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Via Electronic Submission

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 HFA-305
Rockville, MD 20852

Re: Docket No. FDA–2011–D–0376; Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Submission of Comment

Dear Sir or Madam:

These comments are submitted on behalf of the following entities in response to FDA's Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues ("Draft Guidance"), published on July 1, 2011.

- Advanced Bionutritionals, LLC
- AdvoCare International, LP
- Biocentric Health, Inc.
- Dietary Supplement Manufacturers and Marketers Association
- Essential Formulas Incorporated
- Healthy Directions, LLC
- Jarrow Formulas
- Mercola.com Health Resources, LLC
- New Vitality
- NNC LLC d/b/a Naturade
- P.L. Thomas & Co., Inc.
- Purity Products
- VRP Manufacturing LLC
- Anonymous Commenters

These entities (hereinafter the "Joint Commenters") respectfully submit that FDA must withdraw the Draft Guidance and proceed through rulemaking with regard to implementing the types of policies and requirements set forth in the Guidance Document, as is required under the Administrative Procedure Act ("APA"). The Joint Commenters also urge FDA to reconsider positions articulated in the Draft Guidance that are contrary to the statute and Congressional intent, contrary to science and to reasoned policy

considerations, and overly burdensome, as described more fully below. These include not only new policies but also the agency's continued policy of by treating the New Dietary Ingredient ("NDI") notification provision as a premarket approval provision. In addition, irrespective of the administrative process, FDA must fully analyze the impact on small businesses of compliance with the NDI notification submission requirements under the Draft Guidance.

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INTRODUCTION

On July 1, 2011, FDA issued its long-awaited Draft Guidance on "new dietary ingredients" ("NDIs"). The notice of availability of the Draft Guidance was published in the Federal Register on July 5, 2011. The Draft Guidance is intended to explain FDA's thinking on what constitutes an NDI for purposes of the federal Food, Drug, and Cosmetic Act ("FDCA"), and the agency's regulatory scheme relating to NDIs.

Section 413(d) of the FDCA defines a "new dietary ingredient" as a dietary ingredient that was not marketed in the U.S. prior to October 15, 1994. The statute defines a "dietary ingredient" as a vitamin, mineral, herb or other botanical, amino acid, dietary substance for use by man to supplement the diet by increasing the total dietary intake, or concentrate, metabolite, constituent, extract, or combination of any such substance. FDCA § 201(ff)(1). Section 413(a)(2) of the FDCA requires a manufacturer or distributor of an NDI or dietary supplement that contains an NDI to submit a premarket notification to FDA at least 75 days before introducing an NDI-containing supplement into interstate commerce, unless the NDI and any other dietary ingredients in the supplement "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." When an NDI notification is required, it must include a history of use or other evidence of safety for the ingredient. Based on that information, FDA determines whether it will file the notification with no questions asked, respond to the submitter with questions, or refuse to file the notification at all.

The Draft Guidance, in part, provides guidance as to (1) what FDA considers "present in the food supply" to mean; and (2) what type and quantity of evidence is sufficient to demonstrate safety such that the agency will permit the notification to be filed. The Draft Guidance also addresses the procedures for submitting an NDI notification, the content of an NDI notification, and the types of information that FDA recommends manufacturers and distributors consider in evaluating the safety of a dietary supplement containing an NDI. In addition, the Draft Guidance addresses whether certain substances can be marketed as dietary ingredients in dietary supplements.

While the intent behind the Draft Guidance is commendable, the document raises numerous concerns relating to its basis in law and in reasoned policy that may have a detrimental effect on consumers' access to dietary supplements that can provide significant health benefits. The Draft Guidance could not only cause unwarranted harm to legitimate businesses, it could also deny consumers access to supplements they have relied on for years to maintain and improve their health. FDA's Draft Guidance must be more narrowly tailored to accomplish the agency's primary mission to protect and promote the health of U.S. citizens, without causing unwarranted injury to legitimate businesses and without denying consumers access to products that are important to their health.

ANALYSIS

I. The Draft Guidance Is Unlawful in Numerous Respects.

A. The Changes in Interpretation and Policy Require Notice and Comment Rulemaking.

The Draft Guidance is a rule in the guise of "guidance." The APA defines a "rule" as "the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency . . . ." 5 U.S.C. § 551(4). The Draft Guidance is an agency statement of general applicability and future effect that is designed to implement and interpret sections 413 and 201 of the FDCA and to prescribe binding standards and policies under those provisions. As such, it is a rule within the meaning of the APA. While notice and comment rulemaking is not required for "interpretative rules" or "general statements of policy," 5 U.S.C. § 553(b)(A), the Draft Guidance goes further to announce specific requirements that are binding as a practical matter because the agency routinely rejects NDI notifications that do not meet the standards articulated in the Draft Guidance. In short, the Draft Guidance is a "process-free vehicle[] for agency declaration[] of explicit standards." *See* Gwendolyn McKee, *Judicial Review of Agency Guidance Documents: Rethinking the Finality Doctrine*, 60 ADMIN. L. REV. 371, 377 (2008).

Instead of engaging in notice and comment rulemaking to elicit industry input with regard to the standards to which industry will be held, the agency has engaged in the type of behavior admonished by the court in *Appalachian Power Co. v. Environmental Protection Agency*, 208 F.3d 1015 (D.C. Cir. 2000). As the court explained,

> Congress passes a broadly worded statute. The agency follows with regulations containing broad language, open-ended phrases, ambiguous standards and the like. Then as years pass, the agency issues . . . guidance . . . explaining, interpreting, defining and often expanding the commands in the regulations . . . . Several words in a regulation may spawn hundreds of pages of text as the agency offers more and more detail regarding what its regulations demand of regulated entities. Law is made."

Id. at 1020.

That is precisely what FDA has done in this instance. In 1997, the agency promulgated regulations that contain broad language and set ambiguous standards, for the most part mirroring the broad language contained in section 413 of the FDCA.[1] 21

[1] The only specificity that the agency provides in section 190.6 as to what constitutes evidence of safety is that the submission should "includ[e] any citation to published articles or other evidence" and that "any

C.F.R. § 190.6. Now, fourteen years after the regulations were implemented, FDA has issued a "guidance" that is at least 35 pages long (when printed in *very* small font) detailing what the regulation demands of regulated entities.

Casting the Draft Guidance as merely the FDA's "thinking" is a transparent attempt to impose strict regulatory rules under the guise of non-binding guidance. The Draft Guidance has a clear binding effect. "If an agency . . . treats the document in the same manner it treats a legislative rule, if it bases enforcement actions on the policies or interpretations formulated in the document, if it leads private parties . . . to believe that it will declare [notifications] invalid unless they comply with the terms of the document, then the agency's document is for all practical purposes 'binding.'" *Appalachian Power*, 208 F.3d at 1021. The Draft Guidance lays out precise, universal requirements that must be met before certain substances can be placed in commercial streams. "At any rate, the entire [draft] Guidance reads like a ukase. It commands, it requires, it orders, it dictates." *Id.* at 1023. Such requirements are nothing short of binding regulations, as FDA intends to enforce the requirements as part of its authority under the FDCA. The Draft Guidance substantially changes FDA's enforcement standards for dietary ingredients and prejudices many, if not all, dietary supplement marketers.

Furthermore, as discussed in detail below, the Draft Guidance is contrary to the FDCA in many respects. Because the terms of the Draft Guidance are at such tension with the statute, it is especially inappropriate to avoid the administrative due process requirements of rulemaking, including judicial review. The Draft Guidance's standards are significant changes to prior FDA regulatory standards (*e.g.*, the exclusion of certain synthetic ingredients and probiotics from the definition of a dietary ingredient). As such, FDA must follow its long-established rulemaking procedures to make such changes.

