

July 15, 2019

VIA ELECTRONIC SUBMISSION

Dockets Management Staff
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA's Responsible Innovation in Dietary Supplements; Public Meeting; Request for Comments. 84 Fed. Reg. 14660-14662 (April 11, 2019). Docket No. FDA-2019-N-1388.

The Council for Responsible Nutrition (CRN)¹, the leading trade association that represents dietary supplement and functional food manufacturers and ingredient suppliers, appreciates the opportunity to provide input on supporting and promoting innovations in dietary supplements. CRN applauds FDA for making efforts to examine how it can modernize approaches to regulating a steadily growing dietary supplement industry. The May 16, 2019 public meeting was a positive step toward this goal as the agency provided opportunity for stakeholders to identify challenges and solutions to dietary supplement and dietary ingredient innovation. However, with this positive step, there needs to be further action on the agency's

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, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and 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 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, 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 and food 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.

part to demonstrate that it is committed to modernizing its approach, including providing thoughtful responses to stakeholders' recommendations. CRN remains concerned about FDA's interpretation of the Dietary Supplement Health and Education Act (DSHEA) as espoused in the agency's first draft guidance on new dietary ingredients (NDIs) in 2011 and again in its revised draft guidance in 2016. If modernization of the approach to regulation is the intention, and if responsible innovation by industry is a priority goal, FDA should remove impediments to longstanding issues regarding permissible dietary ingredients, facilitate industry's understanding of NDI notification requirements, and promote innovation by protecting the intellectual property of those that invest in science to bring new ingredients to the market using the NDI notification process as intended by DSHEA.

I. The scope of dietary ingredients under DSHEA

CRN has on many occasions expressed its perspective to FDA on the scope of dietary ingredients permitted by DSHEA (see CRN's June 2011 comments on defining a "dietary ingredient"²; December 2011 comments on the 2011 NDI draft guidance³; October 2012 comments on the lawful status of synthetic copies of naturally occurring botanical constituents as dietary ingredients⁴; and December 2016 comments on the revised NDI draft guidance⁵). CRN maintains that the Federal Food, Drug, and Cosmetic Act (FDCA) intends a wide variety of dietary ingredients and anticipates innovation of many new dietary ingredients. It requires the term "dietary substance" under Section 201(ff)(1)(E) to encompass ingredients intended to supplement the diet that do not have historical use in conventional food. A plain reading of the language in Section 201(ff)(1)(E), "for use by man to supplement the diet by increasing the total dietary intake," makes clear that a substance that is intended for use to supplement the diet by

² Docket No. FDA-2009-P-0298. CRN comments on Defining a "Dietary Ingredient." June 29, 2011.

³ Docket No. FDA-2011-D-0376. CRN Comments on FDA Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. December 2, 2011.

⁴ Docket No. FDA-2011-D-0376. CRN Comments of lawful status of synthetic botanical constituents as dietary ingredients. October 23, 2012.

⁵ Docket No. FDA-2011-D-0376. CRN Comments on FDA Revised Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. December 12, 2016.

increasing the total dietary intake (even if that increase is from zero intake) is therefore a “dietary substance” that may be a lawful dietary ingredient under Section 201(ff)(1)(E), as long as it meets the other requirements of the statute. The FDCA also allows a synthetic copy of a botanical constituent to be a “constituent” under Section 201(ff)(1)(F) as long as it is chemically equivalent to its nature-derived counterpart. Further, in the revised NDI draft guidance, FDA takes the position that synthetic copies of botanical constituents are excluded from the definition of “dietary ingredient” within the meaning of Section 201(ff)(1)(F) while acknowledging that all other articles listed in the definition—vitamins, minerals, and amino acids—are still dietary ingredients in synthetic form. Vitamins, minerals, and amino acids are some of the constituents of botanicals that humans consume as food. Congress made no reference to the source of dietary ingredients as being natural or synthetic, nor did Congress specify that only some of these categories of dietary ingredients may be produced synthetically while others must only come from natural sources. CRN recommends that chemical equivalence (including consideration of stereochemistry, if applicable), rather than the source of the ingredient, should be the determining factor in whether or not a synthetic copy of a botanical constituent is a dietary ingredient. There are no scientifically justifiable grounds for treating synthetic copies of botanical constituents differently when they are chemically equivalent to their plant-derived, naturally-occurring counterparts. If there are safety concerns, then the NDI notification process provides a way for FDA to evaluate and directly respond to potential safety issues prior to the marketing of these ingredients.

