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December 12, 2016

BY ELECTRONIC DELIVERY

Division of Dockets Management
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Re: **Docket No. FDA-2011-D-0376, Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues**

Dear Sir or Madam:

Hyman, Phelps & McNamara, P.C. submits the following comments on behalf of Nutraceutical Corporation ("Nutraceutical") concerning the Food and Drug Administration ("FDA") Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues ("Draft Guidance Document"). Nutraceutical sells over 7,500 dietary supplements through more than 17,000 health and natural food store partners throughout the United States. Nutraceutical is an integrated manufacturer, marketer, distributor, and retailer of branded nutritional supplements and other natural products sold primarily to and through domestic health and natural food stores.

FDA issued the first iteration of the Draft Guidance Document in July 2011. According to FDA, the Agency received over 140,000 pages of comments, mostly critical.[1] This firm, as well as most industry trade associations, urged FDA to withdraw that draft guidance and issue a new draft, reflecting the serious concerns that the first iteration failed to implement the Dietary Supplement Health and Education Act of 1994 ("DSHEA") as intended. DSHEA established a new, less restrictive, regulatory regime for dietary supplements to address FDA's misapplication of the Federal Food, Drug, and

[1] We submitted comments on behalf of Nutraceutical to the 2011 version of the Draft Guidance Document on December 2, 2011. Many of the issues discussed in our 2011 comments are applicable to the 2016 Draft Guidance Document as well.

Cosmetic Act's ("FDC Act's" or "the Act's") "food additive" requirements, which prevented the marketing of many novel dietary supplements. Yet, FDA's first iteration interpreted key provisions of DSHEA to establish an even more restrictive regulatory regime.

In a June 2012 meeting between FDA and the primary authors of DSHEA (Senators Hatch and Harkin), Commissioner Hamburg committed to issuing a revised draft in order to address the concerns of Congress and industry. FDA's 2016 Draft Guidance fails to address the congressional and industry concerns with the 2011 guidance.

More than four years later, on August 18, 2016, FDA issued the promised revision. However, rather than change any of the positions that had led Congress and industry to demand the revision of the first iteration, FDA has doubled down and simply increased the length of the guidance from 86 to 102 pages. In the Federal Register announcement of the Draft Guidance Document, FDA stated that, instead of revising the agency positions that contravened the provisions of DSHEA, FDA "decided to clarify and better explain [its] thinking on some critical issues" to address "gaps and unclear statements that were subject to confusion and misinterpretation."[2]

In other words, according to FDA's revisionist history, the problem was not that FDA misinterpreted DSHEA in 2011, but that industry and Congress were confused.

FDA's 2016 Draft Guidance Document once again usurps the authority of Congress and deliberately misinterprets key provisions of DSHEA in order to impose illegal restrictions on the marketing of dietary supplements. If implemented, FDA's interpretations would render many dietary supplements that have been widely marketed and safely used for decades unlawful; NDI notifications would have to be submitted for thousands of such products because of the Agency's extra-statutory requirements for formulation-specific and manufacturer-specific notifications; and innovation would be stifled because of FDA's narrow interpretation of the definition of "dietary ingredient." The following comments address the errors of statutory interpretation in the Draft Guidance Document. However, because it is clear from this second FDA effort that the Agency is not willing or able to issue guidance on NDIs that reflects the text and intent of DSHEA, we request that FDA abandon this effort and instead permit industry to develop its own NDI guidance for subsequent discussions with FDA. FDA should continue its

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[2] Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry; Availability, 81 Fed. Reg. 53486, 53489 (Aug. 12, 2016) [hereinafter Draft Guidance (2016)].

recent and effective focus on removing from the market, with industry's cooperation, specific problematic ingredients. This process will assure consumer access to safe products and permit FDA and industry to work in a constructive manner to reach agreement on a regulatory framework that is consistent with DSHEA.

I. Preliminary Comments

Since at least the early 1960s, FDA has repeatedly attempted to control the dietary supplement market in ways that the public, industry, and Congress have found unacceptable. In the 1960s and early 1970s, FDA proposed to issue regulations that would have required FDA's review and approval of vitamin products that exceeded 150% of the U.S. RDA[3] and to require the following disclaimer on vitamin supplements: "Vitamins and minerals are supplied in abundant amounts by commonly available foods. Except for persons with special medical needs, there is no scientific basis for recommending routine use of dietary supplements."[4] The proposed disclaimer was withdrawn after hearings, but the regulation setting limits on potency was finalized in 1973.[5] That regulation was invalidated as arbitrary and capricious by a federal appellate court,[6] and the regulation prompted Congress to add section 411 to the FDC Act through the Proxmire Amendments in 1976.[7] Among other things, section 411 restricts FDA's authority to set maximum limits on the potency of synthetic or natural vitamins or minerals in dietary supplements.

In the 1980s, FDA pursued the theory that novel dietary supplements were in fact unapproved and, therefore, illegal food additives, bringing multiple seizure actions against a variety of products including evening primrose and black currant oil. FDA's arguments that even pure black currant oil in a gelcap or a glass bottle was a food

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3 See e.g., Notice of Proposal to Revise Regulations, 27 Fed. Reg. 5815, 5817 (June 20, 1962); see also Definition, Identity, and Label Statements; Proposed Findings of Fact, Conclusions, and Tentative Order Following a Public Hearing, 38 Fed. Reg. 2152, 2157, 2161 (Jan. 19, 1973).

4 See e.g., Order Staying Effective Date of Regulations; Amending Regulations; and Allowing Additional Time for Filing Objections, 31 Fed. Reg. 15,730, 15,732 (Dec. 14, 1966).

5 See Label Statements; Findings of Fact, Conclusions, and Final Order, 38 Fed. Reg. 20,708 (Aug. 2, 1973).

6 See Nat'l Nutritional Foods Ass'n v. Kennedy, 572 F.2d 377 (2d Cir. 1978); Nat'l Nutritional Foods Ass'n et al. v. FDA, 504 F.2d 761 (2d Cir. 1974), cert. denied, 420 U.S. 946 (1975).

