CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

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VIA ELECTRONIC SUBMISSION

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

Re: Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues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

The Council for Responsible Nutrition (CRN)[1] takes this opportunity to share our views on the agency's Draft Guidance on New Dietary Ingredient (NDI) Notification (Draft Guidance) issued on July 5, 2011. 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. We are joined in these comments by the Consumer

[1] CRN, founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands, as well as the store brands marketed by major supermarket, drug store, and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. In addition to complying with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control, and safety, our 75 plus manufacturer and supplier members also agree to adhere to additional voluntary guidelines, as well as CRN's Code of Ethics. Learn more about us at www.crnusa.org.

Healthcare Products Association (CHPA),[2] the leading U.S. trade association for manufacturers and distributors of nonprescription medicines and dietary supplements.

In the years since Congress enacted the Dietary Supplement Health and Education Act of 1994 (DSHEA),[3] we have provided comprehensive comments and recommendations to the agency on key issues with respect to dietary ingredients and NDI notifications.[4] We wish to serve as a resource for the agency on these issues, and we believe that industry-agency cooperation is the best way to resolve matters of significance with respect to dietary supplement safety and access.

The industry favors and supports the development of *reasonable* guidance on this subject. However, the agency's attempt to redefine the NDI notification process in the Draft Guidance contradicts the letter and spirit of DSHEA. The Draft Guidance would undo nearly two decades of agency practice and policy. It reflects the same FDA inimicality toward dietary supplements that led Congress to enact DSHEA. It would impose significant and unnecessary new burdens on the dietary supplement industry without conferring safety benefits to consumers. It far exceeds the permissible scope of a guidance document, proposing substantive requirements

[2] CHPA, founded in 1881, is a national trade association representing manufacturers and distributors of dietary supplements and over-the-counter medicines (www.chpa-info.org).

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

[4] *E.g.*, CRN Comments for Docket No. FDA-2011-N-0410, Agency Information Collection Activities; Proposed Collection; Comment Request: Premarket Notification for a New Dietary Ingredient (July 25, 2011); CRN Comments for Docket No. FDA-2009-P-0298, Defining a "Dietary Ingredient" (June 29, 2011); CRN Comments for Docket No. 2005P-0305, Pyridoxamine - Citizen's Petition (March 7, 2006); CRN Comments for Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (February 1, 2005); CRN Comments for Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (November 15, 2004); CHPA Comments for Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (February 1, 2005).

that must be the subject of notice-and-comment rulemaking. If FDA were to implement the Draft Guidance in its current form, it would reduce consumer access to safe and beneficial dietary supplements, reduce innovation and growth in the industry, and increase barriers to market entry for new companies and products. For these reasons, we request that FDA withdraw the Draft Guidance, give careful consideration to these comments, and begin the process anew with a Draft Guidance that reflects the statutory language and legislative intent of DSHEA.

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I. Introduction.

In 1994, Congress enacted DSHEA, amending the Federal Food, Drug, and Cosmetic Act (FDCA) to create a new and different program for the regulation of dietary supplements. In the 17 years since the statute's enactment, FDA and the dietary supplement industry have worked together within this legislative and regulatory framework. In our comments and our actions over the past two decades, the dietary supplement industry has been clear and consistent in its approach to interpreting DSHEA and its statutory obligations. The objections we raise in these comments should therefore come as no surprise to the agency.

Below we describe the legislative framework that *must* guide FDA's regulation of dietary supplements. We provide our comments on five significant ways in which the Draft Guidance would undermine the fundamental statutory framework on which regulation of dietary supplements is premised without providing additional consumer benefit. These are: (1) the proposed supplement-focused approach to NDI notification, (2) the restricted approach to chemical alteration, (3) the burden on industry to demonstrate non-NDI status, (4) the proposed ban on synthetic botanicals, and (5) the imposition of food additive safety requirements for NDIs. We then demonstrate that the Draft Guidance constitutes unlawful "rulemaking by guidance."

II. Congressional Intent.

Congress created the regime under which dietary supplements are regulated and marketed when it enacted DSHEA. The primary purpose of the statute was to strike a suitable balance between securing consumer access to a wide variety of dietary supplements and providing FDA with appropriate oversight over the safety of dietary supplements and dietary ingredients. To help ensure broad access to products, dietary ingredients were excluded from the

definition of "food additives" and therefore from the burdensome premarket approval process imposed upon food additives. To ensure FDA oversight over the safety of dietary ingredients, DSHEA required premarket notification to the agency for NDIs, except for those that are a constituent of a food and have not been chemically altered. Dietary ingredients already on the market (old dietary ingredients or ODIs) were excluded from the definition of an NDI.[5]

In the years prior to the enactment of DSHEA, FDA had "a long history of bias against dietary supplements."[6] The agency "pursued a heavy-handed enforcement agenda" against these products by attempting to restrict their marketing in a variety of ways.[7] FDA tried to set minimum and maximum levels for dietary supplements, sought to limit the potency of vitamins, proposed drug regulation for some vitamins and minerals, and finally sought to define and regulate dietary ingredients as food additives.[8] Congress enacted DSHEA to "correct this abuse by rationalizing the treatment of dietary supplements according to the pattern of the existing statute, and in conformity with the original congressional intent."[9] The statute provides that "legislative action that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness" and that "a *rational* Federal framework must be established to supersede the current ad hoc, patchwork regulatory policy on dietary supplements."[10] In DSHEA, Congress expressly crafted broad and comprehensive definitions

[5] FDCA § 413(d).

[6] S. REP. NO. 103-410 (1994), at 14.

[7] *Id.*

[8] *Id.* at 15.

[9] *Id.* at 22.

[10] Pub. L. No. 103-417, § 2(15) (emphasis added).

for dietary supplements and dietary ingredients. It categorically rejected the food additive regulatory regime by excluding dietary ingredients from the "food additive" definition. The three core principles of DSHEA are: (1) a very expansive category of dietary ingredients, (2) a presumption of safety for these products, with the burden on FDA to show otherwise, and (3) the directive that FDA refrain from erecting future hurdles to bar the marketing of safe and healthful dietary supplements. FDA has long acknowledged the unique regulatory framework for dietary supplements in public communications with Congress.[11]

Expansiveness. Congress' intent to authorize the marketing of a wide range of dietary ingredients is evident in its broad and comprehensive definitions of a "dietary

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[11] *E.g., Six Years After the Establishment of DSHEA: The Status of National and International Dietary Supplement Research and Regulation: Hearing Before the H. Comm. on Gov't Reform*, 107th Cong. 136-137 (2001) (statement of Joseph A. Levitt, Esq., Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration):

> When Congress passed DSHEA, it created a unique regulatory framework for dietary supplements. Its purpose was to strike the right balance between providing consumers access to dietary supplements and truthful information about them, while preserving regulatory authority for FDA to take action against supplements that present safety problems or false or misleading labeling.
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> As you know, the regulation of dietary supplements is, for the most part, a postmarketing program. Since Congress considered dietary ingredients marketed prior to the passage of DSHEA to be safe, dietary supplements containing these ingredients are permitted to be freely marketed, just like regular foods (e.g., fresh fruits and vegetables, processed foods and beverages, and seafood). Should safety problems arise after marketing, the adulteration provisions of the statute come into play.

