a formulation potentially negatively alters the safety profile of the finished product, to demonstrate that the combination is reasonably expected to be safe under the recommended conditions of use.

We continue to disagree with FDA's 2016 draft guidance recommendation to submit references and information describing the function of each non-dietary used in the dietary supplement containing the NDI, including the technical effect and the quantity needed to achieve that technical effect. Detailed information on non-dietary ingredients (i.e., food additive, color additive, or Generally Recognized as Safe (GRAS) substance) does not contribute to the understanding of the safety of the supplement containing the NDI under recommended conditions of use. All lawful non-dietary ingredients have already been approved, notified, or affirmed as safe in accordance with the FDCA and FDA regulations.

FDA has never sought to premarket review formulations of food ingredients, such as formulations with ingredients that have gone through the GRAS notification process. There is no justification for FDA to review combinations of NDIs plus existing legal dietary ingredients and other ingredients when the use of the NDI is within the range of safe intake levels and does not violate use restrictions described in a prior NDI notification acknowledged by FDA.

IV. Conclusion

We urge FDA to reconsider its overreaching interpretation of the NDIN requirement and recommendations for the level of safety information that should be included in an NDIN. Further, the NDIN should only contain information that is truly consequential for the safety evaluation of the NDI and dietary supplements containing the NDI.

Thank you for considering our comments.

Sincerely,

Haiuyen Nguyen
Vice President, Regulatory & Nutrition Policy

[8] FDCA § 402(f)(1)(A).