B. The Proposed Definition of "Dietary Supplement" Cannot Be Squared with the Statute.

The Draft Guidance addresses whether certain substances meet the definition of a "dietary supplement" under the FDCA. In a number instances, the Draft Guidance reflects an interpretation of "dietary supplement" that is contrary to the statute.

1. The Prior Marketing Clause Applies to Substances Rather Than to Active Moieties.

According to the Draft Guidance, the "article that is approved as a new drug" or "authorized for investigation as a new drug" within the meaning of the prior marketing clause in section 201(ff)(3)(B) of the FDCA may be the active moiety of the substance rather than the substance itself.[2]

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reference to published information offered in support of the notification shall be accompanied by reprints or photostatic copies of such references." 21 C.F.R. § 190.6(b)(4).

[2] The Draft Guidance provides the following example:

> For example, assume that Substance A, which is a constituent of a plant and has never been marketed as an article of food or as a dietary supplement, is a botanical dietary ingredient under

This position, first articulated in the agency's response to the BioStratum, Inc. citizen petition, is contrary to the plain meaning of the statute. Letter from FDA to Kathleen M. Sanzo, Esq. (Jan. 12, 2009) responding to citizen petition dated July 29, 2005 (Docket No. FDA-2005-P-0259). The prior marketing clause of the "dietary supplement" definition does not exclude "moieties," which may be submolecular components of substances. It rather excludes an "article" that is "approved as a new drug" or "authorized for investigation as a new drug" for which substantial clinical investigations have been instituted, if the product was not first marketed as a dietary supplement or a food. Importantly, as the agency noted in its response to the BioStratum petition, FDA does not approve active moieties, which may be submolecular components of active ingredients. Rather, the agency approves the active ingredients themselves, and new active ingredients containing old active moieties must be separately approved.[3]

Consistent with this fact, the prior marketing clause of the dietary supplement definition refers to "articles" approved by FDA rather than atoms or groups of atoms that may be found within a molecule. The term "article" simply cannot be interpreted to mean atoms or groups of atoms that can be identified within the drawing of a molecule. Because the statute has plain meaning, FDA has no discretion to interpret the statute in a different manner. *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984). Moreover, even if the statute were deemed ambiguous, which is not the case, such an interpretation would be impermissible because the term "article" is used throughout the FDCA to refer to things that FDA regulates, and submolecular atomic structures are not things that FDA regulates. Agency interpretations of ambiguous statutory provisions must be reasonable to be lawful. *Id.*

2. FDA's Narrow Definition of "Amino Acid" in the Draft Guidance is Contrary to the Plain Meaning of the Statute.

Under Section 201(ff)(1) of the FDCA, the term "dietary supplement" includes a product that contains an "amino acid," and the provision on its face includes *all* amino acids. In the Draft Guidance, however, FDA reiterates the position taken by the agency in response to the OVOS Natural Health, Inc. citizen petition, which significantly limits the universe of amino acids that qualify as dietary ingredients to an "alpha-amino carboxylic acid used as a constituent of proteins or peptides." Letter from FDA to OVOS Natural Health, Inc. (Feb. 23, 2011), denying the citizen petition dated June 25, 2009

> section 201(ff)(1)(C) of the FD&C Act. A drug company is studying a salt of Substance A, "Substance A hydrochloride," as an investigational new drug under an IND. In this situation, the relevant article for purposes of whether Substance A can be used in a dietary supplement is not Substance A hydrochloride, but Substance A itself, because Substance A is the active moiety that is being studied for its possible therapeutic action. Any compound that delivers Substance A is excluded from being used in a dietary supplement.

Draft Guidance at 13.

[3] The court's decision in *Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000), makes this reasonably clear, holding that the term "article" in the prior marketing clause may refer to finished products and to active ingredients of those products.

(Docket No. FDA-2009-P-0298). This would exclude beta- and gamma-amino acids in a way that is inconsistent with the FDCA.

This is contrary to the plain meaning of "amino acid." For example, THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (Houghton Mifflin Company 4th ed. 2000) defines "amino acid" as "[a]n organic compound containing an amino group (NH_2), a carboxylic acid group (COOH), and any of various side groups . . . ." Likewise, THE BANTAM MEDICAL DICTIONARY 17 (Bantam Books 2d rev. ed. 1996) defines "amino acid" as "an organic compound containing an amino group (-NH_2) and a carboxyl group (-COOH) . . . ."

These definitions encompass all organic compounds containing both an amino group and a carboxylic acid group, regardless of the carbon to which the amine group is attached. Because the statute has plain meaning, the rule of *Chevron* precludes FDA from interpreting the statute in a different manner.

3. Probiotics Made Through New Fermentation or Manufacturing Techniques Are Not New Dietary Ingredients.

FDA states in the Draft Guidance that fermentation using a fermentation medium different from one used to make conventional foods in the food supply is an example of a process that chemically alters an article of food present in the food supply within the meaning of section 413(a)(1) of the FDCA (and therefore necessitates submission of an NDI notification). Regardless of the fermentation and/or manufacturing processes used for probiotics, the end result is a specific microorganism of a specific genus, species, and strain. In other words, improvements in fermentation and production procedures in order to improve culture yield, performance and stability/survival under applicable conditions do not impact the identity or phenotypic characteristics of a strain. Accordingly, changes in the fermentation and/or manufacturing processes used for probiotics cannot reasonably be considered "chemical alteration" within the meaning of section 413(a)(1) of the FDCA absent evidence that the fermentation changes cause changes in the identity or phenotypic characteristics of a strain.

Making new production techniques into new dietary ingredients would contravene Congress's purposes in passing the statute. Congress wanted to ensure broad and open access to safe dietary supplement products. Since the passage of DSHEA over 17 years ago, companies have developed fermentation processes that better preserve the integrity of the ingredients and that may also render safer products. Congress clearly did not intend to favor less safe dietary supplements over those that are safer. Nor did Congress intend to stifle incentives to find new and efficient means to culture probiotics through innovative fermentation techniques. To the contrary, Congress cautioned that "the Federal role in dietary supplement regulation . . . is not to take actions to impose regulatory barriers limiting or slowing the flow of safe products . . . to consumers." S. REP. NO. 103-410, at 2 (1994). Yet FDA's proposal attempts to do through regulatory fiat that which Congress expressly prohibited, namely, to create a rule defining a dietary ingredient based on the ingredient's manufacturing process. Nowhere in DSHEA does

Congress provide FDA with this authority. Moreover, FDA cannot propose a radical change to the underlying statutory authority through the implementation of a guidance document.

4. FDA Cannot Exclude All Members of a Species that Contains Human Pathogens.

FDA indicated in the Draft Guidance that it "regards all members of a species that contains human pathogens as potentially harmful to human health, and therefore inappropriate for use as dietary ingredients. . . ." Draft Guidance at 22. This narrowing of permissible dietary ingredients on the part of FDA is contrary to the statute.

By its plain meaning, the statute requires that a company (1) establish that a certain strain or subspecies of microorganism meets the statutory definition of a dietary ingredient, (2) establish the safety of that strain or subspecies, and (3) submit an NDI notification to FDA (if the ingredient is an NDI and was not used in food). The statute contains no limitation regarding strains or subspecies from microorganism species that also contain pathogenic microorganisms. Because the statute has plain meaning, *Chevron* precludes such an interpretation.