Dietary Supplements: What Seniors Need to Know: Hearing Before the Special Comm. on Aging, 111th Cong. 119 (2010) (testimony of Joshua M. Sharfstein, M.D., Principal Deputy Commissioner, Food and Drug Administration):

> The way I think about DSHEA is that it balances access against risk. There is a very clear feeling in the law, like Congress and the public, that they want access to supplements that they—that are important to people, and many people in the United States, and so that people can put them on the market without a prereview by FDA, and particularly for the products that have been marketed, historically.

supplement" and a "dietary ingredient." A dietary supplement is "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)…"[12] Subparagraph (E) -- sometimes called the "catch-all" provision -- expressly provides for a limitless number of dietary ingredients, including new, never-before-marketed ones, requiring only that the labeling demonstrates an *intent* to supplement the diet. Congress also took an expansive view when it "grandfathered" *all* dietary ingredients marketed in the United States prior to October 15, 1994 as ODIs, and gave no authority to FDA to convert such ingredients into NDIs based on technological innovation.[13]

Safety. Congress' presumption of the safety of dietary ingredients is evident in its explicit pronouncement that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare."[14] Anchored by this presumption, DSHEA established a safety standard for NDIs that is distinctly different from the standards applicable to food additives and conventional food ingredients. All dietary supplements and dietary ingredients, new and old, are subject to an adulteration provision prohibiting products that present a "significant or unreasonable risk of illness or injury."[15] But for NDIs that require notification, the notifying party must simply show that these ingredients "will reasonably be

[12] FDCA § 201(ff)(1).

[13] FDCA § 413(d).

[14] Pub. L. No. 103-417, § 2(14).

[15] FDCA § 402(f)(1)(A).

expected to be safe."[16] Congress explicitly concluded that this standard is more appropriate for these presumptively safe ingredients than the "reasonable certainty of no harm" standard applicable to food additives[17] and the "generally recognized as safe" (GRAS) standard applicable to other conventional food ingredients.[18] The statute authorizes FDA to declare a dietary supplement adulterated if it contains a dietary ingredient for which an NDI notification should have been, but was not, provided to the agency. But the statute does not allow FDA to declare a product adulterated just because it disagrees with the characterization of the evidence submitted in an NDI notification. Rather, FDA bears the burden under Section(f)(1)(B) of the FDCA to show that the evidence is inadequate to support a determination that the NDI is reasonably expected to be safe.[19]

Removal of Barriers to Marketing. Congress' intent to remove barriers to the marketing of dietary supplements is evident in its declaration that "although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government *should not take any actions to impose unreasonable regulatory barriers* limiting or

[16] FDCA § 413(a)(2).

[17] 21 C.F.R. § 180.1(a) (providing that "there is a reasonable certainty that the substance is not harmful").

[18] FDCA § 201(s).

[19] In Section III of the Draft Guidance, FDA cites a "recent concern by both the agency and industry regarding the presence of undeclared active ingredients in products marketed as dietary supplements" as helping to "highlight the necessity for marketers of dietary supplements to submit NDI notifications as an important preventive control to ensure that the consumer is not exposed to potential unnecessary public health risks in the form of new ingredients with unknown safety profiles." Although the presence of undeclared active ingredients is indeed cause for concern, the NDI notification process cannot address intentional fraudulent economic adulteration. FDA has ample authority to take enforcement action against manufacturers and distributors with undeclared ingredients in their products.

slowing the flow of safe products…to consumers."[20] This goal pervades the language and structure of DSHEA. In its expansive scope of the definitions of the dietary supplement and dietary ingredient categories, its broad "grandfathering" of ODIs, and its less burdensome and narrow premarket review process, DSHEA *requires* FDA to abandon its prior "heavy-handed"[21] approach to the regulation of dietary supplements. As recently as June 2011, Senator Hatch -- a principal author and sponsor of DSHEA -- joined with Senator Harkin to write FDA in support of an NDI notification guidance that would be "consistent with the legislative compromise enshrined in [DSHEA]."[22] The Senators emphasized that "the intent of the law was to give FDA the tools necessary to help ensure the safety of dietary supplements and the accuracy of the limited claims allowed for them, but *also to minimize the regulatory burdens that might inhibit consumer access to lawfully manufactured and labeled supplement products*."[23]

The Draft Guidance violates the unambiguous Congressional intent in enacting DSHEA and the underlying goals of the statute. DSHEA was an act of deliberate legislative intervention to end years of enforcement abuses and impermissible restrictions on the marketing of dietary supplements. But the Draft Guidance would bring a return to the pre-DSHEA regime. It would greatly expand the number of dietary ingredients defined as NDIs. It would convert the NDI notification process into a requirement of premarket proof of safety indistinguishable from the food additive requirement. It would impermissibly impose on industry the burden of proof to

[20] Pub. L. No. 103-417, § 2(13) (emphasis added).

[21] S. REP. NO. 103-410 (1994), at 14.

[22] Letter from Tom Harkin and Orrin G. Hatch, U.S. Senators, to Margaret Hamburg, M.D., Commissioner of Food and Drugs, Food and Drug Administration (June 21, 2011).

[23] *Id.* (emphasis added).

establish an ingredient's non-NDI status. It would prohibit the marketing of nature-identical synthetic botanicals. It would trigger an avalanche of needlessly duplicative NDI notifications without any basis in law, public health policy, or science. In short, the Draft Guidance would be an abrupt departure from nearly two decades of the way that the dietary supplement industry has interpreted and complied with DSHEA, without FDA enforcement action. In the following pages, we discuss in detail five ways in which the Draft Guidance clearly undermines the legislative language and intent of DSHEA.

III. FDA's *Supplement*-Focused Approach to NDI Notification.

According to Sections IV(C)(1) and IV(C)(2) of the Draft Guidance, FDA would require the submission of an NDI notification by each and every manufacturer or distributor of each and every dietary *supplement* that contains an NDI. This unprecedented approach to the NDI notification process is contrary to the plain statutory language and the legislative history of DSHEA, and is inconsistent with the agency's own longstanding policy statements and practices. Such a policy is not grounded in practical realities or science, and it would result in industry members submitting burdensome and duplicative notifications that waste both industry and agency resources without providing any consumer safety benefit.

A. The Plain Language of DSHEA Does Not Require or Permit FDA to Require Supplement-Specific NDI Notifications.

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

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

> (2) There is a history of use or other evidence of safety establishing that the ***dietary ingredient*** when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, ***the manufacturer or distributor of the dietary ingredient or dietary supplement*** provides the Secretary with information, including any citation to published articles, ***which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe***.[24]

The plain language of DSHEA clearly contemplates *ingredient*-focused notifications. The sole requirement is that FDA receive adequate information on which *any* party may rely to conclude that its NDI-containing dietary supplement is reasonably expected to be safe.

This requirement is satisfied when companies submit NDI notifications for dietary ingredients that establish permissible ranges for safe use of the ingredient in a wide variety of products. In one specific example, a manufacturer submitted an NDI notification characterizing its product as "a bulk ingredient which will be used in supplements to promote maintenance of bone health." It recommended a maximum intake of 2,500 mg of the NDI per day in the notification.[25] This NDI notification paves the way for the safe and permissible marketing of an entire range of dietary supplements containing this ingredient. It satisfies the statutory requirement because "at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor ***of the dietary ingredient***…provide[d] the Secretary with information…which [was] the basis on which the manufacturer or distributor has concluded that ***a dietary supplement containing such dietary ingredient*** will reasonably be

[24] FDCA § 413(a) (emphasis added).