7 See Health Research and Health Services Amendments of 1976, Pub. L. No. 94-278, Title V (amending the FDC Act by adding section 411).

additive led to unusually strong rebukes by two appellate courts, one of which found that FDA's argument "pervert[ed] the statutory text, undermine[d] legislative intent, and defenestrate[d] common sense,"[8] while the other described FDA's theory as an "Alice-in-Wonderland approach," and "an end-run around the statutory scheme."[9] Congress stepped in again: 18 years after the Proxmire Amendments, Congress passed DSHEA, clarifying that FDA has no authority to regulate dietary supplements as food additives.

In passing DSHEA, Congress recognized that dietary supplements could make significant contributions to public health while reducing the cost of health care. Congress further recognized that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare."[10] Accordingly, DSHEA was intended to ensure that the flow of safe dietary supplements to consumers would not be impeded by unreasonable regulatory barriers. In relevant part, the Congressional findings state:

> [A]lthough 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 slowing the flow of safe products and accurate information to consumers.[11]

Congress therefore established a separate statutory framework for dietary supplements to ensure that they would not be subject to the requirements applicable to drugs or to food additives. DSHEA amended the FDC Act to, among other things, (1) encompass a broad range of dietary ingredients within the definition of dietary supplement; (2) make clear that dietary ingredients are not subject to regulation as food additives; (3) exempt dietary ingredients marketed before October 15, 1994 from regulation as NDIs; (4) subject NDIs to a premarket notification process (as opposed to a premarket approval process); (5) exempt from the premarket notification requirement any NDI that is present in the food supply and has not been chemically altered; (6) provide separate safety standards for dietary supplements and ingredients, as well as NDIs; and (7) impose upon industry the duty to ensure that dietary supplements are safe, but impose upon the federal government the burden of proof to show that a dietary supplement does not meet the applicable safety standards. Taken together, these provisions evince clear

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8 U.S. v. 29 Cartons of * * * An Article of Food, 987 F.2d 33, 39 (1993).

9 United States v. Two Plastic Drums, 984 F.2d 814 (7th Cir. 1993).

10 DSHEA § 2(14).

11 Id. § 2(13).

intent on the part of Congress to create a statutory framework for supplements that struck an appropriate balance between ensuring safety and minimizing unnecessary and unreasonable regulatory requirements.

As explained in detail below, the 2016 Draft Guidance Document (as was true of the first iteration in 2011) ignores the balance struck by Congress in passing DSHEA, in favor of a regulatory approach so restrictive that, if fully implemented, would severely disrupt the market for dietary supplements and impose extraordinary burdens on industry and FDA, with no apparent benefit to public health. FDA has once again attempted "an end-run around the statutory scheme."[12]

II. Definition of Dietary Ingredient

A. Dietary substances for use by man to supplement the diet by increasing the total dietary intake—Section 201(ff)(1)(E)

1. The language and structure of section 201(ff)(1)(E) demonstrate that clause (E) ought to be read inclusively, not exclusively.

Section 201(ff)(1) of the FDC Act defines the term "dietary supplement" in part as "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)."[13]

This definition presents an increasingly widening scope of substances that may be included as dietary ingredients in a dietary supplement: clauses (A) through (D) list specific substances that consumers have long used to supplement the diet – i.e., a vitamin, a mineral, a botanical, an amino acid – and clause (E) then broadens the scope of dietary ingredients to include other orally ingestible substances that do not fall into the categories listed in clauses (A) through (D) and that are intended "for use by man to supplement the diet by increasing the total dietary intake," as opposed to, for example, substances intended as drugs; finally, clause (F) broadens the scope even further by including "a concentrate, metabolite, constituent, extract, or combination" of any ingredient in clauses

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[12] See supra note 9.

[13] FDC Act § 201(ff)(l).

(A) through (E). This reading of section 201(ff)(1), and of clause (E) in particular, is supported by the exclusionary clause in section 201(ff)(3)(B): i.e., where Congress intended to exclude certain substances from classification as a dietary ingredient, the FDC Act does so explicitly in section 201(ff)(3)(B), which excludes ingredients that have been approved as a new drug, certified as an antibiotic, or licensed as a biologic, among others.

Therefore, although the Act does not define the term "dietary substance" for the purposes of clause (E), that clause ought to be read as a catch-all category.

2. The Draft Guidance Document's interpretation of clause (E) is unsupported by law and science and rests on an implausible reading of the text.

The Draft Guidance Document interprets clause (E) too narrowly, such that a substance other than a vitamin, mineral, botanical, or amino acid, or a concentrate, metabolite, constituent, extract, or combination of those ingredients, can never be a dietary ingredient unless the substance is "commonly used as human food or drink." This interpretation all but forecloses the possibility of truly novel or innovative dietary ingredients, including, for example, many probiotics.

The Draft Guidance Document reaches this narrow interpretation by citing Webster's dictionary definition of "dietary" (i.e., "of or relating to . . . an organism's usual food and drink") and concluding that Congress must therefore have intended "dietary substance" to mean a substance "commonly used as human food or drink." The Draft Guidance Document finds further evidence for its interpretation in the phrase "by increasing the total dietary intake," stating that "[o]ne cannot increase the 'total dietary intake' of something that is not part of the human diet in the first place."[14]

This reading is implausible in part because the Act elsewhere indicates that presence in the food supply, let alone common consumption, is not necessarily a predicate to the marketing of a dietary ingredient. Section 413(a), which provides for the marketing of new dietary ingredients ("NDIs"), states in part that an NDI may be legally marketed if "[t]here 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 . . . ."[15] Thus,

[14] Draft Guidance (2016) at 38.

[15] FDC Act § 413(a) (emphasis added).

the Act clearly contemplates that dietary ingredients without a history of use, but supported by other evidence of safety, may be marketed in a dietary supplement.