CRN again recommends FDA re-evaluate its narrow stance on the scope of permissible dietary ingredients under DSHEA. In short, FDA should issue a final NDI guidance that reflects congressional intent that Section 201(ff)(1)(E) includes ingredients that have no prior use in conventional food, provided they are intended to supplement the diet by increasing the total dietary intake of that substance, whether the increase is from zero or another level of intake. FDA should also recognize that Section 201(ff)(1)(F) allows for synthetic copies of botanical constituents to be dietary ingredients just as synthetic copies of vitamins, minerals, and amino acids (which are also constituents of botanicals) are dietary ingredients.

II. Understanding exceptions to the NDI notification requirements

In comments to FDA's 2016 revised NDI draft guidance, CRN explained that clarity is needed surrounding (1) dietary ingredients that are pre-DSHEA and therefore do not require notification; and (2) dietary ingredients that are new but do not require notification because they are "present in the food supply as an article used for food in a form in which the food has not been chemically altered." CRN also offered an interpretation of "food supply" under 21 U.S.C. § 350b(a)(1) that contrasts with FDA's narrow interpretation. CRN recommends that FDA modify its position to reflect that a dietary ingredient with prior use in a dietary supplement is considered "present in the food supply" and therefore excluded from the NDI notification requirement (provided it is not chemically altered). Dietary supplements and their ingredients are "food" and this interpretation is consistent with not only the plain language of the FDCA, but also the history of "food."

In comments⁶ to FDA following the October 3, 2017 public meeting on development of a list of pre-DSHEA dietary ingredients, CRN recommends that FDA create an expansive list covering three types of dietary ingredients that are potentially eligible for use in dietary supplements without an NDI notification: pre-DSHEA dietary ingredients, NDIs with a successful notification, and NDIs potentially exempt from the notification requirement (NDIs present in the food supply that have not been chemically altered). This list could be compiled from existing FDA resources, such as ingredients in 21 C.F.R. § 100 et seq., in the Substances Added to Food inventory (formerly Everything Added to Foods in the United States (EAFUS)), and in the GRAS Notice Inventory and SCOGS Review Database. Similarly, foods in the global food supply could also be added by looking to other global food databases, such as the European Union food additives database. This expansive, authoritative list will help industry assess whether a dietary ingredient is indeed an NDI requiring a notification and reduce confusion and

⁶ FDA Docket No. FDA-2017-N-4625. CRN comments on Development of a List of Pre-Dietary Supplement Health and Education Act Dietary Ingredients; Public Meeting; Request for Comments. December 4, 2017.

burden on both FDA and industry by eliminating unnecessary submission and review of notifications for dietary ingredients that do not require a notification in the first place.

An additional consideration is assessment of whether an NDI notification is required because of manufacturing changes. We acknowledge that manufacturing processes may change significantly over time. Many of these changes can improve the manufacturing efficiency or the purity of dietary ingredients, but do not affect the identity or safety of the ingredient when compared to the previous version of the same ingredient. CRN agrees with FDA that when a manufacturing process has changed for a dietary ingredient, the regulatory status of the resulting dietary ingredient is dependent on the extent to which such change impacts that ingredient. This is the case for all dietary ingredients, including pre- and post-DSHEA ingredients (i.e. NDIs that did not require a notification and NDIs that were successfully notified). CRN requests that FDA clarify that an NDI notification for an existing dietary ingredient would be required only when the manufacturing change results in either a change in the identity of the dietary ingredient (e.g., a change in specifications needed to chemically characterize the ingredient), or a change that has a potential significant adverse impact on the safety of the ingredient for the intended use in a dietary supplement. Moreover, CRN recognizes that some manufacturing changes would result in minor changes in the relative amounts or ratios of known constituents of a dietary ingredient. In these cases, FDA should allow for the submission of an abbreviated NDI notification in which a firm demonstrates substantial similarities between their dietary ingredient and the existing dietary ingredient through a compositional analysis.