[25] AlgaeCal, Inc./AlgaeCal (June 17, 2009) (FDA Report No. 594). The report number is based on FDA's filing system for individual NDI notifications. Throughout these comments, we cite to the agency's NDI "acknowledgment" letters by report number.

expected to be safe."[26] In this case, the notification provided sufficient information establishing the safety of the bulk NDI in a range of dietary supplements containing the dietary ingredient. There is simply *no* statutory basis for FDA to require duplicative notifications from parties who later seek to use this NDI in formulations at levels already documented in the NDI notification to have a reasonable expectation of safety.

To the extent that an NDI that is the subject of a notification may have known interactions with other ingredients, such interactions can be included in the recommended conditions of use for that NDI, along with a precaution that dietary supplement formulations should not combine specified ingredients with the NDI. 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.[27] 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 not contemplated by the earlier notification, or in combination with ingredients that potentially 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.

[26] FDCA § 413(a)(2) (emphasis added).

[27] 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.

B. The Agency's Own Longstanding Regulatory Practice Supports *Ingredient*-Specific, Not Supplement-Specific, Notifications.

In the Draft Guidance, FDA asserts that the thousands of dietary ingredients and dietary supplements on the market, compared to the few hundred NDI notifications the agency has received, demonstrate that the industry has long failed to submit numerous required notifications. But the industry has long understood both Section 413(a)(2) and FDA's policy to permit reliance on *ingredient*-specific NDI notifications, and has so informed FDA.[28] First, FDA's "acknowledgments" of ingredient-focused NDI notifications without objection over the years demonstrate its open endorsement of an ingredient-focused approach. These notifications frequently are for the dietary ingredient itself, with potential use by multiple downstream product manufacturers who will formulate the dietary ingredient with safe and suitable excipients and other dietary ingredients, and provide recommended ranges for safe use of the NDI in finished products.[29] The agency cannot now argue it was unaware of the industry's interpretation and past practices, particularly when it clearly condoned and accepted them.

[28] *E.g.*, CRN Comments for Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (November 15, 2004), at 5 (stating that "CRN notes that the NDI notification may be submitted by a supplier of the *ingredient* or by a manufacturer in the pre-launch phase of product development, and it may not be possible at that point to submit actual labels or labeling, although it would be possible to describe the intended uses.") (emphasis added).

[29] *See, e.g.*, Nephro-Tech 1, LLC/calcium formate (May 11, 2010) (FDA Report No. 658) (characterizing the ingredient as "a bulk ingredient that will be used in supplements to provide an added source of calcium to the diet."); Sabinsa Corporation/SelenoForce (September 15, 2009) (FDA Report No. 613) (stating an intent to market SelenoForce "in bulk to dietary supplement manufacturers" and stating that the dietary supplements containing the NDI "will be in capsules, tablet, granules, and powder form." The notification stated how finished dosage manufacturers would be instructed to label the supplements and provided a permissible range of SelenoForce in the product.); E.I. du Pont de Nemours and Company/EPA rich triglyceride oil (April 3, 2009) (FDA Report No. 582) (characterizing the product as "intended for use in dietary supplements…[that]…will be sold in forms suitable for

(continued…)

Second, FDA has indicated in several forums that it did *not* anticipate the submission of numerous NDI notifications. In a 1995 memorandum confirming FDA's decision to create a docket to house NDI notifications, the agency stated that, "*We do not expect many of these submissions*, thus we wish to place all of the submissions into the same docket, as opposed to a separate docket for each submission."[30] In its preamble to the NDI regulation, FDA estimated the total number of businesses that would be affected by the proposed rule to be "*no more than the number of new ingredients* (estimated to be 0 to 12 per year)."[31] Even as recently as this year, in assessing the industry burden to collect data to comply with the NDI notification process, FDA estimated it would receive 55 premarket notifications per year.[32] The agency cannot now argue that thousands of necessary NDI notifications are "missing" when its own estimates of the appropriate number of NDI notifications were quite low and clearly were linked to the number of dietary *ingredients*.

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dietary supplements." The company recommended a maximum EPA intake of 2 g/day.); Archer Daniels Midland Company/BeneFlax Flax Lignan Extract (October 10, 2006) (FDA Report No. 378) (characterizing the ingredient to "be sold in bulk form to finished product manufacturers of dietary supplements" and noting a permissible range for the product.); Access Business Group LLC/Kakadu Plum Concentrate (September 7, 2005) (FDA Report No. 300) (characterizing the product as a "new dietary ingredient for use in dietary supplement [product]s" that are expected to deliver 100-800 mg Kakadu Plum Concentrate per day); Medipharm USA/Lactobacillus F19 (September 2, 2003) (FDA Report No. 209) (contemplating multiple manufacturers using the ingredient and recommending the amount of bacteria that should be added to finished products).

[30] Memorandum from Linda S. Kahl, Ph.D., Acting Director, Division of Programs and Enforcement Policy, Office of Special Nutritionals, to Jennie Butler, Dockets Management Branch (September 25, 1995), Docket No. FDA-1995-S-0039-0001 (emphasis added).

[31] 62 Fed. Reg. 49886, 49891 (September 23, 1997) (emphasis added).

[32] It characterized this number as "an average based on the Agency's experience with notifications received during the last 3 years. FDA received 77 notifications in 2008, 39 notifications in 2009, and 48 notifications in 2010, for an average of 55 notifications." 76 Fed. Reg. 51986, 51987 (August 19, 2011).

C. A Supplement-Focused Approach to Notifications is Unsupported by Science or Public Policy.

Shifting from an ingredient-focused approach to a supplement-focused approach for NDI notifications at this point would make little sense for either FDA or the dietary supplement industry. It would needlessly strain industry resources to generate -- and agency resources to review -- duplicative supplement notifications when valid ingredient notifications have already been submitted. FDA does not seem to recognize the true burden this new proposed policy would place on the agency. Using estimates from the Draft Guidance, there are 1,000 new dietary supplements introduced to the market each year, but there have been only 700 NDI notifications since the agency began reviewing them.[33] The backlog of NDI notifications that FDA now appears to be requesting -- more than 16,000 (1,000 NDIs per year for 17 years minus the 700 NDI notifications actually submitted) -- would cripple the agency. The magnitude of this FDA-projected backlog is reminiscent of what caused the breakdown of the GRAS affirmation petition process. The NDI notification avalanche would precipitate an even greater failure.[34]

A supplement-focused approach to NDI notifications would not logically accord with the realities of the dietary supplement industry. Dietary ingredient suppliers typically have

[33] Draft Guidance, at Section III. The Draft Guidance juxtaposes these estimates -- along with the estimate of 55,600 dietary supplement products on the market -- in order to suggest that the industry has failed to file required NDI notifications for the vast majority of products on the market. These estimates do not take into account all the dietary supplement products comprised of ODIs and NDIs derived from food.

[34] FDA in the past reviewed and affirmed self-determinations of GRAS status, but due to the rising backlog of petitions, FDA proposed in 1997 to replace the procedure with a simpler GRAS premarket notification system. 62 Fed. Reg. 18938 (April 17, 1997). Although this proposed regulation has not yet been promulgated in final form, FDA immediately abandoned the GRAS affirmation process after the proposal was published and has been implementing the GRAS premarket notification system ever since.

access to the proprietary data and information that establish the safety of their ingredients. These parties are in the best position to generate, analyze, and present this safety information to FDA as part of the NDI notification process. Finished product manufacturers that purchase bulk ingredients for downstream use rely on the ingredient suppliers for assurances that an appropriate NDI notification has been submitted. But under the Draft Guidance, they would need to seek the relevant information from the ingredient suppliers and begin the arduous process of reconstructing a duplicate dossier to establish safety. This might require seeking access to proprietary information, which ingredient manufacturers may not wish to divulge or which may prove very costly to obtain. Ingredient manufacturers that provide confidential information to their customers under a nondisclosure agreement for use in a submission also have a legitimate concern that their customers may not redact all of the confidential information in a submission.