Had Congress intended that clause (E) only permit dietary substances already in the food supply, it would have specified this limitation. In fact, Congress did specify this limitation in another context, stating that a dietary supplement that contains an NDI is not adulterated if it contains "only dietary ingredients which have been present in the food supply as an article used for food . . . ."[16] That the Act does not use this language in section 201(ff)(1)(E) indicates that Congress did not intend such a limitation to apply in clause (E) and that the Draft Guidance Document misinterprets that clause.[17]

FDA's interpretation results in a regulatory scheme that defies logic. Under FDA's interpretation, a substance without a history of common use in conventional foods (i.e., a novel substance, or even a food that is only consumed by a small population) cannot be a dietary substance, and therefore cannot be a dietary ingredient under section 201(ff)(1)(E). This closes the door to the marketing as a dietary ingredient of many dietary substances consumed by humans that are not "commonly used," as well as all novel substances, unless they fall into one of the other categories listed in 201(ff)(1), or are first the subject of a Generally Recognized as Safe ("GRAS") affirmation or food additive approval and are commonly used as conventional foods.

First, there is no scientific rationale for imposing additional regulatory hurdles to the marketing of a dietary ingredient based solely on its categorization under section 201(ff)(1). Yet the Draft Guidance Document's interpretation would do just that: a novel substance derived from a botanical would qualify as a dietary ingredient (under section 201(ff)(1)(C)), but (because FDA interprets section 201(ff)(1)(E) as applying only to substances in the food supply) a novel substance derived from an animal or other non-botanical source could not qualify as a dietary ingredient without first undergoing a GRAS determination or food additive approval, being introduced into interstate commerce, and being commonly used as a conventional food. Second, this interpretation would have the bizarre effect of rendering dietary ingredients a more restrictive category than food additives and GRAS ingredients—i.e., virtually any substance could be

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16 Id. § 413(a).

17 The misinterpretation is also evident in the extreme outcome that would result if the Draft Guidance Document's definition of the word "dietary" were applied consistently throughout section 201(ff) – i.e., the list of "dietary ingredients" in section 201(ff)(1)(A)-(D) would be interpreted as including only those vitamins, minerals, botanicals, and amino acids that are commonly used as human food or drink, and as excluding vitamins, minerals, botanicals, and amino acids that are not commonly used as food or drink.

approved as a food additive or deemed GRAS for food use, but only certain commonly consumed substances could be marketed as dietary ingredients. Whereas DSHEA was intended to address FDA's overzealous regulation of dietary supplements through the more restrictive food additive and GRAS requirements, the Draft Guidance Document would impose a more limiting regulatory regime through DSHEA than existed prior to DSHEA, and a regime that is more restrictive than that applied to conventional foods.[18]

Rather than twisting the language of section 201(ff)(1)(E) in a way that conflicts with the plain meaning of the statute and that upends the purpose of DSHEA, a more reasonable interpretation of clause (E) is that a "dietary substance" is any edible substance that can be consumed orally and that is intended "to supplement the diet by increasing the total dietary intake,"[19] as opposed to, for example, a replacement for conventional food or meals or a substance intended to have drug effects. This interpretation preserves the plain reading of the text, the structure of section 201(ff)(1), and the intent of the statute, and it avoids distinctions that have no basis in science.

B. Synthetic dietary ingredients

1. There is no scientific rationale for permitting a natural dietary ingredient to be marketed while prohibiting the marketing of a chemically identical synthetic copy, and the FDC Act recognizes that natural and synthetic ingredients ought to be treated identically.

Nothing in the language of section 201(ff)(1) suggests that Congress intended that synthetic and natural dietary ingredients be treated differently. Indeed, the dietary supplement provisions of the FDC Act do not distinguish between natural and synthetic

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[18] FDA's narrow interpretation of § 201(ff)(1)(E) is also inconsistent with § 413(a), which provides for the marketing of new dietary ingredients (NDIs), i.e., dietary ingredients not marketed in the United States before October 15, 1994. The language of that section makes clear that presence in the food supply is not necessarily a predicate to the marketing of certain NDIs:

> 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 . . . .

(Emphasis added.) Thus, an NDI can be marketed based on evidence of safety other than a history of use, and in the absence of evidence that it is a "dietary substance" as defined by FDA (i.e., in the absence of evidence of common use as human food or drink).

[19] FDC Act § 201(ff)(1)(E).

ingredients, and any distinction (between natural substances and chemically identical synthetics) for the purposes of dietary ingredient status is without scientific basis. Moreover, the equivalence of natural and synthetic dietary ingredients was established by Congress and accepted by FDA long before the enactment of DSHEA.

Added to the FDC Act by the Proxmire Vitamin and Mineral amendment, FDC Act section 411 recognizes the equivalence of natural and synthetic vitamins, minerals, and "other ingredient[s]" of foods for special dietary use.[20] FDC Act section 201(ff)(1) must be read in light of section 411, which plainly permits the use of any synthetic ingredient in a food for special dietary use. Indeed, FDA regulations deem a food misbranded if its labeling represents, suggests, or implies that a natural vitamin in a food is superior to an added or synthetic vitamin.[21] Thus, FDA and the FDC Act have long recognized that natural and identical synthetic food ingredients ought to be treated identically.

2. The Draft Guidance Document's distinction between synthetic and natural botanicals (and botanical extracts) is not grounded in law or science.

The Draft Guidance Document states that synthetic vitamins, minerals, and amino acids qualify as dietary ingredients, whereas synthetic botanicals and botanical extracts do not. It provides no scientific or policy rationale for the distinction and instead bases its conclusion on an idiosyncratic interpretation of section 201(ff)(1). The Draft Guidance Document states that synthetic vitamins, minerals, and amino acids qualify as dietary ingredients "because a vitamin, mineral, or amino acid is defined by its nutritional function . . . and not by its state of matter like a botanical," whereas "[a]s defined in the glossary, an herb or botanical includes only plants, algae, fungi, their exudates . . . and their physical parts. A substance that has been synthesized in a laboratory or factory has never been part of an herb or other botanical, and therefore, is not a dietary ingredient under section 201(ff)(1)(C) of the FD&C Act."[22] Thus, a synthetic copy of a constituent or extract of a botanical cannot qualify as a dietary ingredient, even though it may be indistinguishable from its naturally occurring counterpart.

