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VIA ELECTRONIC SUBMISSION

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

Re: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry; Availability. 81 Fed. Reg. 53486-53489 (Friday, August 12, 2016). Docket No. FDA-2011-D-0376.

The Council for Responsible Nutrition (CRN)[1] appreciates the opportunity to provide comments on the revised draft guidance for industry entitled, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry" (revised draft guidance). 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.

CRN appreciates that in the revised draft guidance, FDA addresses several issues raised

[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.

in response to the 2011 draft guidance and expands its explanations in certain areas to provide clarification to the industry. Notably, FDA states it is willing to establish an authoritative list of pre-1994 dietary ingredients that are not subject to the new dietary ingredient (NDI) notification requirements. This list would create a safe harbor for newer firms that do not have physical evidence that an ingredient was on the market over 20 years ago. The revised draft guidance also introduces the option for a firm to create a confidential master file, enabling supplement manufacturers to purchase and use NDIs that have safety data on file, while protecting the intellectual property of the firm that originally submitted the notification. In addition, the revised draft guidance clarifies how ingredients that are generally recognized as safe (GRAS) for use in conventional foods can also be used in dietary supplements.

Although CRN views the revised draft guidance as a step forward, we remain concerned about several major issues that, if not resolved, would create significant and unnecessary burdens on the dietary supplement industry without increasing safety for consumers. It has been 22 years since Congress enacted the Dietary Supplement Health and Education Act of 1994 (DSHEA),[2] and industry desires a reasonable guidance on NDI notifications that also fulfills the agency's public health mandate. We wish to collaborate with and serve as a resource for FDA in this endeavor and offer the following comments for the agency's consideration.

[2] Pub. L. No. 103-417, 108 Stat. 4325 (1994).

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I. Defining "dietary ingredient"

CRN appreciates that in the revised draft guidance, FDA further elaborates on its interpretation of Section 201(ff)(1) of the Federal Food, Drug and Cosmetic Act (FDCA), which defines categories of dietary ingredients that can be used in or as dietary supplements. This fundamental question of what is a dietary ingredient is the first consideration in the process of determining when to submit an NDI notification. However, CRN remains concerned that FDA's narrow interpretation of Section 201(ff)(1) is not supported by law and is prohibited by the rules of statutory construction.

CRN has repeatedly expressed concerns about the agency's mistaken position on synthetic copies of botanical constituents (June 2011 comments on defining a "dietary ingredient,"[3] December 2011 comments on the 2011 draft guidance,[4] and October 2012 comments on the lawful status of synthetic botanical constituents as dietary ingredients[5]). In short, the law 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. It 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.

A. The plain language and legislative history of DSHEA supports a broad meaning of "dietary ingredient."

In the revised draft guidance, FDA's narrow interpretation of the FDCA's definition of "dietary ingredient" is inconsistent with a plain reading of DSHEA and goes beyond Congress's

[3] FDA Docket No. FDA-2009-P-0298. CRN comments on Defining a "Dietary Ingredient." June 29, 2011.
[4] FDA Docket No. FDA-2011-D-0376. CRN Comments on FDA Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. Dec. 2, 2011 (hereinafter "CRN Comments on 2011 Draft Guidance.")
FDA Docket No. FDA-2011-D-0376. CRN Comments of lawful status of synthetic botanical constituents as dietary ingredients. Oct.23, 2012.

intent in enacting the statute. As stated in *Brown & Williamson Tobacco v. FDA*, "[it is a] basic proposition that agency power is 'not the power to make law. Rather, it is the power to adopt regulations to carry into effect the will of Congress as expressed by the statute.'"[6] The same principle would apply to agency guidance documents. Using the well-settled traditional tools of statutory construction and interpretation, FDA's proposed interpretation of "dietary ingredient" contravenes the will of Congress as expressed by the statute.

Under *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the first question is whether the law itself makes the intent of Congress clear because "if the intent of Congress is clear, that is the end of the matter; for the court as well as the agency, must give effect to the unambiguously expressed intent of Congress."[7] As we explain below, Congress's intent is clear when this section is viewed within the law as a whole. Indeed, courts have said that statutory construction "must not be guided by a single sentence or member of a sentence but look to the provisions of the whole law, and to its object and policy."[8] This approach is consistent with the traditional rules of statutory construction used to ascertain congressional intent, which include: (1) the overall statutory scheme; (2) legislative history; (3) the history of evolving congressional regulation in the area; and, (4) a consideration of other relevant statutes.[9]

Congress enacted DSHEA in 1994 as an amendment to the FDCA to ensure a suitable balance between maintaining consumer access to a wide variety of dietary supplements and providing FDA with appropriate oversight of the safety of dietary supplements and ingredients.[10]

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153 F.3d 155, 161 (4th Cir. 1998), citing *Ernst & Ernst v. Hochfelder*, 425 U.S. 185, 213-214 (1976)(citations omitted).

[7] 467 U.S. at 842-843.

[8] *Brown & Williamson Tobacco*, 153 F.3d at 162 (citations omitted).

[9] *Id.*

[10] "Legislative action that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness." Pub. L. No. 103-417, § 2(15)(A).

DSHEA added the definitions of "dietary supplement" and "dietary ingredient" to the FDCA in Section 201(ff)(1). That provision states:

> The term "dietary supplement"—
>
> (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
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> (A) a vitamin;
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> (B) a mineral;
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> (C) an herb or other botanical;
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> (D) an amino acid;
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> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
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> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

The "catch-all" provision in subparagraph (E) demonstrates that Congress intended a wide variety of dietary ingredients, provided that they are intended to supplement the diet and meet other requirements of the statute. The language in subparagraph (E) refers simply to "a dietary substance for use by man to supplement the diet by increasing total dietary intake," with no additional constraints on the history of use for the substance or its origin. Thus, Congress did not intend to limit this category to only substances commonly used for human food or drink.

In addition, the Senate Report accompanying DSHEA identifies Coenzyme Q_{10} (CoQ_{10}; commonly synthesized), glucosamine, and primrose oil as examples of substances expected to be

included in the provision.[11] Notably, the language of this provision shifted from "nutritional substance" in earlier draft bills to "dietary substances" in the enacted law so that a wider range of dietary ingredients would be covered under this provision.

In previous regulation, FDA acknowledged the breadth of the dietary ingredient definition in the preamble to its regulation on requirements for nutrient content claims, health claims, and statements of nutritional support for dietary supplements.[12] In explaining why it had authority to extend its rules governing nutrient content claims under the Nutrition Labeling and Education Act of 1990 (NLEA) to a broad range of dietary ingredients in dietary supplements, the agency stated:

> . . . the legislative history of "other nutritional substances" reveals that its coverage is broad and could, in appropriate circumstances, include dietary ingredients without RDI's or DRV's (136 Congressional Record S 16609 (October 24, 1990)). In a discussion between Senators Metzenbaum and Symms before the passage of the 1990 amendments, Senator Symms stated: *** * *** **'**What follows is a list of a few of the items and foods that I believe would fall under the "other similar nutritional substances" category established by this bill: Primrose oil, black currant seed oil, cold pressed flax seed oil, "Barleygreen" and similar nutritional powdered drink mixes, Coenzyme Q 10, enzymes such as bromelain and quercetin, amino acids, pollens, propolis, royal jelly, garlic, orotates, calcium-EAP (colamine phosphate), glandulars, hydrogen peroxide (H_2O_2), nutritional antioxidants such as superoxide dismutase (SOD), and herbal tinctures.' Based on this colloquy, the agency interprets the list of dietary ingredients that fall under the definition of "dietary supplement" in section 201(ff) of the act as an explication of "other similar nutritional substances."[13]

Senate Report from Committee on Labor and Human Resources to Accompany S. 784 (DSHEA), Senate Report No. 103-410, at 8-9 (Oct. 8, 1994). CRN is aware that in an unprecedented move, at the signing of the bill certain members of Congress attempted to disclaim the legislative history of DSHEA, including the Senate Report. Congressional Statement of Agreement on DSHEA. 140 Cong.Rec. 14801 (daily ed. Oct.7, 1994).