Finally, when one balances the significant burden this approach would impose against the purported scientific or consumer safety benefit it would yield, supplement-focused notification is not an effective regulatory strategy. The same concerns are better addressed through dietary ingredient notifications that specify potential ingredient interactions and through enforcement of compliance by manufacturers with the GMP regulations in 21 C.F.R. Part 111 to deal with potential manufacturing-related issues. If FDA already has the information necessary to establish a reasonable expectation of safety for multiple products in a *single* NDI notification, there is nothing to be gained by requesting the duplicative generation and submission of such data. FDA has not publicly identified even one instance in the past 17 years where the ingredient-based approach has resulted in a safety problem with the finished dietary supplements containing such ingredients.

D. Recommendation.

We recommend that FDA return to its historical policy of permitting 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. We strongly urge FDA to delete its proposal to require duplicative data submissions by *every* single manufacturer or distributor for each distinct product containing the NDI. Where an initial NDI notification provides a sufficiently detailed characterization of the NDI and establishes permissible levels for its safe use, future parties are lawfully permitted to rely on such data, rendering separate NDI notifications unnecessary.

IV. FDA's Restricted Approach to Chemical Alteration.

According to Section IV(B)(3) of the Draft Guidance, FDA would view *only* the following processes not to result in chemical alteration of food: "Minor loss of volatile components, dehydration, lyophilization, milling, and formation of a tincture or a solution in water, a slurry, a powder, or a solid in suspension." This pronouncement appears to arise from FDA's mistaken, and overly narrow, reading of the legislative history that accompanies DSHEA. Adopting this restricted list would significantly expand the category of NDIs requiring notification. Neither DSHEA nor its legislative history requires or permits FDA to restrict the processes that do not result in chemical alteration to this very short list. Moreover, such a restriction would not be grounded in science. FDA's historical policy also indicates that the method of manufacture is not determinative of chemical alteration.

A. Neither DSHEA Nor its Legislative History Imposes Specific Restrictions on the Definition of "Chemically Altered."

Section 413(a)(1) of the FDCA, as added by DSHEA, describes a category of NDIs that do not require NDI notifications. These are dietary supplements that contain 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."

The Draft Guidance substitutes the term "conventional food" in places where DSHEA specifically refers to the "food supply."[35] These terms are not directly interchangeable, and FDA cannot use the term "conventional food" to *narrow* the category of NDIs for which notification is not required under Section 413(a)(1). In providing that notification is not required for ingredients which 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 of this inquiry. An ingredient used in herbal tea in China, but that is introduced to the U.S. market after October 15, 1994 is an NDI that does not require notification. FDA may not conflate "conventional food" with the "food supply" in a manner that constrains the application of Section 413(a)(1) and is contrary to the language of DSHEA.

There is no basis in the statute for arbitrarily limiting processes that may be used as long as in fact there is no chemical alteration. Nor is there any basis for asserting that pre-DSHEA methods of manufacture, extraction, or synthesis are the only processes that result in ingredients being deemed ODIs. A wide variety of manufacturing processes are permissible

[35] Draft Guidance, at IV(B).

under the statute, as long as the resulting compounds are identical to those found in the food supply.

When Congress enacted DSHEA, the chief sponsors of the legislation prepared a one-page "Statement of Agreement" that discusses some aspects of the statute.[36] This legislative history states that "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."[37] Nowhere does it state or imply that these are the *only* processes that will not result in chemical alteration. There is simply no evidence to suggest that Congress intended FDA to adopt a static definition of the category of processes that result in chemical alteration. Had it intended this result, Congress could easily have said so in the statute itself or in the Statement of Agreement, *e.g.*, by indicating that "chemical alteration *does not mean*…" as opposed to "does not include…." Courts have held that similarly worded statutory lists are exemplary, not exclusive, and we are confident that the context counsels such a conclusion here.[38]

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[36] 140 CONG. REC. 28961 (1994).

[37] *Id.*

[38] *E.g.*, *Samantar v. Yousuf*, 130 S. Ct. 2278, 2287 (2010) (stating that "Use of the word 'include' can signal that the list that follows is meant to be illustrative rather than exhaustive."); *NationsBank v. Variable Annuity Life Ins. Co.*, 513 U.S. 251, 257-58 (1995) (endorsing the Comptroller of the Currency's interpretation that a statutory enumeration of powers defining the "business of banking" was "exemplary, not exclusive" in light of other statutory language indicating the existence of powers beyond the five enumerated); *Massachusetts v. E.P.A.*, 549 U.S. 497 (2007) (Scalia, J., dissenting) ("The word 'including' ... indicate[s] that what follows will be an 'illustrative' sampling of the general category that precedes the word."); *In re APA Transport Corp. Consol. Litigation*, 541 F.3d 233, 241 (3rd Cir. 2008) ("It is a well-established canon of statutory construction that when the word 'including' is followed by a list of examples, those examples are generally considered illustrative rather than exhaustive."); *United*

(continued…)

B. FDA's Restricted Definition of "Chemically Altered" is Not Grounded in Science.

FDA's new proposal to restrict the category of processes that result in chemical alteration has no basis in science. In the Draft Guidance, FDA lists several processes that it *would* consider likely to involve chemical alteration, thus triggering NDI notification. Among these are numerous commonplace manufacturing techniques that the industry has been using for years without chemically altering the underlying ingredients. Even complete synthesis of nature-identical ingredients in the food supply does not constitute chemical alteration. If the final product is chemically identical, as confirmed by analytical methods, to the ingredient found in nature, there is simply no basis in the statute to assert that the manufacturing method triggers an NDI notification. Scientific policy does not support the existence of a pre-specified list of processes that do or do not result in chemical alteration. The only inquiry under the statute is whether the material generated at the *conclusion* of a process is chemically identical to the material found in the food supply.

C. FDA's Historical Policy Demonstrates that Manufacturing Methods Alone Do Not Dictate Chemical Alteration.

FDA has long maintained that the method of a product's manufacture is not a material fact unless it renders a substantive change in the finished product itself. FDA articulated this position most clearly and vigorously in the domain of genetically engineered foods. Despite receiving many comments from stakeholders requesting that the agency impose

States v. Grassie, 237 F.3d 1199, 1215 (10th Cir.2001) ("We regard the statutory use of the word 'including' ... as the preface for a representative or illustrative example, and not as a term of restriction or exclusion for anything not expressly specified."). *See also* 2A N. Singer & J. Singer, Sutherland Statutory Construction § 47.7, p. 305 (7th ed. 2007) ("The word 'includes' is usually a term of enlargement, and not of limitation" (internal quotation marks omitted)).

mandatory disclosure requirements for foods or food ingredients that came from bioengineered sources, the agency stated that 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."[39] Even in this controversial domain, FDA clearly determined that the manner of manufacture was not "material" within the meaning of the FDCA, and therefore concluded that the agency lacked statutory authority to require any special labeling for genetically engineered foods.[40] FDA's attempt to assert that a dietary ingredient's manufacturing method necessarily results in chemical alteration -- even when the finished product is indistinguishable from its natural counterpart -- would completely contradict the agency's longstanding regulatory policy.