As discussed in section I.E2.*a.* below, once the manufacturer/distributor of a dietary supplement submits an NDI notification containing the basis of its safety determination, the burden shifts to FDA to prove in a court of law that the strain poses a significant or unreasonable risk of illness or injury. Thus, the only way that FDA can legally preclude certain strains from being used as dietary ingredients (assuming that they meet the statutory definition of a dietary ingredient) is to prove in court that the strain poses a significant or unreasonable risk of illness or injury or to promulgate a final rule, through notice and comment, banning the ingredient (as the agency did with ephedra). FDCA § 402(f)(1)(A). Moreover, if FDA has significant concern that there is a serious health risk, the agency does have the ability to promulgate an interim final rule prohibiting use of the ingredient in dietary supplements. *Id.* § 402(f)(1)(C).

5. FDA Cannot Exclude Synthetic Botanicals and Herbal Ingredients.

a. The Dietary Supplement Definition Includes Synthetic Botanicals.

The term "botanical" has a plain meaning that includes both natural substances and related synthetic substances. DORLAND'S MEDICAL DICTIONARY defines "botanic" as both "pertaining to botany" *and* "derived from plants." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 185 (26th ed. 1981). The distinction between substances "relating to plants" and substances "derived from plants" is clear. Substances "derived" from plants are natural botanicals and substances "related" to plants are botanicals that are artificial rather than natural. This, without question, includes synthesized substances that mimic substances derived from plants. Thus, under the plain meaning of the statute, synthetic substances that mimic natural botanicals are "botanicals." Under the rule of

Chevron, FDA has no discretion to interpret the statute in a manner that is contrary to its plain meaning.

b. Even If the Statute Were Ambiguous, FDA Could Not Interpret It to Exclude Synthetic Botanicals.

Even if the dietary supplement definition were ambiguous – which is not the case -- FDA could not reasonably interpret the statute to exclude synthetic botanicals.

i. There Is No Basis in Science or Policy for Distinguishing Synthetic Botanicals from Natural Botanicals.

FDA generally draws no distinction between natural and synthetic molecules or substances in its regulation of foods, drugs, biologics, and dietary supplements. The agency has consistently made clear that there is no basis in science or policy for such a distinction. *See, e.g.,* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (May 29, 1992) (stating that FDA has no basis for concluding that bioengineered foods 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). Synthetic versions of naturally-occurring substances are no less likely to be safe and, where necessary, effective.

FDA has not sought to stifle the marketing of synthetic foods, vitamins, drugs, and biologics. Indeed, synthetic products are often superior to their natural counterparts because they can be well-characterized, consistently produced, and formulated without impurities. Synthetic botanicals have the benefit of being produced in a controlled environment. This closed environment eliminates impurities that may occur naturally, *e.g.,* are absorbed from the soil in which the botanicals are grown. Synthetic versions of botanicals are free from these impurities. This is as true of synthetic botanicals as it is for other substances, and there is no reasonable reason to treat dietary supplements differently from other categories of FDA-regulated products when it comes to use of synthetic substances.

The interpretation of the statute suggested in the Draft Guidance would preclude the development of higher-quality botanical supplements. It would also stifle innovation. It is incumbent on the agency to interpret the statute in a manner that provides consumers with the greatest benefits.

ii. The Agency Does Not Distinguish Synthetic Substances from Natural Substances in Analogous Statutory Provisions.

For dietary ingredients other than botanicals, FDA does not distinguish between synthetic and natural substances. Synthetic vitamins, synthetic minerals, and synthetic amino acids all qualify as dietary supplements. There is no basis in the wording of the statute, in the legislative history of the statute, in science, or in policy for distinguishing

synthetic botanicals from these other synthetic nutrients. An interpretation of the statute that would distinguish botanicals in this manner would be arbitrary and capricious, smacks of regulatory fiat, and would thus not satisfy the reasonableness standard of *Chevron*. Moreover, such a substantive redefining of the term botanicals to exclude synthetic would at a minimum require notice and comment rulemaking that can be challenged in court

Moreover, Section 351 of the Public Health Service (PHS) Act defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." Public Health Service Act of 1944, P.L. 78-410, § 351, 58 Stat. 682 (1944). Although this definition obviously applies to substances derived from animals and plants, FDA acknowledges that it also applies to synthetic versions of such substances. There have been numerous synthetic substances that have been licensed as biologics. *See* FDA, Licensed Biological Products with Supporting Documents, *available at* http://www.fda.gov/biologicsbloodvaccines/ucm133705.htm. This further precludes an interpretation of the dietary supplement definition that would exclude synthetic versions of natural botanicals under *Chevron*.

iii. Synthetic Dietary Botanical Substances are Dietary Ingredients within the Meaning of Section 201(ff)(1)(E).

Section 201(ff)(1)(E) includes within the definition of dietary supplement any "dietary substance for use by man to supplement the diet by increasing the total dietary intake." Where plant-derived substances are part of the diet and synthetic versions of the same substance are offered as supplements, those synthetic substances must be deemed "to supplement the diet by increasing total dietary intake." *Id.* Just as synthetic vitamin C and synthetic calcium are intended to supplement the total dietary intake of vitamin C and calcium, synthetic alfalfa and synthetic peppermint are intended to supplement the total dietary intake of vitamin A and vitamin B_2, respectively.

6. All Naturally-Occurring Components of Food Must be Considered Dietary Ingredients.

In the Draft Guidance, FDA indicates that some naturally-occurring components of food may not be dietary ingredients at all. Specifically, FDA states, "the fact that the component [of food] may have been isolated as part of an analytical chemical procedure to examine the composition of the previously marketed food before October 15, 1994, is not sufficient to establish that the component is a pre-DSHEA dietary ingredient or *even that it is a dietary ingredient at all*." Draft Guidance at 14 (emphasis added).

This position is in direct contravention to the statutory language defining a dietary supplement. As noted above, section 201(ff)(1)(E) clearly and unambiguously includes "a dietary substance for use by man to supplement the diet by increasing the total dietary intake" within the definition of a "dietary ingredient." The plain language of the statute

thus provides, in unambiguous terms, that all foods and food components used for the purpose of supplementing the diet are "dietary ingredients." FDA's attempt to differentiate certain naturally-occurring constituents of food from others is reminiscent of what Congress and the courts deemed to be FDA's history of "nonsensical," "Alice in Wonderland" regulation of dietary supplements. *See* S. REP. NO. 103-410, at 16, 21 (citing *U.S. v. Two Plastic Drums—Viponte Ltd. Black Currant Oil—Traco Labs, Inc.*, 948 F.2d 814 (7th Cir. 1993); *U.S. v. 29 Cartons of—an Article of Food—Oakmont Investment Co.*, 987 F.2d 33 (1st Cir. 1993)). Contrary to FDA's position, *Chevron* requires that FDA apply the plain meaning of the law.

C. The Proposed Standards for "Old" Dietary Ingredients Are Unreasonable and Unlawful.

"New dietary ingredient" is defined in section 413 of the FDCA as "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." It necessarily follows that dietary ingredients that were marketed in the United States before October 15, 1994, are not NDIs and are considered "old" dietary ingredients (or "grandfathered" or "pre-DSHEA" dietary ingredients).

1. FDA's Interpretation of "Old" Dietary Ingredients under the Draft Guidance Is Contrary to the Statute and Congressional Intent.

According to the Draft Guidance, in order for a dietary ingredient to avoid classification as a new dietary ingredient (*i.e.,* instead be classified as an "old," "grandfathered," or "pre-DSHEA" dietary ingredient), the dietary ingredient must have (1) been sold or offered for sale (2) as a dietary supplement, in bulk as a dietary ingredient for use in dietary supplements, or as an ingredient in a blend or formulation of dietary ingredients for use in dietary supplements (3) in the United States (4) before October 15, 1994, and (5) not have undergone any changes in manufacturing processes that would alter the chemical composition of the ingredient or (6) changed the composition of materials used to make the ingredient.[4] Furthermore, the marketer of the

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[4] The agency states:

> The mere presence of a substance as a component of a conventional food that was marketed before October 15, 1994 does not establish that the substance was marketed as a dietary ingredient before that date . . . . If the food component fits into one of the dietary ingredient categories (for example, if it is a metabolite or extract of another dietary ingredient) but was not marketed as a dietary ingredient before October 15, 1994, it would be a [sic] NDI.