[12] 62 Fed. Reg. 49859 (Sept. 23, 1997).

[13] *Id.* at 49859-60.

The list referenced by FDA includes dietary ingredients generally marketed in synthetic form, such as CoQ_{10}, and dietary ingredients that had not historically been used to supplement the diet, such as H_2O_2. FDA's acceptance of this broad range of dietary ingredients is consistent with the fact that neither the language of DSHEA nor the legislative history reveals any congressional intent to exclude from the definition of "dietary ingredient" synthetic versions of food or botanical components and other nutritional substances that have not previously been used to supplement the diet. FDA's position in the revised draft guidance is inconsistent with the intent of DSHEA and past agency interpretations of permissible dietary ingredients and should be revised accordingly.

Further, the statutory provisions relating to NDIs do not prohibit or otherwise distinguish chemically equivalent synthetic ingredients. Section 413 of the FDCA defines "new dietary ingredient" as a dietary ingredient not marketed in the United States before October 15, 1994.[14] That section also requires that NDIs be notified to FDA unless the dietary ingredients "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."[15] Thus, when Congress wanted to impose a historical use requirement on dietary ingredients, it did so clearly. Congress did not include limitations on synthetic ingredients, or any requirement for historical use of a substance to supplement the diet under Section 201(ff)(1)(E), and FDA therefore should not exceed its authority by imposing its own limitations through guidance.

This is not the first time that the agency has sought to limit the sale of dietary supplements through a misinterpretation of the law. CRN notes two key cases where courts invalidated FDA's attempts to impose restrictions on dietary supplements without legislative

[14] 21 U.S.C. § 350b(d).
[15] 21 U.S.C. § 350b(a)(1).

authority. First, prior to *Chevron* in 1974, the Second Circuit applied the rules of statutory construction and held that FDA did not have the authority to classify as drugs dietary supplements that exceeded the Recommended Daily Allowances.[16] In 1993, after *Chevron*, the Seventh Circuit concluded that black currant oil encapsulated with glycerin and gelatin was not a food additive that requires proof of safety prior to marketing, and therefore FDA must provide evidence of adulteration before taking enforcement action against this product.[17] The court also found the agency's interpretation of the statute contrary to the language and intent of the Act.[18] Of note, the court stated that one of the established principles of statutory construction is that "courts should rein in broad and general statutory language when such language is immediately coupled with more limiting language or a specific enumeration."[19] Thus, if broad language is <u>not</u> immediately coupled with limiting language, the agency must recognize that broad language and follow the intent of Congress. Moreover, "the language of the Act must be read in the light of the statute as a whole: its design, objectives, and policy."[20]

The language in Section 201(ff)(1)(E), "for use by man to supplement the diet by increasing the total dietary intake," does not require the substance being supplemented to be customarily consumed or to be consumed historically. A plain reading of the statute makes clear that a substance that is intended for use to supplement the diet by 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.

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[16] *National Nutritional Foods Assoc. v. FDA*, 504 F.2d 761, 788-789.
[17] *United States v. Two Plastic Drums*, 984 F.2d 814 (7th Cir. 1993).
[18] *Id.*at 817, citing *Demarest v. Manspeaker*, 498 U.S. 184 (1991).
[19] *Id.* at 817-818 (citations omitted).
[20] *Id.* at 818 (citations omitted).

B. There is no statutory distinction between synthetic vitamins, minerals and amino acids and synthetic copies of botanical constituents.

In the revised draft guidance, FDA excludes synthetic copies of botanical constituents 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.[21] 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 the dietary ingredients as 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. FDA's interpretation stands in contrast to the statutory language in FDCA Section 411, added by the Proxmire Amendments in 1976 to bar FDA from imposing maximum limits on the potency of "any synthetic or natural vitamin or mineral" and from classifying "any natural or synthetic vitamin or mineral" as a drug solely because it exceeds the level of potency which FDA determines is nutritionally rational or useful.[22] This language makes clear that Congress did not view the terms "vitamin" and "mineral," standing alone, as inherently meaning the natural form of these dietary ingredients; otherwise, there would have been no need in the Proxmire Amendments to specify natural as well as synthetic vitamins and minerals.

These amendments document that by 1976, Congress was well aware that vitamins and minerals were marketed in both natural and synthetic forms. Once Congress had established in the Proxmire Amendments that vitamins and minerals should be treated the same way by FDA

[21] As an initial matter, CRN acknowledges that FDA has clarified that a synthetic copy of a botanical constituent could be used as a dietary ingredient under Section 201(ff)(1)(E) once it has been determined to be Generally Recognized as Safe (GRAS) for use in conventional food and subsequently introduced into the food supply.
[22] FDCA § 411(a)(1)(A) & (B).

regardless of whether they are naturally or synthetically derived, it did not need to specify this fact again in DSHEA, after those amendments had been effective for nearly twenty years.

Botanical constituents have been synthesized long before vitamins, minerals, and amino acids were synthesized. For example, cinnamic acid and related cinnamates, which can be obtained from oil of cinnamon or from balsams, have been synthesized for over a century.[23] Dozens of synthetic flavors derived from botanicals were in wide use in the food supply before the Food Additives Amendment of 1958 and thus were GRAS, as reflected in FDA's GRAS regulation for synthetic flavoring substances and adjuvants.[24] In particular, that listing includes synthetic botanical constituents such as cinnamaldehyde and vanillin. Vanillin is a constituent that occurs naturally in vanilla but was synthesized in the 1950s[25] and is generally used in food in its synthetic form. Similarly, FDA's food additive regulation for synthetic flavoring substances and adjuvants, currently codified at 21 C.F.R. § 172.515, listed numerous synthetic botanical constituents such as cinnamates or related substances even when first promulgated in 1964.[26] Accordingly, where Section 201(ff)(1)(A)-(D) identifies vitamins, minerals, botanicals, and amino acids as dietary ingredients, Congress intended to include both the naturally and synthetically derived forms of these ingredient categories without exclusion.

C. The FDCA and DSHEA require that chemically equivalent materials be treated equally, regardless of their source.

[23] 2 Thomas E. Thorpe, A Dictionary of Applied Chemistry 17 (1912), available at http://www.ebooksread.com/authors-eng/t-e-thomas-edward-thorpe/a-dictionary-of-applied-chemistry-volume-2-hci/page-17-a-dictionary-of-applied-chemistry-volume-2-hci.shtml (citing Farb. vorm. Meister, Lucius and Briiniii-r, D. B. P. 53671 ; Eng. Pat. 4946; J. Soc. Chem. Ind. 1891, 358; Rainer Ludwig Claisen, Zur Darstellung der Zimmtsäure und ihrer Homologen, 23 Ber. 976 (1890), available at http://gallica.bnf.fr/ark:/12148/bpt6k90720c/f978.image.r=berichte%20der%20deutschen%20chemischen.langEN, in support of the statement that "[e]thyl cinnamate may be obtained direct from benzaldehyde by means of ethyl acetate and sodium.").

[24] 21 C.F.R. § 182.60, originally codified at 21 C.F.R § 121.101. 26 Fed. Reg. 3991 (May 9, 1961).

[25] The Merck Index 1419 (10th ed. 1983).

[26] 29 Fed. Reg. 14625 (October 27, 1964).

Chemical equivalence, 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 issues prior to the marketing of these ingredients.