Similarly, the FDCA recognizes the United States Pharmacopeia and National Formulary (USP-NF) as the official drug compendia of the nation.[41] The current USP-NF comprises thousands of monographs that describe specifications for prescription and over-the-counter active ingredients, dietary ingredients, and food ingredients. These specifications

[39] 57 Fed. Reg. 22984, 22991 (May 29, 1992). The agency reaffirmed this belief in developing its 2001 guidance on this same topic. *See* Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering (January 2001) (stating that "The agency is still not aware of any data or other information that would form a basis for concluding that the fact that a food or its ingredients was produced using bioengineering is a material fact that must be disclosed under sections 403(a) and 201(n) of the act.").

[40] FDA's position has been upheld in court. *See, e.g., Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166 (D.D.C. 2000) (rejecting a direct challenge to FDA's 1992 Statement of Policy regarding the labeling of bioengineered foods); *Stauber v. Shalala*, 895 F. Supp. 1178 (W.D. Wis. 1995) (finding that FDA did not act arbitrarily and capriciously in not requiring the labeling of dairy products derived from cows treated with bovine somatotropin (bST)).

[41] FDCA §§ 201(g)(1), 501(b), 502(e)(3), 505(g).

describe finished ingredients, and not the manufacturing processes used to develop them, as sufficient to assure purity, quality, and strength.

D. Recommendation.

We recommend that FDA not impose a static and unscientific definition for processes that result in chemical alteration. Rather, the agency should retain a flexible, science-based approach that permits case-by-case determinations of whether the end result of a given process is chemically identical to the material present in the food supply. This is what the statute, sound science, and agency precedent require.

V. FDA's Allocation of the Burden of Proof to Demonstrate Non-NDI Status.

Section IV(A)(8) of the Draft Guidance would impermissibly require the industry to bear the burden of proof and overcome stringent evidentiary restrictions in order to prove the non-NDI status of a dietary ingredient. DSHEA clearly requires FDA to prove that a dietary ingredient is an NDI that requires a notification, in the event of a dispute.

A. DSHEA Does Not Impose the Burden of Proof on Industry, Nor Does it Prescribe Evidentiary Standards for Demonstrating the Non-NDI Status of Ingredients.

Section 413(d) of the FDCA, as added by DSHEA, sets forth a simple, date-based definition of an NDI. The term NDI means "a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994." If FDA were to allege that a dietary supplement is being illegally marketed without an NDI notification for a dietary ingredient in the product, under standard rules of evidence it would bear the burden of proof to demonstrate the NDI status of that ingredient. In the Draft Guidance, FDA would not only reverse this burden and place the burden of proof on the industry, but it would require parties to produce

contemporaneously created written documentation to prove non-NDI status. This policy lacks any legal or rational justification.

B. FDA's Proposed New Evidentiary Requirements Would Be Illegal, Burdensome, and Particularly Disadvantageous to Newer Market Entrants.

FDA's proposed new evidentiary requirements and refusal to accept affidavits attesting to recollection of historical events contradict the legislative history of DSHEA, have no basis in the statute, and would be onerous for all industry members. These proposed policies contradict DSHEA's express directive that the federal government "not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products…to consumers."[42] Such policies would have a disparate negative impact on newer market entrants. It may be impossible for newer companies to secure access to the types of contemporaneously created pre-DSHEA marketing documentation FDA proposes to require. Affidavits are routinely admitted as evidence in courts of law, and there is no rational basis for FDA to refuse to admit them for this purpose. These rigid restrictions are excessive, needless, and unfairly punitive to adopt 17 years after the statute was enacted. In the Draft Guidance, FDA cites the pyridoxamine petition and its refusal there to recognize CRN's affidavit as evidence that pyridoxamine was marketed prior to the filing of an investigational new drug application (IND) for the ingredient. CRN objected to that view then, but lacked standing to fight it. We stated that the agency's position was wrong at the time, and we maintain that it is still wrong today.

In Section IV(A)(10) of the Draft Guidance, FDA rejects the existence of an authoritative list of ODIs, stating that "Each supplement manufacturer or distributor is responsible for establishing that the dietary ingredients in its dietary supplements comply with

[42] Pub. L. No. 107-417, § 2(13).

the NDI notification requirements." Any suggestion that *each* manufacturer or distributor must have independent proof that an ingredient is an ODI, or else file an NDI notification, is unlawful. As stated above, the definition of an NDI is entirely date-driven; once *any* ingredient's ODI or NDI status has been established -- such as by reference to an industry list -- the entire industry lawfully may rely on such a finding. The lists that were prepared by industry experts familiar with pre-1994 product formulations are entitled to substantial evidentiary weight.[43] These lists constitute prima facie evidence of pre-1994 use, and they must play a role in FDA's consideration of whether an ingredient is an NDI. If FDA questions the inclusion of an ingredient on such a list, the agency bears the burden of proof in such a challenge. FDA had the opportunity to prepare a definitive list at the time DSHEA was enacted and chose not to do so.[44] FDA's failure to undertake this effort cannot now be used as an excuse to attempt to shift the burden of proof to the industry.

C. Recommendation.

We recommend that FDA not attempt to impose the burden to demonstrate an ingredient's non-NDI status on each manufacturer and distributor, as this will disregard the collective wisdom the industry has amassed over the years. DSHEA was intended to preserve

[43] *E.g.*, National Nutritional Foods Association (now Natural Products Association (NPA)), 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.

[44] 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).

access to a wide range of dietary supplements and to discourage needless regulatory hurdles to their marketing. The industry should self-determine whether ingredients are ODIs or NDIs, and FDA should bear the burden of proof if it chooses to challenge such determinations.

VI. FDA's Proposed Ban of Synthetic Botanicals.

Section IV(D)(2) of the Draft Guidance states that, as a matter of law, a synthetic copy of a constituent of a botanical cannot be considered either a "constituent" or an "extract" of a botanical within the meaning of Section 201(ff)(1)(F) of the FDCA, as such a compound was never actually a part of the botanical, nor was it extracted. These are the only statements in the Draft Guidance that address the regulatory status of synthetic dietary ingredients and -- coupled with FDA's recent treatment of specific synthetic botanicals (*e.g.*, homotaurine) -- they appear to suggest that FDA takes the position that synthetic dietary ingredients cannot qualify as "dietary ingredients" at all. It appears that FDA is proposing a ban on nature-identical synthetic botanicals in the absence of statutory authority and in violation of its longstanding policies without additional benefit to public health or safety.

CRN has been attempting to address this issue with FDA since at least 2004, and the agency has never responded to us or addressed the merits of our argument.[45] We recently submitted an extensive set of comments on the marketing of synthetic dietary ingredients in

[45] CRN Comments for Docket No. 2004N-0454, Premarket Notification for New Dietary Ingredients (November 15, 2004), at 3 (stating, in reference to Section 201(ff)(1)(E) of the FDCA, "We also view the term as encompassing synthetic equivalents of the naturally-occurring substances.").

response to FDA's denial of a petition to market synthetic homotaurine.[46] We append these to the current set of comments, and reiterate our key concerns in brief below.

A. DSHEA Cannot be Read to Prevent Synthetic Botanicals from Qualifying as Dietary Ingredients.

One explicit Congressional goal in enacting DSHEA was to secure consumer access to a wide variety of safe and potentially beneficial dietary supplements and dietary ingredients.[47] The broad language of DSHEA includes in the definition of a dietary ingredient both synthetic ingredients that are identical to ingredients found in nature *and* those that had not previously been intended for use in supplementing the diet.[48]

Synthetic ingredients clearly may be marketed under Section 201(ff)(1)(E) of the FDCA, the "catch-all" provision that encompasses dietary substances "for use by man to supplement the diet by increasing the total dietary intake." This category is limitless. Its only prerequisite for a dietary ingredient -- presuming that the ingredient meets other provisions of the statute -- is the labeled intent that the dietary ingredient is for use to supplement the diet. The concept of "intended use" is one that permeates the FDCA generally, and it is grounded in the manufacturer's or the distributor's representation for how the substance should be used. Where Congress intended to impose a historical use requirement in DSHEA, it did so clearly. Congress

[46] CRN Comments for Docket No. FDA-2009-P-0298, Defining a "Dietary Ingredient" (June 29, 2011) (attached as Appendix A).

