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via Electronic Submission
Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-N-4625 – Development of a List of Pre-Dietary Supplement Health and Education Act Dietary Ingredients; Public Meeting; Request for Comments (82 FR 42098 (September 6, 2017))

The Council for Responsible Nutrition ("CRN") appreciates the opportunity to provide comments regarding the processes and standards that FDA should utilize in developing an authoritative pre-Dietary Supplement Health and Education Act ("pre-DSHEA") list of dietary ingredients. CRN is the leading trade association representing dietary supplement and functional food manufacturers, marketers, and ingredient suppliers.[1]

CRN supports FDA's willingness to develop an authoritative list of pre-DSHEA dietary ingredients and values FDA's holding of the October 3, 2017 public meeting to discuss issues relating to the creation of this list. As discussed at the meeting, such a list could be beneficial to FDA, industry, and consumers, so long as it is appropriately crafted and tailored. CRN recommends that, if FDA decides to use its limited resources towards creating a pre-DSHEA dietary ingredients list, the agency should take additional steps to provide clarity with regard to the regulatory status of a broader list of potential dietary ingredients exempt from the new dietary ingredient ("NDI") 75-day premarket notification ("Notification"). CRN suggests that FDA expand the authoritative list to also include NDIs with a Notification filed without objection and NDIs that are potentially exempt from the Notification requirement. A broad list will help provide transparency and clarity as it would cover three potential types of dietary ingredients: pre-DSHEA dietary ingredients, NDIs with a successful Notification, and NDIs potentially exempt from the Notification requirement. CRN shares FDA's commitment to ensure that dietary supplements on the market are safe and firmly recognizes that all dietary ingredients are subject to a broad adulteration standard, regardless of whether they are subject to the Notification requirement.

[1] 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.

I. Background

The dietary supplement industry strives to provide safe and beneficial products to consumers, and DSHEA was enacted to ensure consumers have access to safe dietary supplements.[2] When enacting DSHEA, Congress recognized that dietary supplements are generally safe[3] but also understood that there may be situations where safety assessments are needed as part of product innovation. Consequently, DSHEA requires any NDI (*i.e.*, a dietary ingredient marketed after October 15, 1994), unless exempt, to submit a Notification to FDA establishing its safety under the intended conditions of its use.[4] Pre-DSHEA dietary ingredients that were marketed prior to October 15, 1994 are not subject to this Notification requirement. Although these pre-DSHEA dietary ingredients do not necessarily require a Notification, they are still subject to a broad adulteration standard. Under 21 U.S.C. § 342(f)(1)(A), a dietary supplement is adulterated if it "presents a significant or unreasonable risk of illness or injury," and consequently there must be adequate evaluation of safe use regardless of whether the dietary ingredient is a pre-DSHEA ingredient or an NDI.

Despite DSHEA's enactment over twenty years ago, today the dietary supplement industry lacks a finalized guidance to assist companies with determining their Notification requirements. FDA's draft guidance documents to date have set forth FDA's thinking regarding Notification requirements, and industry has embraced its obligation to file Notifications. However, the industry still encounters ambiguity when assessing whether a dietary ingredient is indeed an NDI requiring a Notification. Further, filing Notifications for dietary ingredients that do not require a Notification results in a significant and unnecessary burden for both FDA and the dietary supplement industry.[5] Thus, creation of an authoritative pre-DSHEA dietary ingredient list would help to ensure that Notifications are not filed for exempt dietary ingredients. But, as CRN presented at the October 3rd public meeting, an expansive, fluid list covering three types of dietary ingredients that are potentially eligible for use in dietary supplements without Notification will provide greater clarity and certainty to companies with regard to compliance with regulatory requirements. CRN offers the below comments as a follow up to the presentations and discussions from the October 3rd public meeting.