Draft Guidance at 13.

> If the substance was present in the pre-DSHEA dietary supplement as a food additive rather than as a dietary ingredient, but does fit within one of the enumerated categories of dietary ingredients in section 201(ff)(1) of the FD&C Act [21 U.S.C. § 321(ff)(1)], then it would be a [sic] NDI.

"old" dietary ingredient must have sales records, manufacturing records, commercial invoices, or other documentation that establishes the marketing took place in the United States, the identity and form of the marketed ingredient, and whether the ingredient was marketed as a dietary ingredient or for some other purpose.[5] As explained below, this interpretation is contrary to the plain meaning of the statute and to Congress's obvious intent.

a. The Definition of "Marketing" Is Contrary to the Statute.

In the Draft Guidance, FDA states, "[w]hat matters is whether the ingredient was marketed *as a dietary ingredient*—meaning in or as a dietary supplement, or for use in dietary supplements—in the U.S. before October 15, 1994." Draft Guidance, at 13 (emphasis added). This limitation is directly contrary to the statute. The statute requires that the ingredient be "marketed," rather than "marketed as a dietary ingredient." FDA will find no dictionary that defines "market" as "market as a dietary ingredient." Thus, *Chevron* clearly precludes such an interpretation.

Even if the wording of the statute were unclear, which is not the case, Congress's intent is not unclear. Congress intended to ensure that the public had free and wide access to safe dietary supplement products. S. REP. NO. 103-410, at 17 (1994). Specifically, Congress stated its intent was "to improve the health status of the people of the United States...by ensuring that the Federal Government erects no barriers that impede the ability of consumers to improve their nutrition through the free choice of safe dietary supplements." *Id.* An interpretation that would stretch the wording of the statute to erect barriers to impede the dietary supplement market would conflict with the intent of Congress and thus violate the dictates of *Chevron*.

Id. at 15.

The agency further states :that "[t]he only kind of marketing that is relevant to whether a dietary ingredient is a [sic] NDI is marketing in the U.S. before October 15, 1994." *Id.* FDA then narrowly defines "marketing" as "selling or offering the dietary ingredient for sale (1) as a dietary supplement, (2) in bulk as a dietary ingredient for use in dietary supplements, or (3) as an ingredient in a blend or formulation of dietary ingredients for use in dietary supplements." *Id.*

Finally, FDA states that even if a dietary ingredient was marketed as a dietary ingredient before October 15, 1994, a change in the manufacturing process that alters the chemical composition or structure of the ingredient would most likely result in an NDI and a notification to FDA would be required. *Id.* at 17. As an example, the FDA states, "using a solvent to prepare an extract from a pre-DSHEA dietary ingredient creates a [sic] NDI because the final extract contains only a fractionated subset of the constituent substances in the original dietary ingredient." *Id.* Additionally, the agency states "changes that alter the composition of materials used to make the ingredient, such as using a different part of a plant . . . , would create a [sic] NDI." *Id.*

[5] FDA goes on to state that in order to show a dietary ingredient is not new, a dietary supplement marketer would need documentation consisting of "written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994." *Id.* The agency elaborates that examples of adequate documentation would include such things as "sales records, manufacturing records, commercial invoices, magazine advertisements, mail order catalogues, or sales brochures." *Id.* Affidavits not supported by objective evidence are insufficient, as are industry-published lists of "old dietary ingredients." *Id.* at 15-16.

b. The Evidentiary Requirements Regarding Marketing Are Inconsistent with the Statute.

The types of evidence that FDA is expecting of dietary supplement companies is also unreasonable and unlawful. To avoid classification as a new dietary ingredient, section 413(d) requires only that a dietary ingredient have been marketed in the United States before October 15, 1994. Industry-compiled lists of grandfathered dietary ingredients and affidavits from persons who marketed such dietary ingredients prior to that date are reliable evidence.

In the Draft Guidance, FDA states that it expects "written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994" as evidence of marketing in the U.S. prior to October 15, 1994. Draft Guidance, at 8. Specifically, the agency states that sales records, manufacturing records, commercial invoices, magazine advertisements, mail order catalogues, and sales brochures are examples of adequate evidence. *Id.* However, in the absence of any indication that such records would be required seventeen (17) years later, most businesses did not keep these types of detailed records from before October 1994. Instead, and quite commendably, industry took the initiative to compile reliable contemporaneous information concerning which dietary ingredients companies had been using prior to that date. Specifically, in early 1995, the American Herbal Products Association ("AHPA") informed its members that it was compiling a list of botanical dietary ingredients that were marketed in the United States before October 15, 1994. At that time, industry had access to the documents FDA is now requesting. AHPA's list and the three (3) other lists compiled contemporaneously with the passage of DSHEA – those of the Council for Responsible Nutrition ("CRN"), National Nutritional Foods Association ("NNFA"), and Utah Natural Products Alliance ("UNPA") – are reliable evidence that ingredients were marketed in the U.S. prior to October 1994.

There is nothing in the statute indicating that such evidence is insufficient. Nor is there language in the statute indicating that affidavits, which are accepted in courts of law as evidence, would not be sufficient. In fact, the FDA was presented with the aforementioned lists from 1995 to 1997, and it did not accept nor reject them. The agency failed to articulate its position on the evidence necessary for a dietary ingredient to be grandfathered at the time it was presented with the lists. Further, the agency was completely silent as to what would render an ingredient an NDI. If the agency wanted a strict interpretation of DSHEA, it should have defined an NDI when it was squarely presented with the issue in the mid-to-late 1990s. Seventeen (17) years after DSHEA was enacted, fourteen (14) years after the implementing regulations were promulgated, and at least fourteen (14) years after the agency was presented with proposed lists of "grandfathered" dietary ingredients, it is a little late for FDA to be suddenly concerned with the industry's interpretation of the evidence required to demonstrate the grandfathered status of a dietary ingredient. Moreover, the agency's position is not simply an interpretation of the statute. Rather, it is the evidence that FDA believes is

necessary to support that a particular ingredient is an "old" dietary ingredient. In other words, it is substantive in nature and requires notice and comment rulemaking

c. *The Attempt to Block Continuing Access To Dietary Supplements Is Contrary to Congressional Intent*

Moreover, the effect of FDA's position on the evidentiary requirements regarding marketing is contrary to Congressional intent. Given that companies have not retained the types of records identified by FDA (because the companies did not know that they would need to), very few dietary ingredients will be able to satisfy this burden. As a result, many dietary ingredients that were safely marketed prior to October 15, 1994, and continue to be safely marketed as "grandfathered" dietary ingredients will be subject to the NDI notification requirements under the terms of the Draft Guidance. This will, in many cases, require that companies either discontinue sales (at least temporarily) of products or risk enforcement action by the agency. As noted above, however, DSHEA was passed in an effort "to assure citizens have *continued* access to dietary supplements." S. REP. NO. 103-410, at 17 (emphasis added). FDA's position on evidence would clearly constitute a barrier to citizens' continued access to dietary supplements, contrary to Congressional intent.