[47] "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).

[48] FDCA § 201(ff)(1)(E).

did not impose a historical use requirement on this catch-all provision. It is entirely a forward-looking assessment.

FDA has previously acknowledged the breadth of Section 201(ff)(1)(E) of the FDCA in the preamble to its regulation on requirements for nutrient content claims, health claims, and statements of nutritional support for dietary supplements.[49] The agency stated that a substance such as CoQ10 -- which is commonly synthesized -- falls within the broad range of dietary ingredients that Congress contemplated.[50] FDA's acceptance of a 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 synthetic versions of natural botanical components from the definition of a "dietary ingredient."

B. FDA's Proposal to Prohibit the Marketing of Synthetic Ingredients Would Contradict Longstanding Agency Policies.

FDA has a long history of recognizing that synthetic ingredients can be identical to natural ingredients and should be treated no differently. Its new proposal to prohibit the marketing of synthetic botanicals makes no sense in light of these longstanding policies.

Most significantly, FDA's nutrition labeling regulation states that a food would be deemed misbranded if its labeling states or implies "that a natural vitamin in a food is superior to an added or synthetic vitamin."[51] This prohibition dates back to the late 1960s, when the agency

[49] 62 Fed. Reg. 49859, 49860 (September 23, 1997).

[50] *See id.* (quoting from the legislative history of "other nutritional substances" -- a precursor to "dietary ingredients" -- statements that numerous ingredients not traditionally or historically viewed as food substances would be included, such as primrose oil, black currant seed oil, amino acids, and hydrogen peroxide).

[51] 21 C.F.R. § 101.9(k)(4).

vigorously defended its position on this issue during two years of public hearings on special dietary food regulations.[52] As recently as the late 1990s, FDA reaffirmed the validity of the prohibition, stating that it is "aware of nothing that establishes that a claim of difference between the natural and synthetic version of the same form of a nutrient is not misleading."[53] Denying the validity of synthetic botanicals would suggest that FDA now views a material distinction between synthetic and natural versions of identical ingredients. This radical shift makes no sense in light of the agency's historical policy.

Several concrete examples illustrate that FDA recognizes the equivalence of naturally extracted sources and synthetic sources of ingredients. FDA has affirmed as GRAS both natural and synthetic riboflavin,[54] vitamin A,[55] and vitamin D.[56] FDA approved the food additive Vitamin D3 in both natural and synthetic forms.[57] And FDA has acknowledged NDI notifications for nature-identical synthetic botanical ingredients without objection in the past.[58] As previously discussed, and as evinced in the domain of genetically engineered foods, FDA has

[52] These hearings took place between 1968 and 1970. *See* 38 Fed. Reg. 2143, 2147, 2150 (January 19, 1973) (summarizing FDA's conclusions based on the hearings, including its finding that "There is no nutritional difference between a vitamin provided by a synthetic source and the same vitamin provided by a natural source….").

[53] 62 Fed. Reg. 49826, 49841 (September 23, 1997).

[54] 21 C.F.R. § 184.1695(a).

[55] 21 C.F.R. § 184.1930(a).

[56] 21 C.F.R. § 184.1950.

[57] 21 C.F.R. § 172.380(a).

[58] *E.g.*, Roche Vitamins, Inc./zeaxanthin (March 22, 2001) (stating that "Roche synthetic zeaxanthin is identical to natural zeaxanthin.") (FDA Report No. 96).

long maintained that the method of a product's manufacture is not a material fact unless it renders a substantive change in the product itself.[59]

If FDA were to attempt to prohibit synthetic botanicals from qualifying as "dietary ingredients" altogether, it would have the unintended consequence of stifling scientific progress, perhaps even in ways that could prove detrimental to public health or have negative environmental consequences. Manufacturers typically have more control over synthetic processes than over natural extraction processes, and this can yield tangible safety and quality benefits for consumers. Synthetic processing can eliminate potentially harmful variables such as pesticide contamination, the presence of foreign materials, and the uptake of minerals and toxins from the soil. Chemical synthesis also ensures greater consistency in output quality, as variations in climate or geographic region no longer pose concerns. Discouraging the industry's use of synthetic processing may negatively affect the environment. For example, if a chemical component of a plant has beneficial health effects, but turns out to be virtually impossible to extract from its natural source on a commercial scale or such an extraction is environmentally detrimental, FDA's position would prohibit the use of a chemically identical synthetic version. The result would be to deny consumers access to a safe and beneficial ingredient or to force a manufacturer to produce it in an unsustainable or environmentally irresponsible manner. This simply is not what Congress intended.

C. Recommendation.

We strongly urge FDA to confirm that synthetic botanical ingredients may lawfully be marketed. FDA should explicitly acknowledge that these are valid dietary

[59] *See supra* Part IV.C.

ingredients that may be marketed under either Section 201(ff)(1)(E) or Section 201(ff)(1)(F) of the FDCA.[60] A bio-identical synthetic ingredient is both a "constituent" of a botanical and an ingredient intended to supplement the diet by increasing the total dietary intake.

VII. FDA's Imposition of Food Additive Safety Requirements for Dietary Supplements.

Sections VI(B) and VI(C) of the Draft Guidance detail in great specificity the rigorous science that FDA proposes to require in future successful NDI notifications. There would be no distinction between these new proposed safety requirements and the burdensome process for seeking approval of a food additive. Congress deliberately removed dietary supplements from the food additive regulatory regime in DSHEA, but the Draft Guidance would ignore the statute by adopting the same safety standards as those that apply to food additives. FDA subjects food additives to a lengthy premarket review process, the successful result of which is a conclusive finding of safety. In contrast, when FDA acknowledges an NDI notification without objection, the agency states in its response letter that this does *not* constitute a finding by FDA that the NDI or the dietary supplement containing the NDI is safe or not adulterated under Section 402 of the FDCA. FDA has not expressed any intent to change this practice. Thus, under the Draft Guidance, NDIs would be held to the same rigorous safety standards that FDA uses

[60] In its denial of the homotaurine petition, FDA appears to have been receptive to the use of Section 201(ff)(1)(E) as a route for the marketing of synthetic dietary ingredients. But in that case, the agency imposed an "historic use" requirement, seeking evidence that *synthetic* homotaurine had historically been used to supplement the diet by increasing the total dietary intake. We strongly disagree that any historic use requirement applies to Section 201(ff)(1)(E) of the FDCA for reasons discussed fully in our comments at Appendix A. We do not address these arguments in the current set of comments because FDA did not address Section 201(ff)(1)(E) at all in the Draft Guidance.

to confer a finding of "safety" on food additives, but NDIs would not qualify for an equivalent finding.