Many synthetic copies of botanical constituents are, in fact, chemically equivalent to their naturally-occurring counterparts.[27] Indeed, FDA has viewed synthesized and naturally-derived chemically equivalent materials as the same when it sought to ban a substance. In the preamble to its final rule banning ephedrine alkaloids, FDA disagreed with comments that asserted that naturally-sourced ephedrine alkaloids were safer than synthetic versions of the same isomer. The agency stated:

> We are not persuaded by any of the available evidence that ephedrine from botanical sources is materially different from ephedrine from pharmaceuticals with respect to chemistry, potency, or physiological and pharmacological effects. Chemically, any isomer with the same conformation from one source, including botanical sources, is identical to the same isomer from another source. For example, (-)-ephedrine from Ephedra (*Ephedra sinica* Stapf) is chemically indistinguishable from synthetic (-)-ephedrine manufactured by a pharmaceutical company.
> . . .
>
> We do not agree, therefore, that current evidence establishes that ephedrine alkaloids from botanical sources, including from botanical extracts, are different from, or are any safer than, pharmaceutical ephedrine alkaloids.[28]

[27] If a constituent is not actually present in a botanical, or the synthesized version is not chemically equivalent to the naturally-occurring constituent, then FDA should not allow it to be marketed as a synthetic botanical constituent, and the agency has ample authority to preclude the marketing or take enforcement action against such products. The marketer would have to show the agency through its NDI notification that the substance is a dietary ingredient under some other statutory basis.
[28] 69 Fed. Reg. 6788, 6807 (February 11, 2004).

Thus, FDA treated chemically indistinguishable synthetic copies and nature-derived botanical constituents as equivalent when the agency sought to ban a dietary ingredient, but in the case of allowing even demonstrably safe synthetic copies of botanical constituents to be dietary ingredients, FDA treats such substances as irreconcilably different from their nature-derived counterparts. There are no legal or scientific grounds upon which the agency could legitimately make such a distinction. However, the agency attempts to create a distinction in the revised draft guidance by permitting some dietary ingredients (e.g., vitamins, minerals, and amino acids) to be synthetic while prohibiting others (botanical constituents), even though these ingredients all have the same purpose—to supplement the diet. This approach contradicts Congress's intent apparent in the plain language of the law.

D. FDA's interpretations of "metabolite" and "amino acid" materially narrow Section 201(ff)(1).

The revised draft guidance states that a "metabolite" may be synthetically produced, provided that the starting material is a dietary ingredient and the production process mimics the metabolic process in the body following ingestion. This requirement is unreasonable because many metabolic processes have not been fully elucidated. It is not possible to develop a manufacturing process that mimics a metabolic pathway that has not been scientifically confirmed. FDA should consider the chemical identity of the end product (the metabolite), not the starting material or how the metabolite was synthetically produced. There is no safety or scientific rationale for the agency's interpretation. Moreover, a plain reading of the statute and legislative history provides no indication that Congress intended to restrict the term "metabolite" as described by FDA in the revised draft guidance.

In addition, FDA also narrows the definition of "amino acid" as "an alpha-amino carboxylic acid used as a constituent of proteins or peptides." However, the statutory definition

of "dietary ingredient" only includes the term "amino acid" with no reference to "alpha-amino acid." Because Congress did not expressly limit or narrow this category, it is inappropriate for FDA to limit "amino acids" to "alpha-amino carboxylic acids" through guidance.

Recommendations:

Congress anticipated a wide variety of dietary ingredients under DSHEA, and established the NDI provision to enable companies to innovate and bring new dietary ingredients to the market once FDA has received information on their safety. The final guidance should reflect 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.

CRN also recommends that FDA revise its definition of "metabolite" and "amino acid" to align with the language and intent of DSHEA. A synthetic "metabolite" should be evaluated on the chemical identity of the finished dietary ingredient (the metabolite) and not the starting material or manufacturing method. In addition, the term "amino acid" should not be restricted to only alpha-amino carboxylic acids used as a constituent of proteins or peptides.

II. Exceptions to NDI notification requirements

According to Section 413 of the FDCA, an NDI notification is not required for a dietary ingredient that satisfies either of two exclusions: (a) the dietary ingredient is a "pre-DSHEA" dietary ingredient;[29] or (b) the dietary ingredient is present in the food supply as an article used

[29] 21 U.S.C. § 350b(d).

for food in a form in which the food has not been chemically altered.[30] CRN appreciates FDA's willingness to create an authoritative list of pre-DSHEA dietary ingredients and the agency's additional clarification with regard to the status of ingredients with a history of use in the food supply. However, as noted in our previous comments to the agency, we remain concerned that a narrow interpretation of these exclusions will result in unnecessary NDI notifications for products with a long history of safe use.

A. In collaboration with industry, FDA should implement reasonable procedures to develop a list of pre-DSHEA dietary ingredients.

A "pre-DSHEA" dietary ingredient is one that was "marketed" in the United States prior to October 15, 1994. Section 413(d) of the FDCA further provides that a pre-DSHEA dietary ingredient is excluded from the definition of a "new dietary ingredient" and therefore notification to FDA is not required.[31] Both the original and revised draft guidance specify that "marketed" in the United States refers to dietary ingredients that were sold as or in a dietary supplement or as a bulk dietary ingredient for use in dietary supplements in the United States. CRN recognizes and appreciates that the revised draft guidance provides an expanded explanation of what it means to be "marketed" as a dietary ingredient, and what documentation would be accepted as evidence of being marketed prior to October 15, 1994. However, FDA should give careful consideration to the process and substantiation needed to verify the pre-DSHEA status of dietary ingredients.

CRN supports FDA's willingness to develop an authoritative list of pre-DSHEA dietary ingredients that would provide a "safe harbor" from the NDI notification requirements. For companies that started business after 1994 and do not have access to pre-1994 records, such a list would be an essential component of doing business. CRN has previously commented that the

[30] 21 U.S.C. § 350b(a)(1).
[31] 21 U.S.C. § 350b(d).

definition of an NDI is date-driven; once the pre-DSHEA status of a dietary ingredient has been established, the entire industry may lawfully rely on such a finding.[32] It is unreasonable to require each manufacturer or distributor to have independent proof that an ingredient was marketed pre-DSHEA, or else file an NDI notification. Thus, a single authoritative list of pre-DSHEA dietary ingredients created by FDA will provide needed certainty and consistency across the industry. We also appreciate that the revised draft guidance affirmatively acknowledges that any FDA-generated list would not be all-inclusive; instead, any ingredient not included on the pre-DSHEA safe harbor list could still qualify as a pre-DSHEA dietary ingredient. In such cases, a firm would maintain its own records of the pre-DSHEA marketing of a dietary ingredient.

In the revised draft guidance, FDA states that the industry is primarily responsible for supplying evidence of pre-DSHEA marketing. However, over two decades have passed since the enactment of DSHEA and substantive records for these ingredients may no longer exist. We also note that FDA had the opportunity to prepare a definitive list in 1994 but chose not to do so.[33] Therefore, developing an authoritative list of pre-DSHEA dietary ingredients will require extensive collaboration between FDA and the industry. To that end, CRN strongly encourages FDA to consider evidence such as lists of pre-DSHEA dietary ingredients that were compiled by dietary supplement trade associations.[34] As FDA is aware, the trade association lists were

[32] Docket No. FDA-2011-D-0376. CRN comments: Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. 76 Fed Reg.39111 (July 5, 2011)

In contrast, FDA undertook the task of developing a list of grandfathered GRAS ingredients when the Food Additives Amendment was enacted in 1958, e.g., 23 Fed. Reg. 9511 (December 9, 1958), 24 Fed. Reg. 9368 (November 20, 1959), 25 Fed. Reg. 880 (February 2, 1960), 25 Fed. Reg. 7332 (August 4, 1960), 26 Fed. Reg. 938 (January 31, 1961) (now codified in 21 C.F.R. Parts 182 and 184).