However, FDA's parsing of section 201(ff)(1)(C) creates a distinction between natural and identical synthetic ingredients that DSHEA does not contemplate. As

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[20] Id. § 411.

[21] 21 C.F.R. § 101.9(k)(4).

[22] Draft Guidance (2016) at 38.

discussed in section II.A above, an accurate interpretation of section 201(ff)(1)(E) permits as a dietary ingredient virtually any safe substance (other than those excluded in section 201(ff)(3)(B)). For example, a synthetic botanical or botanical extract is a lawful dietary ingredient because it is a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" under section 201(ff)(1)(E), irrespective of the applicability of section 201(ff)(1)(A)-(D) and (F) to synthetic ingredients. FDA thus creates a distinction between natural botanicals and botanical extracts, on the one hand, and synthetic botanicals and botanical extracts, on the other, that is not evident in the language of DSHEA.

Importantly, synthesis of a constituent or extract of a botanical presents no risks that are not presented by synthesis of vitamins or of the metabolite of an amino acid, for example, and potentially offers the same benefits in terms of relative ease and consistency of production. Rather than subjecting certain synthetic substances to additional regulatory hurdles based on arbitrary distinctions, we urge the Agency to acknowledge the precedent set by Congress in section 411 of the Act and to recognize the equivalence of all synthetic and natural dietary ingredients. This approach would avoid the type of unnecessary delay that was seen as a result of the Agency's initial efforts to assert that synthetic conjugated linoleic acid ("CLA") was not a dietary ingredient. This approach would also be consistent with precedents established by FDA in other regulatory areas, such as biotechnology, where FDA has consistently held to the view that the Agency regulates products, not processes.[23]

III. Definition of an NDI

A. "A dietary ingredient that was not marketed in the United States before October 15, 1994"

1. A plain reading of the statutory definition of an NDI

The FDC Act defines "new dietary ingredient" as "a dietary ingredient that was not marketed in the United States before October 15, 1994 . . . ."[24] The definition is significant because an ingredient's status as an NDI may trigger the requirement (from section 413(a)(2)) to submit an NDI notification to FDA or, absent such notification,

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[23] See e.g., Coordinated Framework for Regulation of Biotechnology: Announcement of Policy; Notice for Public Comment, Executive Office of the President, Office of Science and Technology Policy, 51 Fed. Reg. 23,302, 23,303 (June 26, 1986) (stating that FDA "would regulate genetic engineering products no differently that [sic] those achieved through traditional techniques").

[24] FDC Act § 413(d).

could render a dietary supplement containing the ingredient adulterated (under sections 413(a)(1) and 402(f)). A plain reading of the definition indicates that an NDI is any edible, orally ingestible (i.e., "dietary") substance that, before October 15, 1994, was not lawfully marketed in the United States.

2. A dietary ingredient need not have been marketed in a dietary supplement for it to have been "marketed in the United States before October 15, 1994."

FDA significantly broadens the scope of ingredients that would be considered NDIs. Although the statutory definition is simple (i.e., "not marketed in the United States before October 15, 1994"), the Draft Guidance Document states that a history of marketing before October 15, 1994 is insufficient to render an ingredient an old (or, "pre-DSHEA") dietary ingredient; rather, it says that "[w]hat matters is whether the ingredient was marketed as a dietary ingredient . . . ."[25] FDA cites no statutory or other basis for this added requirement. Indeed, because there was no legally defined category of "dietary ingredients" before DSHEA, FDA creates a complex test out of whole cloth; it states that, for purposes of NDI status, "dietary ingredients" are substances that "(1) if marketed today, would qualify as 'dietary ingredients' under 21 U.S.C. 321(ff)(1); and (2) when marketed before October 15, 1994, were intended for use as or in a product that would now be a 'dietary supplement' as defined in 21 U.S.C. 321(ff) and that would not also meet the definition of a drug."[26]

This novel and restrictive interpretation runs counter to the plain language of the statute. Section 413(d) does not state that a dietary ingredient is an NDI unless it was marketed "as a dietary supplement ingredient." Rather, section 413(d) uses the term "marketed" without qualification. Had Congress intended to qualify that term, it would have done so, as illustrated by its qualification of the term "marketed" with the phrase "as a dietary supplement or as a food" in section 201(ff)(3)(B).

Moreover, the Agency's interpretation runs counter to the purposes of DSHEA and the regulatory structure created by section 413. Section 413 was plainly intended to address the safety of dietary ingredients that had no history of use at the time of DSHEA's passage. For a dietary ingredient that does not predate DSHEA (i.e., an NDI), the Act requires a safety review: such an ingredient renders a dietary supplement adulterated unless the ingredient has "been present in the food supply . . . "[27] – i.e.,

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[25] Draft Guidance (2016) at 14 (emphasis in original).

[26] Id.

[27] FDC Act § 413(a).

unless, after October 15, 1994, it has been the subject of an NDI notification, a food additive approval, or a GRAS determination, or is a constituent of such an ingredient. On the other hand, for pre-DSHEA dietary ingredients, section 413 recognizes that their prior marketing supports a presumption of safety in part because, before DSHEA, all food ingredients were subject to the same safety standard, i.e., reasonable certainty of no harm under the conditions of intended use.

In addition, FDA's position that only pre-DSHEA ingredients that were marketed as dietary ingredients or dietary supplements are exempt – and that ingredients previously marketed in conventional foods are not – implies that conventional foods, categorically, cannot provide a basis for a presumption of safety even if, as is often the case, an ingredient was widely consumed in conventional foods and less frequently in a dietary supplement.