A. DSHEA Specifically Carved Dietary Ingredients Out of the Food Additive Category.

Prior to the enactment of DSHEA, FDA attempted to regulate dietary supplements through a variety of means. At one point, having failed to regulate these products as "drugs," the agency attempted to classify dietary ingredients as unapproved food additives. If successful, the agency would have been able to impose on particular dietary ingredients the same requirements for premarket approval as it applied to chemicals added to food for nonnutritive purposes. To justify this attempt at regulation, FDA argued in one case that because gelatin is regulated as food, any type of food (*e.g.*, black currant oil) contained in a gelatin capsule is thus a food additive. The Seventh Circuit characterized this reasoning as an "Alice-in-Wonderland approach" the only justification for which was "to allow the FDA to make an end-run around the statutory scheme."[61] The First Circuit reached the same conclusion in a case with similar facts, stating:

> FDA's reading of the [FDC] Act is nonsensical….The proposition that placing a single-ingredient food product into an inert capsule as a convenient method of ingestion converts that food into a food additive perverts the statutory text, undermines legislative intent, and defenestrates common sense. We cannot accept such anfractuous reasoning.[62]

On the heels of FDA's failed attempts to regulate dietary supplements as food additives, Congress spared dietary supplements from this regulatory pathway in DSHEA. There

[61] *United States v. Two Plastic Drums… Viponte Ltd. Black Currant Oil*, 984 F.2d 814, 819-820 (7th Cir. 1993).

[62] *United States v. 29 Cartons of…an Article of Food*, 987 F.2d 33, 37, 39 (1st Cir. 1993).

is absolutely no question that Congress intended to remove dietary supplements from the food additive category, as evinced by the section of DSHEA entitled "Exclusion from Definition of Food Additive."[63] This provision amended the definition of a food additive in Section 201(s) of the FDCA to state that such term "does not include…an ingredient described in paragraph (ff) [the definition of a "dietary ingredient"] or intended for use in, a dietary supplement."[64] FDA cannot now seek to undo by guidance a distinction that Congress so clearly secured in legislation.

B. The FDCA Imposes Different Safety Standards for Conventional Food Ingredients, Food Additives, and NDIs, but the Draft Guidance Would Unlawfully Obliterate these Distinctions.

In spite of the clear exemption of the dietary supplement category from the food additive regulatory provisions, the Draft Guidance seeks to import food additive safety requirements into the NDI notification process. Throughout the Draft Guidance, FDA makes reference to the Redbook (Toxicological Principles for the Safety Assessment of Food Ingredients) as an authoritative source for information on how to demonstrate safety of dietary supplement ingredients.[65] The Redbook is the official FDA manual for evaluating food additives. It imposes a significantly higher threshold for safety than the "reasonable expectation of safety" standard Congress specified for dietary supplements. The use of the Redbook would thus be completely inappropriate in the evaluation of an NDI. Indeed, the rejection by Congress of the food additive standard for evaluating the safety of dietary ingredients necessarily means that the Redbook cannot be used for that purpose. All references to the Redbook must be

[63] Pub. L. No. 103-417, § 3.

[64] FDCA § 201(s)(6).

[65] *E.g.*, Draft Guidance, at VI(B)(23), VI(B)(28), VI(B)(35), and VI(B)(40).

removed from the Draft Guidance and replaced with a set of safety principles that are appropriate for the intended use and meet the DSHEA standard of a reasonable expectation of safety.

The FDCA establishes a clear hierarchy of safety standards applicable to food additives and GRAS substances on the one hand, and dietary supplements on the other. Food additives and GRAS substances are held to the highest safety standard, a "reasonable certainty of no harm."[66] GRAS substances require the general consensus of qualified experts that a food substance has been shown to be safe under the conditions of its intended use. As previously discussed, Congress held the view that dietary supplements were a low-risk product category.[67] Therefore, DSHEA imposed a justifiably distinct safety standard for NDIs, the reasonable expectation of safety.[68] The NDI notification process must be administered with this safety standard in mind, and *not* by reference to concepts from either the food additive or GRAS requirements.

Also inappropriate is 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.[69] In support of this unprecedented statement, FDA cites only the language from a *proposed* European regulation on novel foods,[70] which proposal ultimately was not adopted.[71] A 25-year period has

[66] 21 C.F.R. § 180.1(a) (providing that "there is a reasonable certainty that the substance is not harmful").

[67] Pub. L. No. 103-417, § 2(14).

[68] FDCA § 413(a)(2).

[69] Draft Guidance, at Section VI(B)(9).

[70] Draft Guidance, at note 27.

[71] See http://www.europarl.europa.eu/oeil/FindByProcnum.do?lang=2&procnum=COD/2008/0002.

no scientific basis. It is far too long for dietary ingredients. It has never been imposed by FDA even under the GRAS standard for conventional foods.

The Institute of Medicine's (IOM) Tolerable Upper Intake Levels (ULs) represent an example of an alternative approach to assessing nutrient safety. The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population.[72] In designing a method to assess ULs, IOM considered developing a mathematical model that could be generically applied across nutrients. It ultimately concluded such an approach was not feasible because "scientific information regarding various adverse effects and their relationships to intake levels varies greatly among nutrients and depends on the nature, comprehensiveness, and quality of available data."[73] IOM's UL assessment strategy is based on risk assessment, which "requires that information be organized in rather specific ways but does not require any specific scientific evaluation methods. Rather, risk assessors must evaluate scientific information using what they judge to be appropriate methods; and they must make explicit the basis for their judgments, the uncertainties in risk estimates, and when appropriate, alternative interpretations of the available data that may be scientifically plausible."[74] FDA should consider adopting a similarly flexible approach to evaluating the safety of dietary ingredients.

[72] IOM, DIETARY REFERENCE INTAKES: A RISK ASSESSMENT MODEL FOR ESTABLISHING UPPER INTAKE LEVELS FOR NUTRIENTS 4 (1998).

[73] *Id.* at 5.

[74] *Id.* at 7 (internal citations omitted).

The NDI notification process is merely a premarket notice to FDA, and involves agency *review* (not approval) of the information which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient is reasonably expected to be safe. FDA does not ultimately determine whether the ingredient is in fact safe or generally recognized as safe. As discussed previously, a manufacturer or distributor at best receives an "acknowledgement" from FDA, stating that the agency's acceptance of the notification for filing is a procedural matter and does *not* constitute a finding by FDA that the NDI or the supplement containing the NDI is safe or not adulterated. In fact, DSHEA squarely imposed the burden of proof on FDA to show that a dietary supplement is adulterated.[75] In light of the fact that FDA makes no safety determinations based on NDI notifications, and merely "acknowledges" and "files" them, together with the fact that the agency bears the burden of proof to show adulteration, it would be completely inappropriate for the agency to hold NDIs to the rigorous standards that it applies to products that are subject to a lengthy and conclusive premarket approval process.[76]

It is undisputed that FDA's review of even food additive petitions has deteriorated over the years.[77] The agency has approved only a handful of direct human food additives since

[75] FDCA § 402(f)(1).

[76] Under Section 413(b) of the FDCA, as added by DSHEA, a party may file a petition with FDA requesting that the agency issue an order prescribing the conditions under which the use of an NDI will reasonably be expected to be safe. The existence of this petition process appears to be a legislative acknowledgment of the non-definitive nature of the NDI notification process under Section 413(a)(2), to which the Draft Guidance is addressed.