E.g., National Nutritional Foods Association (now Natural Products Association), NNFA List of Dietary Supplement Ingredients In Use Before October 15, 1994 (April 1996), available at http://www.fda.gov/ohrms/dockets/dockets/05p0305/05p-0305-cr00001-03-NNFA-List-vol1.pdf; CRN List of Dietary Ingredients "Grandfathered" Under DSHEA (September 1998), available at www.fda.gov/ohrms/dockets/dockets/05p0305/05p-0305-cr00001-04-Council-For-Responsible-Nutrition-vol1.pdf.

prepared by industry experts familiar with pre-DSHEA product formulations, and therefore these lists should provide prima facie evidence of pre-DSHEA marketing. CRN also encourages FDA to give substantial evidentiary weight to affidavits attesting to recollections of historical events. Not giving significant consideration to these two sources of credible evidence imposes unreasonable regulatory barriers that may significantly limit the availability of historically safe, pre-DSHEA products to consumers.

In addition, the revised draft guidance introduces a new requirement for the documentation of pre-DSHEA marketing to include a "precise description of the identity of the ingredient marketed." FDA further states that documentation of an ingredient's identity should be "sufficiently precise to uniquely identify the ingredient." CRN is concerned that the available documentation of pre-DSHEA marketing does not include extensive details or "identity specifications" for the dietary ingredients that were marketed.

Although FDA indicates that it will accept written business records, promotional material (e.g., advertisements and catalogs), and press reports as marketing evidence, these documents often refer to ingredients in general terms and are unlikely to provide detailed "identity specifications." For example, a company might possess a 1992 advertisement for "Echinacea capsules" that includes a picture of the product label. However, this marketing evidence does not include information about the specific plant part used to make the product, as this was not required information for a pre-DSHEA product label. As such, the precise identity information would not be available in this type of pre-DSHEA marketing documentation. In this case, which may be common for many pre-DSHEA dietary ingredients, a botanical expert, reference book, or affidavit could clarify what plant parts have been traditionally used. When considering the totality of evidence (e.g., reference books or affidavits in combination with the marketing

material), a pre-DSHEA Echinacea dietary ingredient may include any Echinacea plant part or extract (water or alcohol) that was commonly used.

CRN recommends that FDA develop a fair and transparent process for reviewing evidence of pre-DSHEA marketing for dietary ingredients. In addition, we further request that the agency consider and communicate to industry how the totality of available evidence, including marketing evidence, expert opinions, *Herbs of Commerce* or other reference literature, and affidavits, can be used to determine the full scope of ingredient preparations that may also be considered as part of the identity description of a pre-DSHEA dietary ingredient.

CRN strongly encourages FDA to take a reasonable approach to generating a list of pre-DSHEA dietary ingredients that uses a sliding scale and considers a broad range of evidence to address gaps in information. If FDA is unnecessarily narrow in its interpretation of pre-DSHEA marketing evidence, the opportunity to develop a meaningful list of pre-DSHEA dietary ingredients will be lost.

Recommendations:

CRN supports FDA's willingness to create an authoritative list of pre-DSHEA dietary ingredients that would provide a "safe harbor" from NDI notification requirements. CRN recommends that pre-DSHEA marketing evidence be broadly applied through a transparent and cooperative process. Further, each scenario should be evaluated based not only on the pre-DSHEA evidence of marketing, but also other sources of credible information, such as trade association lists, subject-matter experts, reference literature, and affidavits, to help specify the full scope of ingredient preparations that could also be considered pre-DSHEA. CRN looks forward to further discussions with FDA about developing a flexible and fair process to evaluate pre-DSHEA marketing evidence.

B. FDA's interpretation of "present in the food supply as an article used for food" in a form in which the food has not been "chemically altered" undermines the law.

In the revised draft guidance, FDA reads narrowly the exclusion from the NDI notification requirement set forth in Section 413(a)(1) of the FDCA.[35] This exclusion states that an NDI notification is not required when a 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."[36]

FDA puts forth a narrow interpretation of "food" and "food supply" whereby it would limit these broad terms to only conventional foods or conventional food ingredients. In so doing, FDA would push dietary supplements out of the "food" category. This interpretation of "food" is inconsistent with not only the plain language of the FDCA but also the history of "food." Dietary supplements and dietary ingredients are "food." They have always been "food." And when they are consumed, they are present in the "food supply." The agency's new and erroneous interpretation of these terms will burden industry unduly and unlawfully.

In addition, the agency continues to interpret the term "chemically altered" broadly. We urge FDA to interpret "chemically altered" to mean only those changes that alter an ingredient's chemical identity or its potential for safe use in dietary supplements. This interpretation is consistent with both congressional intent and the agency's public health goals.

1. "Present in the food supply as an article used for food" covers all food in the food supply—conventional food as well as dietary supplements.

In section IV.B.1 of the revised draft guidance, FDA puts forth an erroneous interpretation of the phrase "present in the food supply as an article used for food" by seeking to limit this phrase to conventional food or conventional food ingredients. This inaccurate

[35] 21 U.S.C. § 350b(a)(1).
[36] *Id.*

interpretation would render "food" and "food supply" so narrow that it would leave out many ingredients long understood to be food—dietary ingredients with a history of safe use in dietary supplements in the food supply. FDA's proposed interpretation also contradicts the plain meaning of "food" in FDA's governing statutes and the longstanding regulatory status of dietary supplements as food.

The agency's new interpretation is squarely at odds with a plain reading of not only DSHEA but also the FDCA as a whole. Section 201(f) of the FDCA defines "food" to mean, in part, "articles used for food,"[37] language echoed by Section 413(a)(1). Since long before DSHEA, the phrase "articles used for food" in the definition of food has been understood to include vitamins, minerals, herbs, and other ingredients consumed in dietary supplements. Furthermore, Section 201(ff), which defines "dietary supplement" and "dietary ingredient," states that "a dietary supplement shall be deemed to be a food" under the FDCA except for certain provisions not relevant to this analysis.[38] DSHEA added Sections 201(ff) and 413(a)(1) to the FDCA simultaneously, a further reason why they should be interpreted together. Thus, Congress required that dietary supplements be considered "food" under nearly all of the FDCA, including Section 413(a)(1). Further, Congress expressly excludes dietary supplements from particular provisions of DSHEA and the FDCA when it wishes to do so. Where Congress wanted to refer to "conventional foods" in DSHEA it did so, as when it used the term "conventional foods" in the definition of dietary supplement.[39] FDA cannot conflate "conventional food" with

[37] The full definition of food in 201(f) is as follows: "The term 'food' means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." 21 U.S.C. § 321(f).
[38] 21 U.S.C. § 321(ff).
[39] A dietary supplement means a product that, among other things, "is not represented for use as a conventional food or as a sole item of a meal or the diet." 21 U.S.C. § 321(ff)(2)

"food supply" in a manner that constrains the application of Section 413(a)(1) and is contrary to the plain language and the intent of DSHEA.

In addition, the overall structure of the FDCA demonstrates that dietary supplements are "food." Section 413 on NDI notifications is at the heart of the FDCA's food provisions, which range from sections 401 to 423. Dietary supplements and dietary ingredients, like food additives and GRAS substances, are important subcategories of food. And like articles from all food categories, they are part of the food supply. FDA's suggestion otherwise, offered for the first time in the revised draft guidance, is contrary to the plain meaning and structure of the statute.