Furthermore, requiring this type of evidence and not providing a standardized list of "old" dietary ingredients prejudices businesses that were not yet formed in October 1994. Newer businesses do not have access to the type of evidence FDA intends to require and would not be able to obtain such evidence from older businesses. FDA would thus impose upon them expenditures of money, resources, and time to submit NDI notification to FDA. This is unfair, has the effect of restraining competition, and is contrary to Congress's stated intent "to assure citizens have continued access to dietary supplements."

d. *FDA's Preclusion of Changes in Manufacturing Are Contrary to the Statute.*

The Draft Guidance requires that companies demonstrate not only that a dietary ingredient was marketed as an ingredient in a dietary supplement in the United States prior to October 15, 1994, but also that the ingredient is manufactured using the same techniques and extraction processes as were used 17 years ago.[6] This additional requirement goes beyond the plain meaning of the statute. FDA is conflating the definition of "new dietary ingredient" with the statutory language exempting certain ingredients in food from the requirement to submit an NDI notification. FDCA section

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[6] FDA states in the Draft Guidance that changes in manufacturing processes that alter the chemical composition or structure of the ingredient will likely require an NDI notification for the resulting compound. The agency provides the following as an example, "using a solvent to prepare an extract from a pre-DSHEA dietary ingredient creates a[n] NDI because the final extract contains only a fractionated subset of the constituent substances in the original dietary ingredient." *Id.* at 17. The agency also states that changes that alter the composition of materials used to make the ingredient, such as using a different part of a plant, would create an NDI. *Id.*

413(a)(1) provides that an NDI notification is not required if 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. FDA is attempting to apply this "chemically altered" standard to the definition of "new dietary ingredient" when the statute contains no such language. As such, the proposed requirement violates the rule of *Chevron*.

Moreover, even if the statute were ambiguous, which is not the case, the interpretation would be contrary to Congress's stated desire for broad and open access to safe dietary supplement products. Over the last 17 years, companies have found safer solvents and extraction processes that not only better preserve the integrity of the ingredients, but also render a safer product. By restricting the status of "old" dietary ingredients to those extraction solvents and processes used in 1994, the Agency would restrict the public's access to higher quality, safer dietary ingredients and supplements.

Such an interpretation would also stifle a company's ability to find new and efficient means to isolate dietary ingredients, since any new manufacturing techniques would mean participating in the overly burdensome and expensive NDI notification process. New and efficient manufacturing methods lead to purer versions of dietary ingredients, lower prices for dietary ingredients and dietary supplements, and the discovery of new dietary ingredients. FDA would thus stifle innovation, increase prices, and deny consumers safer dietary supplement products, in direct contravention of Congress's intent in passing DSHEA.

D. The Requirement to Submit Product-Specific Notifications Is Unreasonable and Contrary to Congressional Intent.

The Joint Commenters recognize that section 413 of the FDCA is poorly drafted and contains inconsistencies. However, FDA's interpretation of that section, as articulated in the Draft Guidance, to mean that NDI notifications must be submitted on a product-by-product basis is nonsensical, unreasonable, and contrary to Congressional intent. The appropriate, reasonable interpretation would be to require that NDI notifications be ingredient specific, not product specific.

Indeed, FDA's interpretation is inconsistent with the necessary implications of the statutory definition of an NDI. Specifically, as discussed in detail above, section 413(d) defines a "new dietary ingredient" to the exclusion of "old" or "grandfathered" dietary ingredients. The key is that the statute provides that *ingredients*, and not *products*, are grandfathered. If Congress had intended for FDA to review dietary supplements at the product level (*i.e.*, the full product formulation), Congress would have grandfathered those *products* that were on the market prior to October 15, 1994. It did not do so.

If Congress had intended to create a dietary supplement product preapproval system, it would have done so. It has done so for other regulated categories of products (*e.g.*, drugs). That was not its intention for dietary supplements. Rather, as discussed more fully below, the purpose of the notification process is to simply have the manufacturer provide FDA with the basis as to why the company believes it has a

reasonable expectation that the ingredient will be safe when consumed. If FDA believes that an ingredient is unsafe, it can either (1) go to court to prove that a dietary supplement that contains the ingredient poses a significant or unreasonable risk of harm under ordinary or recommended conditions of use or (2) engage in notice and comment rulemaking to prohibit the ingredient from being used in dietary supplements across the board. FDCA § 402(f)(1)(A), (B). Accordingly, the agency's interpretation strains credulity by turning the new dietary ingredient notification process into a *de facto* dietary supplement approval process, which is inconsistent with the intent of Congress and is nonsensical. Indeed, it would not only create a significant and unrealistic burden on industry, but it would also engulf the agency to the extent that FDA does not have the resources to actually review and raise concerns regarding the notifications that were submitted (we note that statutorily, FDA cannot deny or reject the filing of a notification).

E. FDA's Transformation of NDI Notifications into Food Additive Petitions Is Contrary to the Statute.

Congress stated explicitly that the purpose of DSHEA was to "clarify that dietary supplements are not drugs or food additives." S. REP. NO. 103-410, at 2. In direct contravention of that intent, FDA is attempting to regulate dietary supplements as food additives through the NDI notification process.

1. Congress Purposely Created Different Safety Standards for NDIs and Food Additives.

In the late 1970s, FDA began attempting to take enforcement actions against dietary supplements as containing unsafe food additives. The courts and Congress recognized that FDA was trying to ban the sale of safe dietary supplement products as unapproved food additives,[7] and Congress made it clear that FDA's regulation of dietary supplements as food additives had forced Congress to intervene. S. REP. NO. 103-410, at 15. As a result of this "Alice-in-Wonderland approach, [which] allow[ed] the 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." *Id.* at 21. Congress explicitly removed dietary supplements and dietary ingredients from the definition of a food additive[8].

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[7] Under this theory, any ingredient added to a dietary supplement is a food additive under FDCA § 201(s) based on affidavits stating that experts did not generally regard the product as safe. *Id.* at 15. The courts recognized that FDA's approach to regulate dietary supplements as food additives was "nonsensical." *Id.* at 16 (quoting *United States v. 29 Cartons, et al.*, 987 F. 2d 33 (1st Cir. 1993)). In the black currant oil cases, FDA's efforts to ban supplements containing black currant oil were rejected by two unanimous decisions of two different three panels in two different United States courts of appeals. *United States v. Two Plastic Drums, et al.*, 984 F.2d 814 (7th Cir. 1993); *29 Cartons, et al.*, 987 F.2d 33 (1st Cir. 1993). In these cases, FDA proceeded under a theory that black currant oil was a food additive because it was added to gelatin capsules. The Seventh Circuit court found that FDA had not shown that black currant oil was adulterated or unsafe in any way. *United States v. Two Plastic Drums, et al.*, 984 F.2d 814 (7th Cir. 1993).

[8] Specifically, section 201(s)(6) of the FDCA states that the term "food additive" does not include an ingredient described in the definition of dietary supplements or any ingredient intended for use in a dietary supplement.

Not only did Congress remove dietary supplements and dietary ingredients from the definition of a food additive, but it also required different standards for demonstrating safety. For an NDI, the safety requirement in the notification is stated in section 413(a)(2) of the FDCA as follows:

> (a) IN GENERAL.—A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements:
>
> (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.

On the other hand, for food additives, the statutory language in section 409(c) of the FDCA is as follows:

> (3) No such regulation [prescribing the conditions under which a food additive may be safely used] shall issue if a fair evaluation of the data before the Secretary— (A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe . . . .

It is abundantly clear from the statute that Congress intended NDIs to be regulated differently from food additives. For dietary supplements, there need only be a "*reasonable expectation of safety*," whereas food additives must be demonstrated "safe." Notably, FDA promulgated regulations defining safe for food additives to mean "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." 21 C.F.R. § 170.3(i). It is thus clear that Congress intended NDIs to be regulated in a more flexible manner than food additives and the imposition of the food additive safety standard would be precluded under the rule of *Chevron.*

2. The Proposed NDI Notification Is Essentially a Food Additive Petition.

a. FDA Has Turned the NDI Notification Requirement into a Premarket Approval Requirement.