III. Potential commercial or marketing advantages to incentivize responsible innovation; and promoting overall compliance with the premarket notification requirement through enforcement

Lack of clarity with regard to what constitutes an NDI that requires notification (as explained above), lack of intellectual property (IP) protection for those who submit NDI notifications, and lack of regulatory enforcement have hindered industry's participation in the

NDI notification process. In particular, lack of IP protection has led some firms to use alternative safety review mechanisms not specifically designed for NDIs, such as the GRAS self-determination approach. This approach addresses safety of new ingredients but does not require disclosure of intellectual property or proprietary data. Although similar in some aspects, GRAS self-determination and NDI notification serve distinct purposes and should not be viewed as substitutes for each other. Further, exclusive use of GRAS self-determinations by firms has the potential to impair FDA's ability to understand when NDIs enter the market because the agency is not notified. While GRAS self-determination is a legitimate pathway to market that ensures the safety of new ingredients, the NDI notification process is the intended pathway for NDIs. To improve compliance with the NDI notification provision, drawbacks of the NDI notification process should be recognized and mitigated. Industry should be incentivized to expend the appropriate resources for safety assessments of NDIs and notify FDA, and the agency should, in turn, rigorously enforce the NDI provision to deter those firms that bring NDIs to the market without going through the proper notification process.

FDA estimates that only about 1100 of the estimated 4000 NDIs have been notified to the agency since the passage of DSHEA⁷. There exists a range of challenges with and potential opportunities to promote and improve compliance with the NDI notification requirement.

A. FDA should protect intellectual property to promote NDI innovation

For those companies that invest in generating the necessary data to establish the safety of their ingredients, the lack of data protection is a major disincentive to submit NDI notifications. Their concern is that "me too" imitators of previously notified NDIs enter the market without the proper safety review; firms that bring these ingredients to market do not generate their own safety data but instead pirate the safety data provided by initial notifiers⁸.

⁷ Tave S. Public Meeting to Discuss Responsible Innovation in Dietary Supplements, Food and Drug Administration, 16 May 2019, Center for Food Safety and Applied Nutrition, College Park, MD. Opening Remarks.

⁸ Mitsubishi's open letter to industry on PQQ. NutraIngredients-USA. 15 Mar 2017, <https://www.nutraingredients-usa.com/Article/2013/10/02/Mitsubishi-s-open-letter-to-industry-on-PQQ>. Accessed 10 July 2019.

This practice promotes an unlevel playing field and disincentivizes compliance by responsible industry.

To date, FDA has not expressed concern about this troubling practice. The agency appears to see itself as a protector of public safety—not a protector of IP investment. However, public safety and IP protection are not mutually exclusive. By participating in the effort to protect ingredient manufacturers' investment in the generation of safety data, FDA can incentivize the submission of more NDI notifications. More notifications will, in turn, better inform the agency as to what new ingredients are entering the market and will foster better assurance that these new ingredients, and supplement products containing them, are safe. In short, public safety can be improved through IP protection.

One approach to providing IP protection is the concept of Master Files. The NDI Master File (NDIMF) represents a useful tool to streamline the collection and protection of data investments made by ingredient manufacturers. As described previously by CRN and others, the NDIMF can house ingredient-specific confidential information and/or safety data, and can be used or cited (with permission) by subsequent notifiers. Each NDIMF should receive a unique file number and description, the contents of which should be protected as trade secrets.

A transparent process is essential for this system to function properly. If an ingredient manufacturer determines its ingredient is an NDI requiring notification, it will need to know which NDI notifications have already been successful. The ingredient manufacturer can then determine whether it is required to generate new safety data for its ingredient or obtain permission to rely on an existing NDIMF through a mutually beneficial business arrangement. In either case, each dietary ingredient manufacturer should submit a separate NDI notification containing safety data generated on its own ingredient or a reference to an existing NDIMF.

FDA will also need to be aware of NDIs entering the marketplace and enforce against those companies that unscrupulously bypass the notification requirement. In many cases, these violating firms market NDIs and claim them to be similar to NDIs that have been properly notified by other firms and fail to generate and submit safety data specific to their ingredients.