II. CRN Recommends Creation of an Expansive Dietary Ingredient List

CRN advocates that FDA develop an expansive and fluid list of dietary ingredients that are generally eligible for use in dietary supplements without Notification. Focusing attention only on pre-DSHEA dietary ingredients may not be the best use of FDA and industry resources. As described below, CRN believes that a more worthwhile effort is one that aims to develop a

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[2] Dietary Supplement Health and Education Act of 1994 (Public Law 103-417, 103rd Congress).
[3] *Id.* at Section 2(14).
[4] *See* 21 U.S.C. 350b.
[5] As CRN has noted in a previous comment, preparation of a successful NDI notification reportedly takes anywhere from 100-350 hours. Further, the cost of developing a successful NDI dossier can become extraordinarily high when considering the expense of conducting scientific studies that as well as the engagement of scientific, regulatory, and legal consultants necessary to navigate the filing process. Taken together, the time and expense invested in an NDI notification is significant, and thus firms should have regulatory certainty whether a notification is required. *See* Docket No. FDA-2011-N-0410: Agency Information Collection Activities; Proposed Collection; Comment Request; Premarket Notification for a New Dietary Ingredient. CRN comment available at: https://www.regulations.gov/document?D=FDA-2011-N-0410-0004.

compilation of not only pre-DSHEA dietary ingredients, but also of NDIs that have been notified to FDA without objection, and substances present in the food supply that are articles used for food that could be eligible for dietary supplement use without Notification. Such an expanded list would be more meaningful to industry and FDA because it provides firms with additional transparency and confidence when assessing a dietary ingredient's regulatory status and serves as a tool for FDA in determining enforcement priorities.

A. A Dietary Ingredient List Should Include Ingredients Determined to be Pre-DSHEA Based on Available Evidence Using a Flexible Standard and a Streamlined Review Process

When determining which dietary ingredients should be included as pre-DSHEA dietary ingredients, CRN recommends that FDA consider all available evidence and develop a flexible standard for concluding whether a dietary ingredient was indeed marketed prior to October 15, 1994. Additionally, CRN recommends that the evaluation process be streamlined through the use of external experts and timelines for evidence submission, review, and update.

However, CRN cautions against having any authoritative pre-DSHEA dietary ingredients list appear as though it is complete and final. Even if FDA reviews an ingredient and does not include it on the list, it could potentially be a pre-DSHEA dietary ingredient if additional marketing evidence becomes available at a later time. As FDA acknowledged in its recent draft guidance, "omission of an ingredient from the [pre-DSHEA dietary ingredient] list would be regarded as neutral and would not affect the ingredient's regulatory status."[6] Consequently, CRN recommends that any authoritative list bear adequate and appropriate disclaimers to signal to industry, consumers, and other stakeholders that exclusion from the list is not dispositive of a dietary ingredient's regulatory status. Additionally, FDA should create a process through which ingredients could be added to the list subsequent to its initial publication, should sufficient evidence be compiled and made available to the agency to establish the pre-DSHEA status of that ingredient.

1. Currently Available Evidence Should be Considered When Determining Pre-DSHEA Status

CRN strongly encourages FDA to begin its evaluation by reviewing available evidence, such as pre-DSHEA dietary ingredients lists curated by industry trade associations. These lists were developed contemporaneously with the implementation of DSHEA and are a useful tool for identifying dietary ingredients that FDA could examine as part of a review process. For example, FDA could start by compiling the existing trade association lists and removing duplicates and substances that are clearly not dietary ingredients (such as acetaminophen). After establishing this initial list, FDA could publish the list and solicit further evidence to evaluate dietary ingredients on the list, using a flexible standard (as described below) and tailoring the listing based on this assessment. That is, FDA could describe the specific form of a dietary ingredient that is pre-DSHEA based on the totality of the available evidence for the specific form. For example, for a botanical dietary ingredient, the list could specify particular plant part(s) or extract(s) that would

[6] *See* IV.A.11 Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry, page 20 (August 2016) (available at: https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf).

be considered pre-DSHEA. The conclusion of this review would be a condensed list that describes dietary ingredients that were sold prior to October 15, 1994.