[77] *Delays in the FDA's Food Additive Petition Process and GRAS Affirmation Process: Hearings Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Gov't Reform and Oversight*, 104th Cong. (1995); *The FDA Food Additive Review Process: Backlog and Failure to Observe Statutory Deadline*, H.R. REP. NO 104-436 (1996).

the 1970s, and even a successful food additive petition can take more than a decade to be approved.[78] Recognizing the breakdown in this system, Congress has intervened by legislation. Since 1997, FDA has been authorized to enter into contracts with outside experts to review and evaluate applications submitted under the FDCA, including those for food additives and GRAS substances.[79] At the same time, Congress created a new and different approach for handling *indirect* food additives, such as packaging materials and other food contact substances.[80] A premarket notification procedure now exists similar to that applicable to dietary ingredients. FDA itself abandoned GRAS affirmations and substituted GRAS notifications. Both the agency and Congress are fully aware that FDA lacks the capacity to implement even the existing food additive regulatory regime. This makes it even more absurd that FDA would attempt to *expand* exponentially the category of products to which food additive-like requirements and procedures would apply.

C. Recommendation.

We recommend that FDA remove *all* references to the Redbook from the Draft Guidance, as the Redbook was designed to assess the safety standard applicable to food additives that Congress expressly rejected for dietary ingredients. FDA should work to formulate a safety standard that meets the statutory requirement applicable to NDIs, the reasonable expectation of

[78] *E.g.*, 61 Fed. Reg. 3118, 3119 (January 30, 1996) (granting approval of Procter & Gamble's food additive petition for olestra).

[79] FDCA § 907, as added by the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 415, 111 Stat. 2296, 2377 (1997).

[80] FDCA § 409(a), as added by the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 309, 111 Stat. 2296, 2354 (1997).

safety. It is unquestionable that the food additive safety standard -- the reasonable certainty of no harm -- cannot lawfully or appropriately be applied to dietary ingredients.

VIII. The Draft Guidance Would Constitute Unlawful Rulemaking.

The Draft Guidance would represent significant and sudden reversals of FDA's historical policies with respect to NDI notification and would impose requirements that can lawfully be proposed and considered only by notice-and-comment rulemaking. We see many reasons to challenge these changes because of their sudden self-contradiction, their procedural impropriety, and their lack of grounding in law, public health policy, or science.

Each of the points we have raised in these comments is consistent with what the dietary supplement industry has been stating and doing for nearly two decades.[81] None of this can come as a surprise to the agency. It is clear that FDA has failed to acknowledge or incorporate much of the feedback we have given the agency over the years. The agency has used the Draft Guidance as an opportunity to announce new and previously unheard-of policies that stand in direct contradiction to both the statute and past agency practice. Courts have looked disfavorably upon reversals in agency policy and practice, and thus we challenge FDA's potential ability to enforce these punitive and radical policy shifts.[82]

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[81] *See supra* note 4.

[82] *See Wyeth v. Levine*, 555 U.S. 555 (2009) (finding that an FDA preamble statement interpreting the FDCA did not merit deference because it was announced without notice and an opportunity for public comment and because it reversed FDA's own prior position without providing a reasoned explanation for doing so); *Schleier v. Comm'r*, 515 U.S. 323, 334 n.7 (1995) (suggesting that to the extent that an agency has not been consistent in its interpretation of its own regulation, it may not be entitled to any deference); *Good Samaritan Hospital v. Shalala*, 508 U.S. 402, 417 (1993) (stating that "the consistency of an agency's position is a factor in assessing the weight that position is due."); *Pauley v. BethEnergy Mines*, 501 U.S. 680, 698 (1991) (noting that "the case for judicial deference is less

(continued…)

From a procedural perspective, the Draft Guidance would constitute impermissible "rulemaking by guidance." The Administrative Procedure Act (APA) defines a "rule" as "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy…."[83] To promulgate rules, an agency must engage in notice-and-comment rulemaking, a process also defined in the APA.[84] In its attempts to upset the balance of DSHEA and to impose new substantive obligations on the dietary supplement industry, FDA has far exceeded the permissible boundaries of a guidance document. The agency cannot institute new regulatory requirements while avoiding formal public input under the appropriate legal framework. Courts have invalidated, or refused to enforce, FDA requirements that have not been promulgated in compliance with the APA.[85]

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compelling with respect to agency positions that are inconsistent with previously held views."); *I.N.S. v. Cardoza-Fonseca*, 480 U.S. 421, 441 n.30 (1987) (stating that an "agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is 'entitled to considerably less deference' than a consistently held view."). *See also F.C.C. v. Fox Television Stations*, 129 S. Ct. 1800, 1811 (2009) (stating that the statutory standard of review "makes no distinction . . . between initial agency action and subsequent agency action undoing or revising that action," but recognizing that there are some circumstances when an agency must "provide a more detailed justification than what would suffice for a new policy created on a blank slate"—for example, when the agency's "new policy rests upon factual findings that contradict those which underlay its prior policy; or when its prior policy has engendered serious reliance interests that must be taken into account.").

[83] 5 U.S.C. § 551(4).

[84] *Id.* §§ 551(5), 553.

[85] *E.g., Bellarno Int'l. Ltd. v. FDA*, 678 F. Supp. 410, 415 (E.D.N.Y. 1988) (finding an import alert to constitute "a substantive rule of general applicability, to which no exceptions would apply, rather than a discretionary general statement of policy," thus requiring notice-and-comment rulemaking); *United States v. Bioclinical Sys., Inc.*, 666 F. Supp. 82, 84 (D. Md. 1987) (stating that "it is through [the notice-and-comment rulemaking] process, not through enforcement actions, that the questions of public health and of technological and economic feasibility posed by the [establishment of a new good manufacturing practice requirement] are to be decided.").

Finally, from a substantive viewpoint, we have discussed the many ways in which the Draft Guidance would contravene DSHEA, Congressional intent, and FDA's historical policies with respect to NDIs. Far worse, the Draft Guidance proposes sweeping reform that would impose significant burdens in the absence of clear benefits. The increased number of NDI notifications that would be generated under a supplement-focused approach, the narrow list of chemical alterations, the increased evidentiary burdens, the ban on synthetic botanicals, and the application of food additive standards to NDIs all lack grounding in public health policy and sound science. Implementing the policies outlined in the Draft Guidance as currently written would restrict dietary supplement access, stifle innovation, and place severe economic and administrative burdens on the industry while doing nothing to improve consumer health or safety in the long run. In particular, these burdens would disproportionally impact small businesses and newcomers to the dietary supplement industry. The futility of the Draft Guidance seems particularly inappropriate in light of our President's recent request that all regulatory agencies examine their regulatory policies to ensure that they are "based on the best available science" and to "identify and use the best, most innovative, and least burdensome tools for achieving regulatory ends."[86] In crafting this Draft Guidance, FDA has clearly violated this Order.

IX. Conclusion.

For the reasons we have described above, the Draft Guidance contradicts DSHEA, Congressional intent, and 17 years of agency policy, while having no basis in either sound science or public health policy. The Draft Guidance would upset the balance between access and safety that Congress so carefully established in DSHEA. It would impose significant

[86] Executive Order No. 13,563, 76 Fed. Reg. 3821 (January 21, 2011).

and needless burdens on the dietary supplement industry, which -- as Congress expressly recognized in DSHEA -- is "an *integral* part of the economy of the United States."[87]

As an industry, we feel a great sense of obligation to ensure that our products are high in quality, beneficial, and safe for consumers. We urge FDA to withdraw the Draft Guidance and work to revise its policies on the NDI notification process to conform to the statutory language and Congressional intent. We remain confident that FDA and the industry can work together to develop appropriate ways to implement the NDI notification process and the safety standards for NDIs in accordance with DSHEA and in recognition of sound science and public health policy.

Respectfully submitted,

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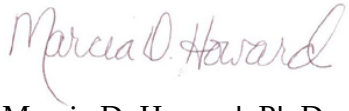

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[87] Pub. L. No. 103-417, § 2(12)(A) (emphasis added).