The pre-DSHEA history of food law provides further evidence that Congress intended "food" and "food supply" in Section 413(a)(1) to include dietary supplements. When Congress passed DSHEA in October 1994, dietary supplements were considered food. In numerous instances at the time, FDA's regulations explained that dietary supplements were food and in the food supply. For example, FDA's regulations on health claims then read as follows:

> Health claim means any claim made on the label or in the labeling of *a food, including a dietary supplement*, . . . Substance means a specific food or component of food, *regardless of whether the food is in a conventional food form or a dietary supplement . . . Dietary supplement means a food*, not in a conventional food form, that supplies a component to supplement the diet by increasing the total dietary intake of that component.[40]

In addition, in January 1994, FDA added to its regulation a RACC—a reference amount customarily consumed per eating occasion—for dietary supplements.[41] The agency added this RACC for dietary supplements to the table in its regulations for foods in the general food supply: "Table 2.—REFERENCE AMOUNTS CUSTOMARILY CONSUMED PER EATING

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21 C.F.R. 101.14 (1994) (emphasis added while emphasis in original omitted). The definitions for "Substance" and "Dietary Supplement" were added in January 1994. *See* Final Rule, 59 Fed. Reg. 395 (Jan. 4, 1994).

[41] Final Rule, 59 Fed. Reg. 354 (Jan. 4, 1994).

OCCASION: GENERAL FOOD SUPPLY."[42] The RACC remains in this regulation (21 C.F.R. § 101.12) and its placement confirms that dietary supplements are one of the many foods present in the food supply as articles used for food.

In 1994, there was no dispute that dietary supplements are simply food in the food supply. The pre-DSHEA dispute between the agency and industry was whether dietary supplements were generic food—akin to an apple or a pot of herbal tea—or whether they were food additives subject to the special regulations for additives. Congress passed DSHEA in part to quell the agency's efforts to classify dietary supplements as food additives.

The leading pre-DSHEA case that established that dietary supplements are articles used for food generally, not food additives, was *United States v. Two Plastic Drums* (1993).[43] In this case, the Seventh Circuit concluded that dietary supplements are "not a food additive, but a food in a generic sense,"[44] adding that because "food additives can be thought of as a subset of food in the broadest sense" its references to "food in the generic sense refers to articles of food not considered food additives."[45] The First Circuit reached the same conclusion in *United States v. 29 Cartons of * * * An Article of Food* (1993),[46] a case whose very title emphasizes that dietary supplements are simply articles of food in the food supply. [47] Given that in 1994, dietary supplements were understood to be food in a generic sense used directly as articles of food—contrasted with food additives that had a special function in food (but which themselves are still

[42] *Id.* at 372.
[43] *United States v. Two Plastic Drums*, 984 F.2d 814 (7th Cir. 1993).
[44] *Id.* at 816.
[45] *Id.* at 816 n.1.
[46] *United States v. 29 Cartons of * * * An Article of Food*, 987 F.2d 33 (1st Cir. 1993).
[47] The full title of *Two Plastic Drums* also demonstrates that the dietary supplement at issue was an article of food: *United States v. Two Plastic Drums, More or Less of an Article of Food, Labeled in Part: Viponte Ltd. Black Currant Oil Batch No. BOOSF 039*.

"food" under the FDCA)—FDA has no basis to now say that food additives, but not dietary supplements, are substances present in the food supply as an article "used for food."

In essence, FDA is trying to do with the NDI notification process now what it attempted with the food additive petition process prior to DSHEA—to shift to manufacturers the burden of proving the safety of all food ingredients, even ones that are common or low risk. As stated by the Seventh Circuit in *Two Plastic Drums*: "The only justification for this Alice-in-Wonderland approach is to allow FDA to make an end-run around the statutory scheme and shift to the processors the burden of proving the safety of a substance in all circumstances."[48] The unofficial legislative history of DSHEA quoted this language from *Two Plastic Drums* when explaining the motivation for DSHEA.[49] In light of this history, it is evident that Congress did not intend to impose the NDI notification process for articles present in the food supply as dietary supplements each time the ingredient is used in a new product. As such, Congress used the term "food" in Section 413(a)(1) and did not specify "conventional food," "conventional food ingredients," "food additives," or "GRAS substances."

[48] *Id.* at 819.

[49] Sen. Rep. 103-410, at 16 (Oct. 8, 1994) ("The FDA's efforts to ban the safe dietary supplement of black currant oil by asserting that it was an unsafe food additive were rejected last year by two unanimous decisions of two different three-judge panels in two different United States courts of appeal [*Two Plastic Drums* and *29 Cartons*]. In both of these cases, FDA asserted that black currant oil (BCO) was a food additive because it was added to gelatin capsules. The Seventh Circuit noted that 'FDA has not shown that BCO is adulterated or unsafe in any way.' The Court described the FDA's effort as an 'Alice in Wonderland' approach. Further, the decision by the First Circuit described FDA's approach as 'nonsensical.' . . . The preceding examples show how the FDA has tried to "protect" the public against "unsafe" products for which there is no evidence that the product is unsafe. . . . The preceding examples show the need for congressional action to assure citizens have continued access to dietary supplements and information about their benefits."). Although this Senate Report is part of the legislative history of DSHEA, the sponsors of the bill from the House and Senate agreed that the "only legislative history for [DSHEA] would be a statement of agreement" read into the Congressional Record by Rep. Waxman. Cong.Rec. H11179 (Oct. 6, 1994); *see also* 140 Cong.Rec. S14801 (daily ed. Oct.7, 1994). The Statement of Agreement was only a few paragraphs, and it did not interpret "food" or "food supply" under 413, though it did address chemical alteration. *Id.*

The unofficial legislative history of DSHEA, discussing the "Alice-in-Wonderland" approach of *Two Plastic Drums*, explained:

> Under present law, a dietary supplement, as with any food, is presumed to be safe. It therefore may be lawfully marketed, unless and until the FDA, by a preponderance of the evidence, shows that the supplement is "injurious to health."
>
> Rather than meet its statutory burden, the FDA has chosen instead to treat dietary supplements as "food additives" . . . Thus, by treating a dietary supplement as a food additive, the FDA seeks to shift to the manufacturer the burden of establishing the supplement's safety, even though the supplement is a substance that already exists in the food supply.[50]

Here, the authors of DSHEA repeatedly emphasized that dietary supplements are just like "any food" in the food supply.

In addition, by narrowing the definition of "food supply," FDA expands the category of NDIs for which notification is required. This expansion contradicts the intent of the exclusion, which was to avoid unnecessary regulatory submissions for ingredients that have a history of safe use. In providing that notification is not required for ingredients that have been "present in the food supply as an article used for food," Congress did not limit the type of food in which the ingredient may be found, nor did it limit the geographic scope. FDA acknowledges the lack of limitation on geographic scope in Section IV.B.2 of the revised draft guidance: "Similarly, ingredients marketed in conventional foods outside the U.S. are exempt from the NDI notification requirement if they are not chemically altered."[51] FDA likewise must acknowledge that ingredients in dietary supplements are exempt if not chemically altered, as they are articles marketed as food in the United States.

[50] Sen. Rep. 103-410, at 21.
[51] Revised NDI Draft Guidance, at IV.B.2.

CRN firmly takes the position that a dietary ingredient with prior use in a dietary supplement should meet the "present in the food supply" criteria and would be exempted from NDI notification requirements if it has not been "chemically altered." Pre-DSHEA dietary ingredients are excluded from the definition of an NDI by Section 413(d) of the FDCA, which excludes them from NDI notification requirements under Section 413(a)(1).[52] Therefore, including dietary supplements as part of the "food supply" in applying the exception from NDI notification requirements mostly affects NDIs that have been successfully notified or NDIs that are in the "food supply" as a result of being used as GRAS substances or food additives after the enactment of DSHEA.