Ironically, FDA takes the exact opposite position in its application of the NDI notification exemption: there, FDA considers a dietary ingredient to be "present in the food supply," and thus potentially exempt from the NDI notification requirement, only if it is present in a conventional food, thus implying that dietary supplements, categorically, cannot provide a basis for a presumption of safety.[28] This inconsistency demonstrates the arbitrariness of FDA's distinction: there is no rational basis for distinguishing between pre-DSHEA conventional food ingredients and pre-DSHEA dietary supplement ingredients for purposes of defining an NDI.

3. It is unreasonable to expect manufacturers to have retained decades-old manufacturing records in order to demonstrate an ingredient's pre-DSHEA status, and the Act includes no such requirement.

The Draft Guidance Document states that a pre-DSHEA dietary ingredient may be rendered an NDI if certain changes have been made to the manufacturing process for the ingredient on or after October 15, 1994. Although FDA does not provide an exhaustive list of such manufacturing changes, it does limit the scope of the types of changes that can trigger NDI status: "if the manufacturing changes do not alter the identity of the ingredient (e.g., there are no changes in physicochemical structure or properties and no changes in purity, impurities or biological properties such as bioavailability or toxicity)

[28] Draft Guidance (2016) at 23.

then the regulatory status of the pre-DSHEA ingredient does not change and no NDI notification is needed."[29]

Manufacturers are unlikely to have detailed manufacturing information from before October 15, 1994—over 22 years ago—and it is unreasonable to expect them to be able to produce such records. Had FDA communicated this requirement in 1994, when DSHEA was passed, manufacturers may have had the opportunity to collect appropriate records and documents. Instead, FDA added this requirement 17 years later in the 2011 draft guidance document (and maintains it in the 2016 revision), when those records no longer exist—a requirement that seems like the very definition of arbitrary regulation.

Moreover, under section 402(f)(1)(D), FDA "shall bear the burden of proof on each element to show that a dietary supplement is adulterated."[30] Thus, if FDA believes that a pre-DSHEA dietary ingredient is, due to manufacturing changes, an NDI, the Agency bears the burden of proof to demonstrate that the ingredient differs in a material way from the pre-DSHEA ingredient. A manufacturer's inability to produce decades-old manufacturing records, or to ascertain the method used to manufacture a pre-DSHEA dietary ingredient, is not sufficient to demonstrate an element of adulteration, and FDA should acknowledge this in order to prevent unnecessary confusion and uncertainty on the part of manufacturers and marketers.

4. Only manufacturing changes that affect the fundamental (i.e., physicochemical) nature of an ingredient render a pre-DSHEA dietary ingredient an NDI.

The Draft Guidance Document takes an overly broad view of the types of manufacturing changes that can render a pre-DSHEA ingredient an NDI. The FDC Act is silent on the issue of manufacturing changes, and the discussion of manufacturing changes in the Draft Guidance Document reflects FDA's attempt to determine whether a currently-marketed dietary ingredient ought to be considered the same substance as a "dietary ingredient [] marketed in the United States before October 15, 1994."[31] Rather than focus on the physicochemical nature of the ingredient – i.e., the fundamental identity of the ingredient – the Agency takes a sweeping view of the types of manufacturing changes that render a pre-DSHEA ingredient an NDI.

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29 Id. at 21.

30 FDC Act § 402(f)(1)(D).

31 Id. § 413(d).

For example, the Draft Guidance Document states that "[m]anufacturing changes that alter the . . . purity and impurities . . . of the ingredient result in an NDI."[32] Therefore, a pre-DSHEA herbal extract that has been improved by manufacturing changes that reduce impurities would, in FDA's view, be considered an NDI even if the reduced impurity levels do not result in any changes to the physicochemical structure, bioavailability, or toxicity of the extract. In addition, the Draft Guidance Document states that mere "solution in water or tincture may change the composition of a pre-DSHEA dietary ingredient enough to make it an NDI for which a notification is required."[33] Therefore, for example, merely making a tea out of a pre-DSHEA herb in order to provide a new means of ingestion would appear to create an NDI even if the tea's bioavailability, toxicity, etc., are identical to that of the pre-DSHEA herb. That FDA's interpretation leads to these absurd results reflects the fact that the Agency's view is overly broad, not based in science, nor required by the FDC Act.

IV. NDI Notification

The FDC Act's NDI notification provisions require that FDA be made aware of information supporting the safety of truly novel dietary ingredients before they are introduced to the market. Specifically, section 413(a)(2) of the Act requires that a marketer or distributor of an NDI must submit to FDA information supporting the ingredient's safety. However, the Act exempts from this notification requirement an NDI that "ha[s] been present in the food supply as an article used for food in a form in which the food has not been chemically altered."[34] In other words, an ingredient that was not marketed in the United States before October 15, 1994 (i.e., an NDI) but that has since been introduced to the U.S. market and is present in the food supply, may be marketed in a dietary supplement and is exempt from the NDI notification requirement provided that the ingredient is in a form not chemically different from its form in the food supply. In other words, the Act considers the NDI's presence in the food supply to be evidence of its safety.

A. "Present in the food supply"

1. An ingredient is "present in the food supply" if it is present in a dietary supplement or a conventional food.

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[32] Draft Guidance (2016) at 21.

[33] Id. at 22.

[34] FDC Act § 413(a)(1).

A plain reading of the statute indicates that dietary supplements are part of the "food supply." Although section 413 does not define "food supply," the Act specifies that dietary supplements "shall be deemed to be food within the meaning of" section 201(f) (except for certain limited purposes).[35] Moreover, the broad definition of "food" in 201(f), i.e., "articles used for food," closely mirrors the language in section 413(a)(1) that exempts NDIs present in the food supply "as an article used for food." Thus, a plain reading of section 413(a)(1) and of the Act's definition of "food" indicate that presence in the "food supply" includes presence in a dietary supplement.

2. The Draft Guidance Document's exclusion of dietary supplements from the definition of "food" lacks a rational legal or scientific basis.