The Draft Guidance essentially codifies FDA's conflation of an NDI with a food additive petition requiring agency approval. This application of the statute is directly contrary to the distinction drawn by Congress between a food additive petition that must be granted by the agency and an NDI which is by the express terms of the statute a "notification."

Section 413(a) of the FDCA expressly permits the marketing of a dietary supplement that contains a new dietary ingredient under the following conditions:

> (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.*

(Emphasis added). Thus, the statute requires only that the manufacturer/distributor of a dietary supplement containing an NDI notify FDA as to the basis of its safety determination and provide that information to FDA. There is no requirement that the manufacturer or distributor obtain FDA approval or clearance.

Nor does the statute suggest that FDA has any authority to create an authorization that may be denied based on the information submitted in an NDI.[9] Once a dietary supplement manufacturer/distributor files an NDI notification that satisfies the regulatory requirements, it has met its statutory burden. FDA has no authority to "reject" or to otherwise object to the filing of an NDI notification based on inadequacy of safety data.

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[9] Where Congress seeks to give FDA authority to impose premarket approval requirements, it does so expressly. *See, e.g.*, FDCA § 515(b) ("a class III device ... is required to have, unless exempt..., an approval under this section of an application for premarket approval"); FDCA § 505(i) ("[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application...is effective with respect to such drug"); FDCA § 201(aa) ("the term 'abbreviated drug application' means an application submitted under section 505(j) for the approval of a drug that relies on the approved application of another drug with the same active ingredient to establish safety and efficacy").

Instead, the FDCA provides an entirely different mechanism for FDA to make a determination that safety data is inadequate.

Under section 402, if FDA believes "there is inadequate information to provide reasonable assurance that [an NDI] does not present a significant or unreasonable risk of illness or injury," FDA will "bear the burden of proof for each element to show that [the] dietary supplement is adulterated." FDCA § 402(f)(1). Furthermore, "a court shall decide any issue ...on a de novo basis." *Id.* § 402(f)(1). Thus, the FDCA clearly contemplates that if FDA believes that there is inadequate evidence of safety for an NDI, the agency has the burden of proving that the product in which the ingredient is marketed poses *a significant or unreasonable risk of illness or injury*. *Id.* § 402(f)(1)(A), (B). Congressional intent on this matter is even more indubitable when viewed in light of the legislative history for DSHEA.

In fact, as discussed above, Congress added section 402 specifically to prevent the "Alice-in-Wonderland approach . . . [which] allow[s] the FDA to make an end-run around the statutory scheme." S. REP. NO. 103-410, at 21 (quoting *United States v. Two Plastic Drums, et al.*, 984 F.2d 814 (7th Cir. 1993)). FDA has nevertheless resurrected the regulatory approach that made the passage of DSHEA necessary. Congress made clear that "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.'" S. REP. NO. 103-410, at 21.

It is thus clear that the 75-day NDI "notification" is intended to be a notification. The notification is not subject to pre-market review by FDA. Once a manufacturer/distributor of a dietary supplement containing an NDI submits the 75-day NDI notification that satisfies the statutory requirements, it may lawfully market its product unless FDA can demonstrate that either there is not a reasonable expectation of safety of the NDI or the product itself poses a significant or unreasonable risk of harm. The legislative history for DSHEA provides that, "[t]he amendment [to the DSHEA bill] also retains the existing law, which does not authorize the FDA to perform pre-market review or approval of dietary supplements." S. REP. NO. 103-410, at 22 (emphasis added). It is thus clear that FDA cannot impose a pre-market approval requirement on NDI notifications per the rule of *Chevron*.

b. FDA Has Imposed Food Additive Petition Standards.

The NDI notification under the Draft Guidance looks substantively like a food additive petition. Indeed, the Draft Guidance repeatedly references THE REDBOOK, the official compilation of requirements for establishing the safety of food additives, as the authority for various safety studies the FDA would demand for NDI notification.

Under the requirements set forth in the Draft Guidance, NDI notifications would become food additive petitions that must be supported by full reports of safety investigations meeting toxicity and tolerability requirements for food additives. Such tests would include short-term toxicity on rodents, sub-chronic toxicity on rodents,

chronic toxicity on rodents, in utero exposure on rodents, and human tolerability clinical trials, just to name a few. Applicants are also required to establish the identity of the additive or dietary ingredient by including information concerning its physical properties and chemical composition. As in food additive petitions, NDI notifications must include recommended labeling, directions, serving size, proposed tolerances, and specifications (*i.e.*, method of preparation, critical safety attributes, synthesis, tests, etc.) for all substances that make up the whole additive or dietary ingredient, as well as for the product in its entirety. FDA would also require NDI notifications to contain a description of the method of manufacture and analytical controls unless the chemical identity and composition of the food additive are unknown, which is not even required to secure approval of a food additive.

It is clear that FDA seeks to impose requirements on NDI notifications that go beyond what would be necessary to demonstrate that a dietary supplement ingredient "will reasonably be expected to be safe." The imposition of stricter food additive standards is thus in direct opposition to the plain meaning of the statute as well as to the clearly expressed intent of Congress in the legislative history of the statute.

c. FDA Has Made an NDI Notification Even More Restrictive than a GRAS Notification.

The Draft Guidance's requirement to submit a new NDI notification for each different dietary supplement formulation (*i.e.*, each time a dietary ingredient is added or substituted) goes even beyond the statutory constraints imposed under the food additive scheme in Generally Recognized As Safe ("GRAS") notices, which address inclusion of ingredients in a general category of food (*e.g.*, bread, cereal, etc.).

Under the GRAS notification program, persons and firms can inform FDA of a determination that the use of a substance is GRAS for its intended use, and FDA will review the information and either issue a "no questions" letter or a letter stating that the notice does not provide a basis for a GRAS determination. The intended use as stated in GRAS notifications is based on categories of food. For example, a particular substance in a GRAS notification can be intended to be used in breads. The notice does not specify that the ingredient may only be used in rye bread or in bread with certain formulations.

Under the Draft Guidance, however, a dietary supplement firm must submit a new NDI notification if the firm substitutes or adds any dietary ingredient to the dietary supplement formulation. For example, if an NDI notification is submitted for a dietary supplement that contains an NDI and 10 vitamins, and if the manufacturer decides to replace, for example, vitamin C with vitamin B, the dietary supplement firm must submit a new NDI. This is far more restrictive than the GRAS notification requirement, and is clearly not as Congress intended.

Congress made clear that dietary supplements were not to be subjected to the strict safety requirements of the food additive regulatory scheme and, obviously, did not intend that dietary ingredients be subjected to standards that are even more restrictive

than those for GRAS substances. The imposition of such requirements would thus violate the rule of *Chevron*.

II. The Draft Guidance Imposes Unwarranted and Disproportionate Burdens on Small and Mid-Sized Businesses.

A. FDA Fails to Address the Impact on Small Businesses.

In discussing the impact of the Draft Guidance's requirements on the dietary supplement industry – in particular, small and mid-sized firms – the Federal Register Notice for the Draft Guidance contains no economic impact statement.[10] However, when FDA provided notice of the final rule "Premarket Notification for a New Dietary Ingredient" ("NDI regulations" or "NDI notification final rule"), codified at 21 C.F.R. § 190.6, it found that the final NDI notification rule would not have a significant economic impact on a substantial number of small entities. 62 Fed. Reg. 49,886, 49,891 (Sept. 23, 1997).