When an NDI is successfully notified to FDA without agency objection and used in a dietary supplement, it becomes legally part of the "food supply." Any additional dietary supplement that contains the same NDI would be exempt from NDI notification requirements because the NDI would be considered "present in the food supply" as an article used for food and not "chemically altered." Therefore, a separate NDI notification would not be required for a dietary supplement that contains a successfully notified NDI combined with other lawfully marketed dietary ingredients in the food supply, including pre-DSHEA dietary ingredients and lawfully marketed NDIs, even if these other dietary ingredients were not described in the original NDI notification provided they were not "chemically altered." CRN acknowledges that the dietary supplement adulteration standard, FDCA Section 402(f)(1),[53] would nonetheless apply to the dietary supplement.

2. FDA's interpretation of the "chemically altered" standard should apply only to changes that alter the identity of the dietary ingredient or that significantly affect the safety of the ingredient.

[52] 21 U.S.C. § 350b(d).
[53] 21 U.S.C. § 342(f)(1).

The "chemically altered" standard governs only the manufacturing of dietary ingredients that have been "present in the food supply" as articles "used for food." CRN appreciates that FDA will consider scientific evidence demonstrating the effect of a particular technology or manufacturing process on the identity or safety profile an ingredient. If a particular technology or manufacturing process does not affect the identity or safety profile an ingredient, then the ingredient would not be considered "chemically altered" and no NDI notification would be required. CRN recognizes that it would not be effective for the supplement industry to provide examples of manufacturing steps or processes that would cause an existing dietary ingredient to be "chemically altered" within the meaning of Section 413(a)(1) and, conversely, of manufacturing steps or processes that would not constitute chemical alteration. Each manufacturing scenario is unique to the ingredient and should be evaluated case-by-case.

The official legislative history of DSHEA—the Congressional Statement of Agreement—gives some examples of physical modifications that do not constitute chemical alteration: "In section 413(a)(1), . . . the term 'chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyophlization, milling, tincture or solution in water, slurry, powder, or solid in suspension."[54]

CRN appreciates FDA's expanded explanation of how these processes do not alter the chemical or molecular composition or structure of an ingredient. CRN agrees with FDA that these processes are not likely to create a change in the safety profile of an ingredient. The revised draft guidance also explains that dehydration, lyophilization, or making a tincture, solution in water, or slurry can change the composition of the ingredient, but only by changing the amount of water (or ethanol, in the case of tincture). CRN agrees with the agency that such minor

[54] Statement of Agreement, 140 Cong.Rec. S14801 (daily ed. Oct.7, 1994)

changes in composition are unlikely to change the safety profile of an ingredient present in the food supply as an article used for food. CRN also appreciates that FDA recognizes it is more efficient and effective from a regulatory and public safety policy standpoint for FDA to focus on the chemical identity and safety of the dietary ingredient, as opposed to the process by which the dietary ingredient is manufactured. This recommendation is in accordance with the agency's approach to regulating other food products and ingredients.

However, CRN disagrees with the agency's position in the revised draft guidance with regard to water or alcohol extractions that include a filtration step, in part because this new position is in plain contradiction to the Congressional Statement of Agreement. A tincture made with alcohol or a solution in water is the same as an extract that uses water or alcohol as the solvent. To make a water extract or alcohol tincture, a dietary ingredient is soaked in water or alcohol for a given period of time. Next, the solid material must be removed from the liquid extract or "tincture" by decanting, straining, or by passive filtration.[55]

The Congressional Statement of Agreement affirmatively states that making an extract using water or alcohol (tincture) does not chemically alter a dietary ingredient.[56] Therefore, FDA must be consistent with the Statement of Agreement by modifying or removing the following text from section IV.B.5 in the revised draft guidance:

> In a typical extraction, however, the first step is solution in water or another solvent, followed by filtration to remove undissolved material. This is a much larger change in the composition of the ingredient. FDA generally regards extraction that includes a filtration step…as a process that chemically alters the source ingredient and therefore triggers the NDI notification requirement for the resulting dietary supplement.

[55] Andrew Chevallier. (2016) Encyclopedia of Herbal Medicine 3rd edition; Making Herbal Remedies, pp. 290. New York, NY: Penguin Random House.
[56] 140 Cong.Rec. S14801 (daily ed. Oct.7, 1994).

In addition, this text also contradicts other parts of the revised draft guidance that correctly interpret the Congressional Statement of Agreement regarding tinctures and water extracts, such as section IV.A.12:

> However, solution in water or tincture would not constitute a "chemical alteration" of a conventional food ingredient (see questions IV.B.4 and IV.B.5.), and therefore, no NDI notification would be needed when a tincture of solution in water made with a conventional food ingredient is used as a dietary ingredients.

FDA should expand the above statement to explain that "a tincture of solution in water made with a conventional food ingredient" necessarily requires decanting, straining, or filtrating to remove undissolved solid material. FDA must remove from the final NDI guidance any unqualified use of the term "filtration" to mean a process that automatically chemically alters the source ingredient and therefore triggers the NDI notification requirement.

CRN recognizes that there are manufacturing processes, such as chromatography, distillation, and certain types of filtration that can be used to remove or concentrate specific components of a tincture, e.g., a particular constituent of a botanical. When these processes are used to change the chemical or molecular composition (i.e., a change to the identity of the ingredient), then the ingredient would be chemically altered and an NDI notification may be required. However, FDA cannot contravene the Congressional Statement of Agreement and suggest that filtration, a process used to remove solid material from a water or alcohol tincture, automatically results in chemical alteration. Thus, we request that FDA modify the above mentioned text in sections IV.B.5 and IV.A.12 of the revised draft guidance.

Recommendation:

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 requirements (provided it is not chemically altered). This

modification would align with the legislative history and statutory recognition of dietary supplements as a category of food.

In addition, CRN requests that the agency interpret "chemically altered" to mean change in the identity of the dietary ingredient (e.g., specifications needed to chemically characterize the ingredient), or change that has a potentially significant negative impact on the safety of the ingredient for the intended use as or in a dietary supplement. CRN appreciates that FDA will consider evidence demonstrating that a particular technology or manufacturing process does not result in a chemical alteration or have any effect on the identity or safety profile an ingredient.

CRN also requests that FDA modify Sections IV.B.5 and IV.A.12 of the revised draft guidance to clarify that tinctures or water extracts of dietary ingredients that have been "present in the food supply" as articles used for food that include a filtration step to remove undissolved material are not "chemically altered," and are thus exempt from NDI notification requirements, in accordance with the Congressional Statement of Agreement.

III. Changes applied to the manufacture of a pre-DSHEA dietary ingredient that would create an NDI

Manufacturing processes for dietary ingredients have changed significantly since October 15, 1994. Many of these changes have improved the manufacturing efficiency or the purity of dietary ingredients, but do not affect the identity or safety of the ingredient when compared to the pre-DSHEA version of the same ingredient. CRN agrees with FDA that when a manufacturing process has changed for a pre-DSHEA dietary ingredient, the regulatory status of the resulting dietary ingredient is dependent on the extent to which such changes impact that ingredient.