Although the FDC Act does not qualify the term "food supply" with any language that suggests it ought to be limited to only certain foods, the Draft Guidance Document states that "present in the food supply" in section 413(a)(1) requires presence in conventional food and that presence in dietary supplements does not constitute presence in the food supply. As discussed above, this interpretation finds no support in the plain language of the Act. Nevertheless, the Draft Guidance Document attempts to suggest a policy-based rationale for its narrow interpretation:

> Interpreting 'food supply' to include dietary supplements for purposes of this exemption from the NDI notification requirement would expand the exception to the point that it would risk swallowing the rule, as prior use in even one dietary supplement manufactured in small quantities and distributed over a small area would exempt all dietary supplements containing the NDI from the notification requirement, even if the intake level and conditions of use were much different. Moreover, such an interpretation would not make sense in light of the purpose of the NDI notification requirement, which is to ensure that dietary ingredients that have not been widely consumed receive a safety evaluation before reaching the marketplace.[36]

In short, the Draft Guidance Document suggests that the presence of an NDI in conventional food would more readily reveal potential safety issues than presence of an NDI in dietary supplements. Taken to its logical extreme, this

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[35] See id. § 201(ff) (the exceptions are for purposes of sections 201(g) and 417).

[36] Draft Guidance (2016) at 23.

means that the presence of an NDI in a single conventional food at low levels and for a limited length of time would suffice to exempt that NDI from notification, whereas the presence of that NDI at substantial levels in potentially more widely consumed dietary supplements at much higher levels would not. This is an absurd result, particularly in light of the fact that the FDC Act and FDA's implementing regulations require that dietary supplement manufacturers determine that their product does not present a significant or unreasonable risk of illness or injury, monitor and evaluate complaints and adverse event reports associated with their product, and also submit serious adverse even reports to FDA—requirements that are not imposed on manufacturers of conventional foods.

Moreover, presence in a conventional food does not, as the Draft Guidance Document suggests, ensure that an ingredient "must meet the safety standards for conventional food ingredients, which are more demanding than those that apply to dietary ingredients used in dietary supplements."[37] FDA acknowledges that the "food supply" includes "ingredients marketed in conventional foods outside the U.S."[38] Thus, FDA essentially implies that a dietary ingredient in a dietary supplement marketed in the United States in compliance with the statutory and regulatory requirements of the FDC Act and its implementing regulations is less safe than an ingredient that is present in a conventional food marketed outside the United States in compliance with foreign regulatory requirements (if any) governing conventional foods. This cannot have been Congress' intent.

FDA's interpretation of "food supply" as including only conventional foods therefore has no basis in the text or aim of the statute. The Act explicitly states that a dietary supplement is a food, and there is no scientific rationale for suggesting that an ingredient's presence in a conventional food can provide a basis for a presumption of safety whereas its presence in a dietary supplement categorically cannot. By requiring NDI notification for ingredients that are present (in dietary supplements) in the food supply, FDA's approach arbitrarily imposes additional regulatory requirements where they are not necessary: indeed, regardless of NDI status or notification requirements, *every* dietary supplement – whether it contains a pre-DSHEA ingredient, an NDI exempt from notification, or a notified NDI – is required by law to be safe and unadulterated.[39]

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37 Id.

38 Id. at 24.

39 See e.g., FDC Act § 301(a), (b), (c) & (v).

B. "As an article used for food"

The Draft Guidance Document appears to interpret the term "article" in section 413(a)(1) to mean that an NDI must be present in the food supply as a "food ingredient," i.e., as a substance intentionally added for a technical or functional effect, in order for it to be exempt from the NDI notification requirement.[40]

We disagree. FDA's interpretation appears to be based on a misreading of the phrase "article used for food."[41] As discussed above, this phrase is a clear reference to the definition of "food" in section 201(f) of the Act. That definition includes "components" of any article used for food.[42] Therefore, a dietary ingredient that is present in the food supply as a component of any article used for food qualifies for the exemption from the NDI notification requirement, assuming the ingredient has not been chemically altered.

C. "Chemically altered"

1. A dietary ingredient is "chemically altered" when a covalent bond has been made or broken, changing the ingredient's chemical properties or reactivity.

The Act does not define the term "chemically altered". However, a plain reading of the text suggests that, for an NDI present in the food supply to be exempt from the notification requirement, it must have the same chemical properties and reactivity as the food or component of food that is present in the food supply. This interpretation is consistent with the obvious purpose of section 413, which is to ensure that FDA is made aware of the introduction into the food supply of dietary ingredients not already present in the food supply.

In relevant part, "chemistry" refers to the chemical properties and reactions of a substance.[43] To "alter" something is to make it different or to change or modify it.[44]

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[40] See e.g., Draft Guidance (2016) at 23; see also id. at 15 (providing the hypothetical "Ingredient X . . . a food additive that was approved for use to sweeten baked goods in 1993 and was marketed for that use before October 15, 1994" (emphasis added), and stating that a dietary supplement containing Ingredient X is exempt from NDI notification requirements in part "because Ingredient X has been present in the food supply as an article used for food . . . .").

[41] FDC Act § 413(a)(1).

[42] Id. § 201(f)(1).

[43] Webster's New Revised Unabridged Dictionary (1994).

Therefore, a dietary ingredient is "chemically altered" if there is a material change in, or modification of, its chemical properties or reactivity, as occurs with the making or breaking of a covalent bond. Where the chemical properties or reactivity of a dietary ingredient present in the food supply are modified, as with the making or breaking of a covalent bond, there might be an effect on the safety profile of that dietary ingredient, and under those circumstances the Act requires an NDI notification.

2. Manufacturing changes that, for example, merely distill or filter an ingredient, but that do not make or break a covalent bond, are not necessarily chemical alterations.

Although the Draft Guidance Document correctly focuses its interpretation of "chemically altered" on modifications that are likely to "affect the safety profile of the ingredient," it also includes a list of overly broad examples of manufacturing processes – other than those that make or break a covalent bond – which "FDA would likely consider to involve chemical alteration."[45] While some of the manufacturing processes, when applied to a specific ingredient, may materially alter the ingredient's properties and safety profile, we ask that the Draft Guidance Document be revised so as not to suggest that the listed manufacturing practices constitute chemical alteration in all cases.