In the notice to the final NDI notification rule, FDA concluded that the majority of firms in the dietary supplement industry would be classified as small businesses under the Small Business Administration's size standards for Food Preparations groups (500 or fewer employees) and Medicinal Chemicals and Botanicals Products (750 or fewer employees).[11] It also assumed that the total number of small businesses potentially affected by the proposed rule would be no more than the number of new ingredients, which it estimated to be 0 to 12 per year. *Id.* Based on this analysis, the agency determined the approximate cost per NDI submission would be $410.00. *Id.* The agency then calculated the cost of compliance with the notification requirement would not likely to be a substantial part of the total cost of introducing a new dietary ingredient. *Id.* This calculation recognized that, before a dietary supplement firm can introduce an NDI on the market, it must first determine that the ingredient can reasonably be expected to be safe. FDA reasoned that the introduction of an NDI and ensuring its safety would include technical, legal, and marketing costs, which are likely to be much larger than the cost of providing the notification to FDA. *Id.*

More recently, on June 3, 2011, one month prior to the release of the Draft Guidance, FDA published a notice requesting comment on the NDI notification requirements under 21 C.F.R. § 190.6. *See* 76 Fed. Reg. 32,214 (June 3, 2011). In this

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[10] When a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. 5 U.S.C. §§ 601-608. The economic impact requirement under the Regulatory Flexibility Act applies to proposed rules that are subject to notice and comment and defined in section 553(b) of the APA.

[11] FDA noted that the dietary supplement industry does not have its own standard industrial classification code. Therefore, the agency determined the industry's products come closest to the industry group's Food Preparations (not elsewhere classified) (Standard Industrial Classification code 2099) and Medicinal Chemicals and Botanical Products (Standard Industrial Classification code 2833). 62 Fed. Reg. 49,886, 49,890.

notice, FDA estimated that it would take a dietary supplement firm approximately 20 hours to prepare an NDI notification. *Id.* at 32,215. Several industry members submitted comments. On August 19, 2011, FDA announced the conclusion of the comments. *See* 76 Fed. Reg. 51,986 (August 19, 2011). In its conclusion, FDA stated that it "estimate[d] that 55 respondents will submit 1 premarket notification each and that it will take a respondent 20 hours to prepare the notification for a total of 1,100 hours." *Id.* at 51,988. FDA did not comment on the burden on small business and did not take into account the burdens associated with this Draft Guidance in its estimations.

The Draft Guidance and related Federal Register Notice indicate that FDA has not adequately determined how the NDI notification regulations or the new requirements under the Draft Guidance will affect small business. FDA's estimated 55 NDI notification submissions a year fails to account for the fact that the Draft Guidance broadens the category of NDIs, specifically those NDIs that must submit an NDI notification, to include many dietary ingredients that were for the past seventeen (17) years, since the enactment of DSHEA, understood to be "grandfathered" or otherwise exempt from the notification requirement. In fact, FDA suggests in the Draft Guidance that more than 1,000 new dietary supplements enter the market annually. Under the Draft Guidance, many of the new dietary supplements will contain an NDI, or due to FDA's long delay, companies will be unable to demonstrate that their ingredients are "grandfathered." *See* Section I.C.1.*b* above. Thus, the number of new supplements requiring an NDI notification under the Draft Guidance will be well over 55 annually, and FDA does not appear to have considered the burden this will impose on small businesses – in addition to the burden imposed by the new substantiation requirements.

FDA's estimations for time and costs for NDI notification submissions have heretofore been low due to the agency's "belie[f] [that] there will be minimal burden on industry to generate data to meet the requirements of the premarket notification program because the agency is requesting only that information that the manufacturer or distributor should already have developed to satisfy itself that a dietary supplement containing a new dietary ingredient is in full compliance with the [FDCA]." *See* 76 Fed. Reg. at 32,215. This is clearly no longer the case.

The Draft Guidance has broadened the scope of the classification of NDIs. Industry has been under the impression since the passage of DSHEA (17 years ago) that many ingredients deemed NDIs under the Draft Guidance did not require notification. In fact, Congress deemed dietary ingredients that were marketed in the United States prior to October 15, 1994, to be presumptively safe. Under the Draft Guidance, however, many of these pre-DSHEA dietary ingredients will be categorically excluded or will be unable to meet documentation requirements. *See* Section I.C.1.*b* above. Because these dietary ingredients were presumed safe, dietary supplement firms will not have documented safety in the manner prescribed by the Draft Guidance. They will thus have to engage in a significant amount of new testing and research to meet the burdensome new requirements.

Additionally, the Draft Guidance would impose dramatic changes in the information and documentation requirements for an NDI notification. Over the last 14 years, since the NDI regulations were promulgated, industry has relied on FDA's statements in the preamble to the final NDI notification rule. There, FDA states the following:

> [T]he manufacturer or distributor is not required to do a complete literature search. It is required only to provide "the basis on which [it] has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe (section 413(a)(2) of the [FDCA]). That is all that the [NDI] regulation requires.
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> * * *
>
> . . . [The manufacturer or distributor] must make a showing as to why it considers that consumption of a new dietary ingredient will be safe.
>
> * * *
>
> . . . In contrast [to the GRAS process], the requirement in section 413(a)(2) of the [FDCA] that a notification be made for a new dietary ingredient provides that *the manufacturer or distributor is to determine whether a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.*
>
> Furthermore, FDA is not persuaded that it is necessary for the agency to provide examples of scientific publications that are adequate to provide the information that can be the basis on which the manufacturer or distributor has concluded that a dietary supplement containing the new dietary ingredient will reasonably be expected to be safe. The agency also is not persuaded that the act requires that a manufacturer or distributor provide to FDA information on all known adverse effects attributable to the new dietary ingredient that is the subject of the submission. Section 413(a)(2) of the [FDCA] requires only that the notification provide information "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 when used under the conditions recommended or suggested in the labeling." Thus, the statute does not specify or limit what evidence a manufacturer or distributor may rely on in determining whether the use of the ingredient will reasonably be expected to be safe. . . .

> FDA does not find that the statute requires that the agency determine the relative merit of different types of evidence of safety, and therefore, the agency is not modifying § 190.6 to specify safety requirements for new dietary ingredients or to establish standards that the evidence of safety must meet.

62 Fed. Reg. at 49,888-89 (emphasis added).

These are the statements that the dietary supplement industry has relied on for the past fourteen (14) years. The new requirements set forth in the Draft Guidance are a dramatic departure from this policy.

The Draft Guidance would require very specific and detailed chemistry, processing, manufacturing, and safety information in NDI notifications. For example, while the agency stated in the NDI notification final rule that a manufacturer or distributor is not required to perform a complete literature search and is required only to provide the literature it relied upon when making the safety determination, the Draft Guidance states that the agency "considers 25 years of widespread use to be the minimum to establish a history of safe use." Draft Guidance at 51. In many cases, dietary supplement marketers will not have based their safety determinations on documentation of "25 years of widespread use." This and other new requirements will impose expenditures of significant amounts of time and money.

Dietary supplement marketers will likely not have such detailed information and documentation in their safety files, as it was not required by the agency before the issuance of the Draft Guidance. As FDA has stated, section 413(a)(2) "does not specify or limit what evidence a manufacturer or distributor may rely on in determining whether the use of the ingredient will reasonably be expected to be safe." *Id.* FDA is trying to specify and limit the type of evidence a manufacturer or distributor may rely on in determining whether the use of the ingredient will reasonably be expected to be safe.

B. Scientific and Other Documentation Requirements in the Draft Guidance Are Unduly Burdensome for Small Businesses.

As discussed above, the Draft Guidance would narrow the category of dietary ingredients that satisfy the requirements for "grandfathered" status. As a result, manufacturers and distributors will not have the detailed documentation that the ingredient is reasonably expected to be safe, since the dietary ingredient was previously presumed safe. The proposed scientific and other documentation requirements for NDI submissions will be overly burdensome for small businesses that may lack the resources to conduct additional studies or toxicological analyses or to gather information that FDA now deems necessary, as articulated in the Draft Guidance.