2. A Flexible Standard Should Be Utilized When Examining Pre-DSHEA Evidence

A crucial component to the successful development of a pre-DSHEA dietary ingredients list is the standard used to evaluate whether there is proof that a dietary ingredient was marketed prior to October 15, 1994. CRN proposes a flexible standard based on the totality of evidence, including marketing materials, labeling, affidavits, literature references, and expert opinions, in order to establish a list that is fruitful for both FDA and industry. The most recent NDI draft guidance describes a rigorous standard that requires ingredient information that is "sufficiently precise" to describe the ingredient's identity.[7] As noted in previously submitted comments, CRN is concerned that although advertisements exist for dietary ingredients prior to October 15, 1994, much of this pre-1994 marketing information would not have the detailed information contemplated by FDA's recent draft guidance. For example, a consumer-facing advertisement for a botanical dietary supplement may indicate specific botanical dietary ingredients, but would not likely list other details such as plant part, extract type, or degree of purification. There are many reasons why pre-DSHEA documentation may lack the specificity that FDA describes in the recent draft guidance; in particular, FDA should consider the pre-DSHEA regulatory environment for advertising and labeling dietary supplements, which did not require all of the detailed information FDA proposes in the 2016 draft guidance. Further, business records and ingredient specification sheets that could potentially contain this information are likely inaccessible as many companies no longer exist and their records are either lost or destroyed. If FDA had initiated a pre-DSHEA dietary ingredients list in 1994, it could have examined the ingredient details the draft guidance proposes; however, this information is not reasonably available over twenty years later. Therefore, the draft guidance's proposed standard may impose an unreasonable regulatory barrier since it may lead to the classification of some dietary ingredients as NDIs when they are in fact pre-DSHEA.

Using a fluid, flexible standard in light of potential historic limitations, such as the "totality of the evidence" approach, can help achieve a pre-DSHEA dietary ingredients list that is accurate and acceptable to both FDA and industry. Additional sources such as reference books, affidavits, and expert opinions can help fill in any potential gaps in information found in advertisements or business records. Consider an example in which the following pieces of evidence exist: (1) a pre-DSHEA botanical supplement advertisement indicates the Latin name of the botanical dietary ingredient, but contains no information on the plant part or type of extract; (2) historical references indicate that the specific botanical part typically used in similar supplement products was the root; (3) experts and reference books establish that such a botanical ingredient was commonly extracted using ethanol as a solvent. In this example, the advertisement in conjunction with historical references, experts and reference books provide strong evidence that the plant part in the advertised botanical supplement was the root and the type of extract was an ethanol extract. Historical evidence and expert testimony such as this would be invaluable for establishing an ingredient's full history and should be taken into account when evaluating whether a dietary ingredient was marketed prior to October 15, 1994. As such, CRN urges that the pre-DSHEA dietary ingredient

[7] *Id*.

review utilize a "totality of the evidence" approach that takes into account many different types of evidence.

3. Pre-DSHEA Evidence Review Can Be Streamlined Through A Defined Timeline and Use of External Experts

After compiling available information, FDA's next step should include a streamlined, tailored review of the evidence in order for this exercise to provide the most benefit. Indeed, due to the large number of ingredients that FDA would likely review, a laborious procedure similar to the OTC monograph process would be inefficient and unnecessarily burdensome. Further, the release of tentative conclusions and use of a notice-and-comment period is not suited for this type of review. Instead, CRN recommends that FDA consider a process with established timeframes with a set period of time for industry and other stakeholders to submit evidence concerning pre-DSHEA status, followed by a set period for FDA review and issuance of the list. For example, one possibility would be for FDA to publish an initial pre-DSHEA dietary ingredients list based on trade association lists (as discussed above) and allow industry 6-12 months to gather and submit additional evidence for these ingredients, as well as evidence for any other potential pre-DSHEA dietary ingredients not included on this list. From here, FDA could release findings regularly according to a set schedule (such as publishing a determination concerning a pre-determined number of ingredients quarterly until all ingredients have been reviewed). Unlike the OTC monograph process, this proposed process would provide pre-established review time periods and clear guidance in an efficient manner.