For example, the Draft Guidance Document states that "[u]se of a botanical ingredient that is at a different life stage than the life stage of the botanical ingredient used as a conventional food" would "likely [be] consider[ed] to involve chemical alteration."[46] Although it may be true that, for certain botanicals, applying the same manufacturing process to starting materials at different levels of ripeness results in finished products with significantly different chemical properties and reactivity, we are not aware that this is true of most botanicals. Similarly, although "chromatography, distillation, and filtration"[47] of an ingredient may result in a substance with significantly different chemical properties and reactivity, that is not universally true. As such, if FDA will not withdraw the Draft Guidance Document in its entirety, we ask that these and other similar examples in section IV.B.4 of the Draft Guidance Document be revised to reflect specific manufacturing practices applied to specific ingredients. The examples should emphasize and explain the differences in properties and reactivity that result from

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44 Id.

45 Draft Guidance (2016) at 27, 25.

46 Id. at 25, 26.

47 Id. at 25.

the manufacturing change, and not the manufacturing change itself. For example: "When [manufacturing process] is applied to Ingredient A, the resulting Ingredient B has [specify relevant difference in chemical properties and reactivity]. If [manufacturing process] has the same or similar effect when applied to a given dietary ingredient, then the resulting dietary ingredient will likely be considered chemically altered."

This approach is consistent with the way other substances in food are defined and regulated. Numerous food additive regulations, GRAS listing and affirmation regulations, and USP monographs establish specifications for food substances by, for example, declaring the chemical name or identity of the substance rather than by establishing manufacturing process specifications or detailed starting material specifications. For example, FDA regulations recognize over 100 essential oils, oleoresins, and extractives as GRAS for their intended use in foods, listing only the common and botanical names of the plant.[48] Establishing more restrictive requirements for essential oils marketed as dietary supplements than for essential oils in conventional foods runs counter to the fundamental purpose of DSHEA. FDA should acknowledge that, in and of itself, the process by which an ingredient is produced is not always determinative of the finished product's characteristics.

3. Use of a different fermentation medium to culture a microorganism is not a chemical alteration.

The Draft Guidance Document suggests that "chemical alteration" includes culturing microorganisms "using a fermentation medium different from the one used to make conventional foods in the food supply."[49] Yet, when addressing the information necessary to demonstrate the safety of an NDI produced by fermentation, the Draft Guidance Document indicates the information should include genus, species, and strain, with no mention of the fermentation medium.[50]

The Agency's position regarding chemical alteration of a microorganism is inconsistent with well established standards.[51] That position is also inconsistent with

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48 See 21 C.F.R. § 182.20.

49 Draft Guidance (2016) at 26.

50 Id. at 86.

51 See e.g., John G. Holt (editor), Bergey's Manual of Determinative Bacteriology (1994); Bergey's Manual of Systematic Bacteriology, 2nd Ed., Springer, New York; see also G. Mogenson et al., Inventory of Microorganisms with a Documented History of Use in Food, 377 Bull. Int. Dairy Fed. 10:10-19 (2002).

FDA's regulations concerning microorganisms in food, which do not specify a fermentation medium.[52]

D. NDI Notification Submission Requirements

1. The NDI notification submission requirement is neither manufacturer-specific nor specific to individual dietary supplements.

Section 413(a)(2) of the Act provides for the submission of an NDI notification to FDA by "the manufacturer or distributor of the dietary ingredient or dietary supplement."[53] The use of the word "or" indicates that the requirement for submission of an NDI notification can be satisfied in full by the manufacturer of the NDI. Under section 402(f), a dietary supplement manufacturer has an independent obligation to ensure the safety of specific dietary supplements, including any dietary supplements formulated to contain a notified NDI, but nothing in the Act requires that each manufacturer, distributor, or marketer of a dietary supplement that contains a notified NDI must also submit a notification for its specific use of the NDI. Indeed, once the first NDI notification has been submitted and the NDI has entered the food supply, the exemption in section 413(a)(1) applies and no additional notifications for that ingredient are required.

2. FDA's interpretation of the NDI notification requirement is not supported by law, is overly burdensome, and may have the unintended consequence of disincentivizing NDI notifications.

The Draft Guidance Document states that, except under very limited circumstances, a dietary supplement manufacturer must submit a separate notification for each supplement that contains an NDI.[54] This conflicts with the plain text of the statute, which states that the notification requirement is ingredient-specific, not specific to the conditions of use or manufacture of the dietary supplement in which the NDI is used: i.e., the notification must provide the basis on which the manufacturer or distributor has

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[52] See FDA, Microorganisms and Microbial-Derived Ingredients Used in Food (Partial List), http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/MicroorganismsMicrobialDerivedIngredients/default.htm.

[53] FDC Act § 413(a)(2)(emphases added).

[54] See Draft Guidance (2016) at 29-30.

concluded that "*a* dietary supplement containing such dietary ingredient will reasonably be expected to be safe"[55]— not *the* dietary supplement formulation, dose, etc. that is the subject of the notification. Nevertheless, the Draft Guidance Document states that an NDI notification must specify – and only covers – the dose, daily intake level, target population, manufacturing process, and formulation of the to-be-marketed product.[56] Thus, in FDA's view, a botanical extract for which an NDI notification has been submitted to FDA may not be included in a dietary supplement that contains another dietary ingredient (even a pre-DSHEA dietary ingredient) unless the original NDI notification contemplated use of the botanical extract with the specific other dietary ingredient. FDA would require a separate NDI notification for the new formulation.