When a manufacturing change occurs, a manufacturer must evaluate (1) whether the change is significant and/or meaningful and (2) whether it results in either a change in the

identity or safety of the ingredient. If there are no changes to identity (the product continues to meet specifications needed to chemically characterize the ingredient) or safety, then no NDI notification is required. This approach is generally consistent with FDA's recommendations on assessing the effects of significant manufacturing process changes, including emerging technologies, on the safety and regulatory status of an NDI that has been successfully notified to FDA.[57] It also aligns with FDA's policies on other FDA-regulated food ingredients.[58]

The revised draft guidance indicates that manufacturing changes may affect the purity of a dietary ingredient or food substance, such as amounts of impurities and contaminants. In the final NDI guidance, FDA should clarify that not all changes to purity would result in an NDI that requires notification. For example, manufacturing innovations have advanced fish oil processing to produce a finished dietary ingredient that contains lower levels of environmental contaminants (e.g., mercury) as compared to pre-DSHEA counterparts. This manufacturing change does not alter the identity of the dietary ingredient. The fish oil manufactured with current methods continues to meet the required specifications to chemically characterize the ingredient and there are no changes in physiochemical structure or properties or biological properties of the fish oil. The only difference is that it now has lower levels of environmental contaminants (e.g., changes to impurities), which make the product safer while continuing to meet specifications. In this example, a manufacturer would evaluate whether this manufacturing change is significant and/or meaningful and results in either a change in identity or a change in the safety of the ingredient. In

[57] FDA, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry. Draft Guidance; August 2016. Question IV. A 13. If the manufacturing change does not alter the chemical or molecular composition or structure of the ingredient or the specifications needed to describe the ingredient, it is not necessary to submit a second NDI notification.
FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives; June 2014 Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm300661.htm

the fish oil example, the identity has not changed and the safety of the ingredient was improved; therefore, the manufacturer would conclude that no NDI notification is required. In the final guidance, FDA should explicitly state that some manufacturing changes that impact purity do not change the regulatory status of pre-DSHEA dietary ingredients.

A similar assessment can be appropriately applied to products manufactured using super critical CO_2 extraction, a manufacturing process that became common after DSHEA. Consider the example in which a manufacturer using a pre-DSHEA dietary ingredient is considering a new supplier that uses super critical CO_2 extraction for that ingredient. Similar to the fish oil example above, the manufacturer must evaluate whether the manufacturing change is significant and/or meaningful and results in either a change in identity or change in the safety of the ingredient. If the manufacturer concludes that there are no changes to identity (the product meets original identity specifications) or safety,[59] then it may not be required to submit an NDI notification. In the case that specific pre-DSHEA identity specifications are not available, dietary ingredient monographs may be used to establish ingredient identity. However, in either case, if the ingredient continues to meet the specifications of an established monograph or a manufacturer's pre-DSHEA specifications for identity, then the manufacturing change is not significant and/or meaningful enough to change the identity of the ingredient.

This type of assessment can also be applied to nanotechnology, changing agricultural or fermentation conditions, using a botanical ingredient at a different life stage, changing solvents, or changing temperature conditions. It would not be effective, or even possible, for CRN to provide specific examples of manufacturing changes or processes that would cause or not cause a

[59] Examples whereby supercritical extraction of botanicals have not changed the safety profile of the extracted ingredient include: Tumeric extracts (21 CFR 182.20); Garlic extracts (21 CFR 184.1317); and Clove extracts (21 CFR 184.1257).

pre-DSHEA dietary ingredient to become an NDI. Each scenario is entirely unique to both the ingredient and manufacturing change. Likewise, it would be difficult to provide examples and data to cover the many different types of dietary ingredients and manufacturing innovations that have occurred over the past two decades. Rather, each manufacturing change must be evaluated by the manufacturer case by case. It is far more efficient and effective from a regulatory and public health standpoint for FDA to focus on the resulting chemical identity and safety of the finished dietary ingredient, as opposed to the process by which the dietary ingredient is manufactured. CRN also notes that this recommendation is in accordance with the agency's approach to changes in the manufacturing process for food products and ingredients in general.[60,61,62]

CRN understands and agrees with FDA's position that manufacturers are obligated to assess whether changes to manufacturing of pre-DSHEA dietary ingredients impact their regulatory status. The revised draft guidance cites[63] the assessment process described in the June 2014 FDA guidance titled, "Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food

[60] FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives; June 2014.

[61] FDA has articulated in the area of genetically engineered foods that the method of product manufacturing is not a "material fact" unless its renders a substantial change in the finished product itself. FDA, in fact, argued against comments that there should be mandatory disclosure requirements for foods/food ingredients that come from bioengineered sources (57 Fed. Reg. 22984, 22991). FDA stated it was "not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding." FDA, Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering; November 2015.

[62] Further evidence that FDA's does not consider a particular process or method of manufacture necessarily to result in a "materially altered" finished product is provided by FDA's stance on the labeling of milk products from cows treated with recombinant bovine somatotropin (rbST) (59 Fed. Reg. 6279 (February 10, 1994)). FDA has noted its concern that the term "rbST free" might imply "a compositional difference between milk from treated and untreated cows rather than a difference in the way the milk is produced."

[63] FDA, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry. Draft Guidance; August 2016, at citation #18.

Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives (hereinafter "the 2014 guidance"). This assessment framework has applicability to NDI considerations. In particular, the principles outlined in the 2014 guidance can be used to assess when a manufacturing change is significant enough to change the identity or safety of a pre-DSHEA dietary ingredient, or an NDI that has been successfully notified to FDA. CRN interprets FDA's reference to this 2014 guidance as a signal to industry that the framework, as well as the examples, found in the 2014 guidance can continue to be used to guide internal assessments of manufacturing changes to pre-DSHEA dietary ingredients, as well as previously notified NDIs.

CRN recognizes that there will be many examples of manufacturing changes that do result in changes in the composition, and therefore identity, of a pre-DSHEA dietary ingredient. However, in some cases, the changes in composition may be minor changes in the relative amounts of various native constituents that were also present in the pre-DSHEA dietary ingredient at similar levels. These minor changes in composition are extremely unlikely to change the safety profile of an ingredient that was previously safely consumed in the food supply. We have seen FDA undertake an assessment of manufacturing changes to a food additive and reach the conclusion that the minor change did not alter the safety of the ingredient.[64] CRN

[64] Under 21 CFR 172.620, carrageenan is described as a "refined hydrocolloid that is prepared by aqueous from specific red seaweeds." Traditionally, carrageenan had been produced by extracting the carrageenan and filtering the extract to remove cellulose and other substances. In the late 1970s, a manufacturing change that was developed resulted in less complete removal of cellulose and a less refined product. Due to limited information about this new process, FDA initially requested that a new food additive petition be submitted. However upon review of the modified manufacturing process, the agency determined that the process used to produce the less refined carrageenan met the aqueous extraction requirement in the regulation, the new material conformed to the food ingredient specifications for carrageenan, and the process was as effective at removing impurities normally found in seaweed as the original manufacturing method. FDA concluded that the only significant difference between the new "carrageenan" and traditional carrageenan was that the former contained more cellulose compared to traditionally refined carrageenan. The agency did not consider the additional cellulose in carrageenan to be a safety concern and concluded that the new product still complied with the regulation for carrageenan. In light of this conclusion, FDA rescinded their earlier request for a food additive petition.

encourages FDA to identify an alternative, streamlined process for industry to notify FDA of post-DSHEA manufacturing changes that result in minor changes in the relative amounts or ratios of known constituents of a pre-DSHEA dietary ingredient. To that end, CRN supports the concept of an abbreviated NDI notification in which a firm demonstrates substantial similarities between their dietary ingredient and the pre-DSHEA dietary ingredient through a compositional analysis. Such an analysis would further establish that human consumption of the dietary ingredient does not introduce any new hazards because the ingredient contains the same constituents at similar levels as the pre-DSHEA dietary ingredient. This approach would be more efficient from both a regulatory and public safety standpoint, and would encourage companies to submit abbreviated notifications for pre-DSHEA dietary ingredients that use newer manufacturing methods, and more comprehensive notifications for entirely new dietary ingredients.