FDA should use external experts to assist the agency with efficient review of potential pre-DSHEA dietary ingredients. These experts would not only provide important subject matter expertise, but could also reduce the burden on FDA personnel. CRN recommends a public nomination process in which FDA and industry identify and select suitable experts. This process could run in conjunction with the dietary ingredient evidence submission process so that experts are retained and ready to review ingredients once the time period for evidence submission has closed.

B. <u>An Authoritative List Should Include a Reliable Compilation of Notifications That Were Filed With No Objection</u>

In addition to creating a list of dietary ingredients that were marketed prior to October 15, 1994, CRN recommends that FDA also include a comprehensive list of Notifications that FDA has acknowledged with no objection. CRN believes that a reliable compilation of these past Notifications will facilitate transparency between FDA and industry, and can be a crucial tool in helping firms assess whether their dietary ingredient is an NDI requiring a Notification. CRN acknowledges FDA's position that NDI notifications are manufacturer/distributor specific. Thus, inclusion of a previously notified NDI on the proposed list does not relieve other firms selling the same dietary ingredient from the burden of determining whether to submit their own Notification. Indeed, any list of past Notifications should bear a disclaimer to this effect similar to what is currently available on the FDA posted notification list.[8] An easily accessible list of past

[8] *See Id.* ("THE FACT THAT A NEW DIETARY INGREDIENT IS LISTED IN THIS TABLE DOES NOT CONSTITUTE A FINDING BY FDA THAT A NEW DIETARY INGREDIENT OR A DIETARY SUPPLEMENT THAT CONTAINS A NEW DIETARY INGREDIENT IS SAFE OR IS NOT ADULTERATED UNDER

Notifications filed without objection would also assist firms with the identification of manufacturers who have adequate Notifications and with the review of publically available safety data.

Further, in addition to a list of Notifications filed without objection as part of an authoritative dietary ingredient list, CRN also recommends that FDA create a readily accessible and searchable database of all past Notifications and the accompanying information and documentation, similar to the inventory of Generally Recognized As Safe (GRAS) Notices[9]. Although FDA has previously posted a list of Notifications, it has not been updated since March 2001.[10] CRN acknowledges that although some Notifications are posted on www.regulations.gov, they are not easily searchable. Thus, Notifications filed over the last 15 years are not readily accessible to the industry. Consolidating all Notifications into a single searchable database would be a crucial tool to help firms assess whether a dietary ingredient is an NDI subject to the Notification requirement. For example, a firm assessing whether a processing change results in an identity change could review manufacturing processes of past Notifications for guidance as to how FDA assesses those manufacturing processes. In addition to providing a helpful assessment tool, a searchable database of the Notification documents would also help firms determine what safety information they need to submit a successful Notification to FDA.

C. FDA's List Should Also Include A List of NDIs that Are Potentially Exempt from the Notification Requirement

The last category of dietary ingredients CRN recommends that FDA include in the authoritative list is NDIs that are potentially exempt from the Notification requirement pursuant to the food supply exemption. Under 21 U.S.C. § 350b, the Notification requirement does not apply to NDIs that "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." CRN acknowledges that any created list cannot explicitly identify whether a dietary ingredient has or has not been chemically altered, and that the burden is ultimately on the dietary ingredient manufacturer/distributor to conduct a chemical alteration analysis. Instead, CRN suggests a list of dietary ingredients in the food supply that are eligible for dietary supplement use so long as they are not chemically altered. This list could be compiled from existing FDA resources, such as ingredients in 21 C.F.R. § 100 *et seq*., in the *Everything Added to Food in the United States* Database[11], and in the GRAS Notice Inventory[12] and SCOGS Review Database[13]. Similarly, foods in the global food supply could also be added by looking to other global food databases, such as the European Union food additive database.[14]

SECTION 21 U.S.C. 342. IN ADDITION, THE LISTING OF A NEW DIETARY INGREDIENT IN THIS TABLE DOES NOT MEAN THAT ANOTHER MANUFACTURER CAN LAWFULLY MARKET THE DIETARY INGREDIENT IN A DIETARY SUPPLEMENT. EACH MANUFACTURER IS RESPONSIBLE FOR ENSURING COMPLIANCE WITH THE FD&C ACT.").