Moreover, the Draft Guidance Document states that a dietary supplement distributor or marketer cannot rely on an NDI notification submitted by the NDI's manufacturer unless that notification is specific to the distributor's or marketer's dietary supplement. And, for example, if one manufacturer submits an NDI notification for a botanical extract, FDA would require every other manufacturer of the extract to either submit its own NDI notification or obtain right of reference to the submitted notification, i.e., via the "NDI Master File," even if the proposed conditions of use of the NDI are the same as those in a previously submitted notification.

Although the Master File concept described in the Draft Guidance Document may reduce the regulatory burden of submitting multiple NDI notifications for the same ingredient, it is an unsatisfactory solution to a problem of the Agency's own invention. Neither the statute nor the public health requires NDI notification for every condition of use and by every manufacturer, distributor, and marketer. Indeed, by requiring separate notifications for each manufacturer, distributor, and marketer of an NDI, the Agency's regulation of NDIs would be more restrictive than its approach to GRAS affirmations and food additive approvals, where the entire food industry may rely on a single affirmation or approval.

The unintended effects of FDA's interpretation could undermine its goal of greater transparency and result in fewer (not more) NDI notifications. By enforcing its burdensome, unsupported approach, which requires a new notification for each use of an NDI, FDA might incentivize manufacturers to find other lawful but alternative means of introducing NDIs into the market. For example, a manufacturer seeking to market an NDI could conduct a GRAS assessment and, if the ingredient is GRAS for use in a food,

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[55] FDC Act § 413(a)(2)(emphases added).

[56] See Draft Guidance (2016) at 29-30.

market the NDI in a conventional food. The NDI could then be marketed in a dietary supplement and, under section 413(a)(1) of the Act, would be exempt from the NDI notification requirement by virtue of its presence in the food supply.

Rather than incentivize end runs around the NDI notification requirement by imposing unreasonable and extra-statutory formulation-, dose-, and manufacturer-specific notification requirements, FDA must apply the statute in a way that is consistent with the text and intent of DSHEA.

V. NDI Safety Standard

A. "Reasonably expected to be safe"

1. There is no basis to require that an NDI meet the safety standard applicable to food additives.

The Draft Guidance Document specifies the information to be included in an NDI notification, which generally tracks, and in some cases exceeds, the information that is required to be included in a food additive petition or GRAS notice. The Act provides no support for imposing more stringent safety requirements on dietary ingredients than on conventional food ingredients. To the contrary, DSHEA was intended in part to ensure that dietary ingredients would not be subject to regulation as food additives.[57] The Act imposes different safety standards on NDIs and conventional food ingredients: a conventional food ingredient must be "safe"—a standard that FDA regulations define in part to mean that "there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use."[58] By contrast, an NDI must "reasonably be expected to be safe" under the conditions of use specified in labeling.[59] Below are just a few examples of provisions in the Draft Guidance Document that impose more onerous requirements on NDIs than are imposed on conventional food ingredients.

Section VI of the Draft Guidance Document specifies that a substantial amount of characterizing and manufacturing information should be submitted not just for the NDI but also for the dietary supplement that contains the NDI. An NDI manufacturer cannot

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[57] See e.g., FDC Act § 201(s)(6) (excluding dietary ingredients from the definition of "food additive").

[58] 21 C.F.R. § 170.3(i).

[59] FDC Act § 413(a)(2).

be expected to have access to all of that information for the supplements in which the NDI will be used. Further, requiring information on the supplements in which the NDI will be used goes beyond what is required in food additive petitions and GRAS notices; those submissions do not require identification of the end user, nor information about the specific composition of the finished product in which the substance will be used.

On the topic of supporting an ingredient's safety based on "history of use," section VI.B.9 states that there is little scientific literature addressing the reliability of "history of use data" generally. Nonetheless, the Draft Guidance Document states that "FDA considers 25 years of widespread use to be the minimum to establish a history of safe use,"[60] and cites a related definition proposed in the European Union. The requirements and procedures applicable to premarket authorization and listing of certain foods for purposes of marketing in the European Union are irrelevant to the requirements and procedures applicable to premarket notifications for NDIs, which are subject to a different regulatory framework. Therefore, such references to European Union standards should be removed from the guidance. Instead of setting a fixed time which is longer than required for GRAS status, the history of safe use should be a reasonable period of time evaluated on a case by case basis.

2. Animal toxicity studies are not always necessary to support the safety of an NDI that does not have a history of use.

Section VI.B.20 specifies that toxicity studies in animals should be included in an NDI notification if there is no history of use data to substantiate safety.[61] Scientifically, however, animal studies are not always necessary to demonstrate the safety of such ingredients. For example, a probiotic that is an NDI but that can be shown to be sufficiently similar to a known, safe probiotic strain should not be required to undergo unnecessary animal toxicity studies. FDA's regulatory approach should recognize that alternate methods (other than animal toxicity studies) may be useful, and in some cases sufficient, to substantiate the safety of an NDI.

VI. Economic Impact

If enforced, FDA's interpretation of what constitutes a dietary ingredient and an NDI, and when an NDI Notification is required, would result in the temporary (or possibly permanent) removal from the market of a large number of dietary supplements that have not caused any known safety issues, but that are currently marketed based on

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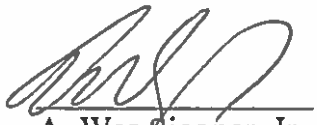
60 Draft Guidance (2016) at 71.

61 Id. at 77.

the industry's consistent, correct reading of the requirements of the FDC Act. Many small businesses and their products would be driven off the market, in part by the costs associated with the preparation of a successful NDI notification (and likely with each subsequent notification for the same ingredient), thus stifling innovation. The direct result will be a contraction of the dietary supplement industry, loss of profits, and loss of employment. In addition, there will be collateral costs to sectors of the industry that depend on the dietary supplement industry (e.g., truckers and retailers) and to consumers, who will be faced with higher prices and a reduced selection of dietary supplements. We therefore urge FDA to withdraw the 2016 and 2011 Draft Guidance Documents, to refrain from implementing its unsupported interpretations of the FDC Act, and to instead work with industry as it develops its own NDI guidance.

Sincerely,



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