Recommendations:

CRN recommends that FDA maintain consistency among all FDA-regulated food ingredients with regard to how the agency and industry should evaluate the safety and regulatory impact of changes in a manufacturing process. For pre-DSHEA dietary ingredients that undergo a manufacturing change, an NDI notification to FDA should be required only when the change results in either a change in the identity of the ingredient (e.g., change to specifications needed to chemically characterize the ingredient) or has a negative impact on the safety of the ingredient when consumed under the recommended conditions of use.

In the final guidance, FDA should also provide for the submission of an abbreviated NDI notification that focuses on chemical identity and safety of the pre-DSHEA dietary ingredient, rather than the process by which the dietary ingredient is manufactured. This approach would

result in a more effective and efficient NDI notification process, thereby improving public safety and promoting sound regulatory policy. Further, this recommendation aligns with the agency's approach to changes in the manufacturing process for other types of FDA-regulated food products and ingredients.

IV. When an NDI notification is required

FDA continues to take a supplement-focused approach to NDI notification requirements. CRN acknowledges that in the revised draft guidance, FDA provides specific scenarios in which multiple notifications for separate dietary supplements containing the same NDI would not be required. While this represents progress from the 2011 draft guidance, in which FDA indicated that each and every finished product containing the NDI would require a notification, CRN maintains the position that "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. FDA has never sought to regulate combinations of conventional food ingredients, and there is no greater reason to do so in the case of dietary ingredients."[65]

Recommendations:

We continue to recommend that FDA permit ingredient manufacturers or distributors to submit NDI notifications that serve as the basis for establishing the safety of an NDI in a range of dietary supplements. Firms should self-determine whether additional notifications are needed based on an evaluation of the safety of the supplement containing the NDI. As stated in our 2011

[65] CRN Comments on 2011 Draft Guidance

comments, "In 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."[66,67] Should a dietary supplement utilize the NDI in a manner that is inconsistent with the serving size range or restrictions on use indicated in an earlier notification, or contain the NDI in combination with other dietary ingredients that may negatively impact the safety profile of the finished product, only then would a separate NDI notification be necessary.

V. Master file

CRN acknowledges that FDA has provided for the protection of intellectual property by allowing for firms to submit confidential NDI master files that contain the manufacturing specifications and other information needed to completely describe the identity of an ingredient. Permitting the submission of master files will further motivate companies to invest in science and develop scientifically supported, branded ingredients.

We understand that FDA has yet to determine the specifics of how the agency will administer the NDI master file submission and management process. CRN requests the opportunity for industry to participate in the development of this process through public comment.

Recommendation:

[66] Reasonable scientists may differ as to which ingredients categorically will or will not affect a product's safety profile. Where FDA disagrees with a particular conclusion, the agency may challenge the adequacy of the information available in existing literature and prior NDI notifications under Section 402(f)(1)(B) of the FDCA.

[67] CRN Comments on 2011 Draft Guidance

CRN recommends that FDA provide industry with the opportunity to participate in the development of the NDI master file submission and management process through public comment.

VI. History of use or other evidence of safety

CRN continues to disagree with FDA's declaration that it considers 25 years of widespread use to be the minimum to establish a history of safe use for a dietary ingredient.[68] As stated previously in our 2011 comments, FDA only cites language from a proposed European regulation on novel foods in support of the declaration that has not been adopted.[69] FDA does not provide a scientific basis for the 25-year period in the revised draft guidance. Further, the agency has never imposed this 25-year period, even under the GRAS standard for conventional foods.

CRN appreciates FDA's decision to remove all references to the Redbook (Toxicological Principles for the Safety Assessment of Food Ingredients), as requested in our comments in response to the 2011 draft guidance. We also agree with FDA's revision to Section VI.B to clarify that the safety standard for NDIs is different from that of food additives, drugs, and other FDA-regulated products, and to explain that notifiers should "compile scientific evidence that provides a basis to conclude that the NDI that is the subject of your notification will *reasonably be expected to be safe* when used under the conditions recommended or suggested in the labeling of the dietary supplement described in the notification"[70] (emphasis added).

Further, CRN appreciates FDA's recognition that a flexible approach is appropriate to evaluate the safety of dietary ingredients. In the revised draft guidance, FDA states that "(t)he amount of information needed to identify an ingredient and provide a basis for a reasonable

[68] Revised NDI Draft Guidance, at VI.B.9.
[69] CRN Comments on 2011 Draft Guidance
[70] Revised NDI Draft Guidance, at VI.B.21.

expectation of safety will vary enormously from notification to notification based on factors such as the complexity of the ingredient, history of use, and the presence or absence of specific safety concerns."[71] In this context, FDA indicates that the recommendations in Section VI about safety information to include in an NDI notification are not requirements. As expressed in our 2011 comments, CRN supports the use of a flexible approach to evaluating dietary ingredient safety. We expect FDA to apply this approach and exercise sound scientific judgment when reviewing the data and information submitted to support the safety of an NDI under the recommended conditions of use.

While recognizing that FDA acknowledges in the revised draft guidance that the recommendations in Section VI are not requirements, CRN is concerned with several of the recommendations outlined in this section. The safety testing recommendations provided in this section focus on traditional toxicity testing in animal models, with some *in vitro* tests for genetic toxicity and human studies to assess absorption, distribution, metabolism, excretion or tolerability. However, there are approaches available that can be used as a tool for prioritization screening of ingredients (i.e., to determine which ingredients should be prioritized for further toxicity testing). These approaches reflect the current and best science, reduce the use of animals, and increase efficiency. Examples of approaches include, but are not limited to, constituent analytical characterization and predictive models such as structure-activity relationships (SAR), quantitative SAR, and read-across approaches. Several of these tools are already widely used by FDA and/or other regulatory and authoritative bodies. FDA should acknowledge in the final guidance that these approaches may be appropriate in the safety assessment of NDIs.

[71] Revised NDI Draft Guidance, at VI.C.10.

CRN disagrees with FDA's position 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. For each dietary ingredient other than the NDI, FDA states that the notification should include a concise evaluation of known safety concerns and describe how the notifier concluded that the combination of ingredients will reasonably be expected to be safe.[72]

CRN contends that the adulteration standard in FDCA Section 413(f)(1)[73] already addresses safety of other dietary ingredients in a dietary supplement containing the NDI. Further, FDA's recommended practice of submitting detailed safety information on existing dietary ingredients already lawfully marketed in dietary supplements is not grounded in science and does not provide any consumer safety benefit. 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.

Similarly, we disagree with FDA's recommendation to submit references and information describing the function of each non-dietary ingredient (i.e., food additive, color additive, or GRAS substance) used in the dietary supplement containing the NDI, including the technical effect and the quantity needed to achieve that technical effect. Non-dietary ingredients should not

[72] 2016 draft guidance at Section VI.C.3
[73] 21 U.S.C. 342(f)(1).

be subject to NDI notification requirements intended for NDIs. Including the identity of each non-dietary ingredient in every dietary supplement containing the NDI, as well as information on the technical effect and quantity needed to achieve such effect for each non-dietary ingredient, does not contribute to the understanding of the safety of an NDI under the recommended conditions of use.

Recommendations:

CRN recommends that in the final guidance, FDA recognize that there are approaches, in addition to traditional toxicity testing that may be appropriate in the safety assessment of NDIs. Such approaches can be used as a tool for prioritization screening of ingredients for further toxicity testing, thereby reducing the use of animals and increasing efficiency.

We also advise FDA to remove recommendations that an NDI notification should include safety information on other dietary ingredients and non-dietary ingredients included in each dietary supplement containing the NDI. These recommendations are not scientifically justified and do not provide consumer safety benefit.

Respectfully submitted,

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