[9] Available at: https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices

[10] *See* New Dietary Ingredients in Dietary Supplements –Background for Industry (last updated August 11, 2016) (available at: https://www.fda.gov/Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/ucm109764.htm).

[11] Available at: https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm115326.htm.

[12] Available at: https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices.

[13] Available at: https://www.accessdata.fda.gov/scripts/fdcc/?set=SCOGS.

[14] Available at: https://ec.europa.eu/food/safety/food_improvement_agents/additives/database_en.

Interpretation of the term "chemically altered" is an important determinant of whether ingredients in the food supply are exempt from Notification requirements. CRN has previously submitted extensive comments in response to the 2011 NDI draft guidance expanding on manufacturing steps or processes that would cause an existing dietary ingredient to be "chemically altered" within the meaning of 21 U.S.C. § 350b(a)(1) as well as manufacturing steps or processes that would not constitute chemical alteration.[15] CRN recognizes that FDA is reviewing industry comments on this complex topic and will offer its interpretation of "chemically altered" in the final NDI guidance. It is noteworthy that when Congress enacted DSHEA, the chief sponsors of the legislation prepared a "Statement of Agreement" that discusses some aspects of the statute.[16] This legislative history states, "the term 'chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, powder, or solid in suspension."[17] CRN reinforces that for any ingredient that is exempt from Notification requirements, the above mentioned processes could be used in ingredient manufacturing without causing the ingredient to be "chemically altered" and changing its exempt status.

A "potentially exempt from Notification" list – in addition to a pre-DSHEA dietary ingredients list and a Notifications filed without objection list – would create a more useful tool for FDA and industry by providing guidance on all three categories of dietary ingredients: pre-DSHEA, NDI with successful Notification, and NDI potentially exempt from the Notification requirement.

III. Development of Any Dietary Ingredient List Should be Separate From a Safety Assessment

All dietary ingredients are subject to the adulteration standard in 21 U.S.C. § 342(f) regardless of their regulatory classification. While FDA must carefully review a Notification dossier for safety, this type of safety analysis, or any safety analysis, should not be part of the proposed dietary ingredient list creation process. The purpose of a pre-DSHEA list and an NDI exempt from the Notification requirement list is only to establish a list of ingredients that are lawful for use in a dietary supplement without submitting a Notification. This analysis is distinct from a safety analysis. Therefore, FDA should maintain this dichotomy in the creation of the dietary ingredient status list because merging the two assessments would not only blur the purpose of the review, but could also overwhelm FDA's review by making the process unwieldy and unproductive. CRN believes any list generated by FDA should clearly and prominently disclaim that any pre-DSHEA dietary ingredient or NDI potentially exempt from Notification present on the authoritative list has not been reviewed for safety and that all ingredients are still subject to the adulteration standard under § 342(f).

IV. Conclusion

Overall, CRN supports FDA's creation of an authoritative list of pre-DSHEA dietary ingredients as it would benefit both industry and FDA. According to the statute, whether a dietary ingredient is pre-DSHEA is date driven. Consequently, once proof has been established that a

[15] CRN May 7, 2013 Comments to Docket No. FDA-2011-D-0376; Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications 76 Fed. Reg. 3911 (July 5, 2011)
[16] 140 CONG. REC. 28961 (1994).
[17] *Id.*

dietary ingredient was sold pre-DSHEA, every firm within the industry may be able to use that ingredient without submitting a Notification so long as all other requirements of the statute are met, including the adulteration standard. In addition, CRN recommends that FDA's review procedure for pre-DSHEA dietary ingredients be separate and distinct from a safety assessment, as the goal is to establish a list of dietary ingredients that were marketed before October 15, 1994. CRN also advocates that in addition to any pre-DSHEA list, FDA expand the list to include a list of NDIs that were notified to FDA without objection and a list of substances used in food that are potential dietary ingredients exempt from the Notification requirement. This expansive authoritative list will provide FDA and industry with clarity as to the regulatory status of a wide variety of dietary ingredients.

Respectfully submitted,

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