With use of the NDIMF, FDA would be able to swiftly identify marketers of NDIs that were not properly notified and enforce against those that bypass the notification requirement.

CRN encourages FDA to clarify the use of an NDIMF and how the contents of the file will be protected by the agency. The utility and integrity of the NDIMF will depend largely on FDA's support and enforcement of its proper use. CRN will submit to FDA an NDIMF framework for consideration in the near future. We hope to help FDA advance steps in the implementation of an NDIMF system that will serve both the industry and the agency.

B. FDA should conduct meaningful, effective enforcement to promote overall compliance with premarket notification

FDA's effective enforcement of the NDI provision is paramount to increasing compliance by industry and meeting the agency's public health mandate. CRN recognizes that FDA has limited resources, which is why we have consistently advocated for increased funding for the Office of Dietary Supplement Programs within the Center for Food Safety and Applied Nutrition. However, FDA must go further than sending Warning Letters to firms when the agency believes they are marketing NDIs that may pose a safety risk to consumers. FDA must take action when any firm violates the law by not submitting the appropriate NDI safety information 75 days before marketing the NDI. Moreover, FDA must make the commitment to enforce by utilizing the breadth of enforcement tools available, including Warning Letters, untitled letters, seizures, administrative detentions, misdemeanor proceedings, fines and disgorgement of profits, as well as debarment and injunctions. By taking action against violators and escalating enforcement tactics when necessary, the agency will send a clear message to industry that it must take seriously its obligation to comply with the NDI provision. FDA will also demonstrate support for responsible firms that use the proper mechanisms to innovate and bring new and safe ingredients to the market.

CRN acknowledges that FDA needs additional resources (e.g., funding, personnel) and technology tools to enhance its ability to conduct meaningful enforcement. In concept, a Mandatory Product Listing that would require dietary supplement manufacturers to provide

manufacturer information, e.g., manufacturer contact information, and product information, e.g., product labels and list of ingredients, would help FDA better understand the landscape of products in the marketplace and target enforcement against violators of the NDI provision. Specifically, a Mandatory Product Listing would help FDA identify products containing NDIs that should have an NDI notification on file but do not, as well as marketers of such non-compliant products.

CRN supports the concept of a Mandatory Product Listing. We anticipate that if such a concept were to move forward to creation, CRN would fully participate in the discussions regarding its framework and implementation. However, for a Mandatory Product Listing to serve as an effective enforcement tool, FDA must be prepared with resources and resolve to take action against violators. Otherwise, the Mandatory Product Listing would just duplicate existing voluntary product label databases (e.g. Supplement OWL) in which only a segment of the industry participates. Consequently, without effective enforcement, a Mandatory Product Listing would not serve its intended purpose to help FDA protect public health.

Conclusion

For many years, both the industry and the agency have reflected on the challenges and opportunities to strengthen dietary supplement regulation and to enhance compliance. Now is the time to take action. CRN urges FDA to take seriously the rational interpretations of the law that industry has submitted on the scope of dietary ingredients and other NDI-related issues. We request the agency to take the lead in providing clarity on pre-DSHEA dietary ingredients and other exceptions to the notification requirement, i.e., creating an authoritative list, to help companies determine what ingredients are truly new and require notification. In general, companies desire to bring new ingredients to market, and FDA has a role in supporting these companies and in facilitating innovation. The agency should incentivize companies to generate and submit safety data for NDIs by establishing mechanisms to protect IP, and one approach is the NDI Master File. However, new tools and mechanisms will not result in significant change to the regulatory landscape without more rigorous enforcement. Enforcement should be a priority and FDA should avail itself of all the enforcement tools it has the authority to use.

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CRN thanks FDA for the opportunity to share our views and is committed to further discussions on this important topic of responsible innovations in dietary supplements.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew Shao".

Andrew Shao
Interim Senior Vice President, Scientific and Regulatory Affairs

A handwritten signature in black ink, appearing to read "Haiuyen Nguyen".

Haiuyen Nguyen
Senior Director, Scientific and Regulatory Affairs