Small businesses may also be unduly burdened by the time needed to complete these newly-required studies. For ingredients that industry previously believed were grandfathered, companies will likely not have the detailed information and testing, as it

was not required by the agency before the issuance of the Draft Guidance. As such, companies may choose to temporarily discontinue sales of products containing the ingredient until such time as an NDI notification has been submitted and the 75-day period has lapsed. While larger businesses may have multiple other products on which they can rely for income, small businesses typically offer fewer products. As such, the inherent delay while a small business waits for studies to be completed is likely to result in a significant decrease in income stream for the small business. As such, small businesses may be adversely affected by the Draft Guidance in a way that larger businesses are not.

Moreover, as discussed above, the Draft Guidance has made clear FDA's expectation that NDI notifications will be product specific as opposed to ingredient specific. Since the passage of DSHEA, industry has acted consistent with its understanding that NDI notifications were ingredient-based and not product-based. As a result of the new requirements in the Draft Guidance, businesses will need to conduct very specific scientific studies, including animal studies and possibly human clinical studies, not just for the ingredient in question but for every product containing that ingredient. Small businesses just do not have the resources to satisfy this burden. They cannot simply raise their prices to offset these new costs.

As such, it can be expected that small businesses will use very similar formulas for different products as a means to save money on research and development costs, substantiation costs, and NDI submissions. Or small businesses may not survive.

It was not Congress's intent when drafting DSHEA to unduly burden small businesses or to limit the range of product formulas utilized by dietary supplement companies. To the contrary, Congress stated, "[T]he Federal role in dietary supplement regulation [. . .] is not to take actions to impose regulatory barriers limiting or slowing the flow of safe products and needed information to consumers." S. REP. NO. 103-410, at 2. Accordingly, we urge FDA to reconsider the effect of the Draft Guidance on small businesses.

CONCLUSION

For the foregoing reasons, the Joint Commenters respectfully request that FDA withdraw the Draft Guidance and propose a draft guidance or regulation consistent with principles set forth in these comments.

Respectfully submitted,

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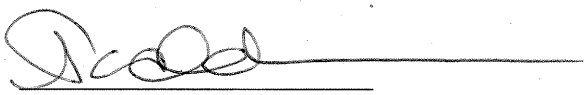
AdvoCare International, LP
Biocentric Health, Inc.
Dietary Supplement Manufacturers and Marketers Assoc.
Essential Formulas Incorporated
Healthy Directions, LLC

Jarrow Formulas
Mercola.com Health Resources, LLC
New Vitality
NNC LLC d/b/a Naturade
P.L. Thomas & Co., Inc.
Purity Products
VRP Manufacturing LLC
Anonymous Commenters

By Their Counsel:



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Dated: 12/02/2011

Exhibit 1

Background and Interests of Joint Commenters

Advanced Bionutritionals, LLC

Advanced Bionutritionals, LLC has offered high-quality dietary supplements since 1995. With 50,000 customers in all 50 states, supplement sales will exceed $17,000,000 in 2011. Advanced Bionutritionals's affiliated management company, Soundview Communication, employs 18 associates at its Atlanta, Georgia headquarters. In addition, the company contracts with 20 freelance writers, photographers, and web designers in the conduct of its operations.

AdvoCare International, LP

AdvoCare International, LP is a health and wellness company headquartered in Plano, Texas that offers world-class energy drinks, nutritional and skin care products along with a rewarding business opportunity. For more than 15 years, AdvoCare has offered nutritional supplements and vitamins of the highest quality developed through comprehensive research and backed by a Scientific Medical Advisory Board.

Biocentric Health, Inc.

Biocentric Health, founded in late 2005, is headquartered in Bethesda, Maryland with a Warehouse and Operations Center in Lancaster, PA. Biocentric Health, a direct-to-consumer nutritional supplement company, product formulations are doctor-inspired and based on the growing evidence that nutritional supplementation can be adjunctive to good health when combined with a proper diet, exercise, sleep and stress management. Biocentric Health products are manufactured at contracted cGMP facilities.

Dietary Supplement Manufacturers and Marketers Association

The Dietary Supplement Manufacturers and Marketers Association (DSMMA) is a new trade organization whose members share the fundamental beliefs that dietary supplements are safe, that the majority of companies willingly adhere to the many regulations governing dietary supplements, and that FDA and FTC already have sufficient authority to prosecute companies that do not follow the law. The mission of DSMMA is to support the continued viability of the dietary supplement industry for raw material suppliers, finished product manufacturers, and marketers through political lobbying, FOIA requests, targeted legal challenges, effective trade negotiations, by effectively engaging the FDA and FTC on issues of industry importance, and timely press outreach.

Essential Formulas Incorporated

In the year 2000, Essential Formulas Incorporated became the exclusive distributor of Dr. Ohhira's Probiotics® in North America and elsewhere. Each year thereafter, sales have grown experientially, and as of today, nearly 12 years after our first sale, more than 1,000,000 boxes of Dr. Ohhira's Probiotics have been distributed in the United State alone. Dr. Ohhira's Probiotics has been distributed worldwide since the mid-1980's without any reports of adverse reactions and EFI's experiences mirror that commendable record. FDA's NDI Guidelines may very well lead to the end of the distribution of Dr. Ohhira's Probiotics in the United States and, consequently, cause the direct loss of more than 14 full time jobs and over 40 part time jobs in the United States, and most likely several dozen jobs in Japan where Dr. Ohhira's Probiotics are skillfully crafted into a finished product. Essential Formulas Incorporated respectfully requests that FDA withdraw its Draft NDI Guidance until further information is provided from the dietary supplement industry and consumers of dietary supplements in the United States.

Jarrow Formulas

Jarrow Formulas, which is based in Los Angeles, California, is a formulator and supplier of superior nutritional supplements. The company was founded in 1977. Today it markets its products in the United States and throughout the world.

Mercola.com Health Resources, LLC

Mercola.com Health Resources, LLC was founded in 1997. It is headquartered in Hoffman Estates, IL. Mercola.com Health Resources, LLC provides high quality supplements, cosmetics, and daily use items to consumers based on the research of Dr. Joseph Mercola. Each product passes the company's rigorous review process before being offered to consumers.

NNC LLC d/b/a Naturade

Naturade® is a leading supplier of high-quality, science-based nutritional supplements and functional food products to the Natural Products trade channel, the Food, Drug, Mass and Club trade channels, as well as the Professional channel since 1926. The company markets a number of products under the brands Naturade®, Symbiotics®, ProSymbiotics® and Ageless Foundation Laboratories®.

P.L. Thomas & Co., Inc.

P.L. Thomas, a New Jersey-based ingredient supplier and marketer, offers more than 50 years of innovation in sourcing and marketing natural, reliable, value-added raw materials for the food, beverage, dietary supplement and cosmeceutical markets. P.L. Thomas specializes in clinically-supported, science-based nutraceuticals; fruit and botanical extracts; natural colors and flavors; and novel delivery systems with ingredients covering a wide range of application-specific conditions.

VRP Manufacturing LLC

VRP Manufacturing LLC has been a researcher, formulator and manufacturer of dietary supplements since 1979. The company currently employs approximately 160 employees in 3 states. The NDI Draft Guidance presents issues and concerns that are crucial for the company's business. The comments submitted concerning the Draft Guidance highlight some of the more important issues the company would like to be considered. Addressing these issues is critical to the company's ability to continue to support its employees and customers' interests.

Anonymous Commenters

Additional companies that manufacture, distribute, and market dietary supplement products have joined in the comments but wish to remain anonymous. All companies have a significant interest in the Draft Guidance, as it will directly affect the day-to-day business of these companies.