

**Before the
U.S. Food and Drug Administration
Washington, D.C.**

***In re* Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Availability, 76 Fed. Reg. 39111 (July 5, 2011)**

Docket No. FDA-2011-D-0376

**COMMENTS OF
ALLIANCE FOR NATURAL HEALTH – USA**

Alliance for Natural Health – USA (ANH), by counsel and in response to the FDA's request for comments in the above-referenced docket, hereby submits this detailed assessment of the agency's draft Guidance document: "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues," published July 5, 2011. In the guidance, FDA provides its interpretation of 21 U.S.C. § 321(ff), 21 U.S.C. § 350b, and 21 C.F.R. § 190.6 concerning "new dietary ingredients" (hereinafter "NDI"). (1) The NDI guidance is in fact a new rule and, as such, is adopted in violation of the Administrative Procedure Act provisions requiring notice and comment rulemaking. (2) The NDI guidance is an ultra vires administrative action because it exceeds the plain and intended meaning of the NDI provisions of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 350b. (3) The NDI guidance is arbitrary and capricious agency action, and an abuse of discretion, because it interprets the NDI provisions of the Act in ways contrary to the plain language and intended meaning of the statute, imposing new and excessive burdens that have no rational relationship to the statutory purpose of the NDI provision and causing the NDI provisions to conflict with the statutory meaning of other DSHEA provisions. (4) The NDI

guidance imposes excessive and anticompetitive requirements on the regulated class that, if enforced, will cause catastrophic economic consequences, greatly reducing the availability of dietary supplements, reducing by a quarter to a half the number of companies in the supplement business, and causing widespread unemployment in this industry sector. *See* Exhibit A: Economic impact assessment of Emory University Professor of Law and Economics Dr. Joanna M. Shepherd Bailey. For those reasons, explained in detail below, the FDA should withdraw the proposed guidance at the earliest possible moment.

Contents

Background of the Commenter3

Comments4

 A. FDA violated the APA by promulgating its new NDI rules through guidance rather than through rule-making 4

 B. Congress intended to preserve access to new dietary ingredients and dietary supplements generally. The NDI Guidance dramatically decreases that access by imposing costly new burdens on the regulated class..... 6

 C. The FDA's Assessment of Economic Burdens is a Gross Underestimation 11

 D. The FDA’s requirement that an ingredient be specifically “marketed” as a dietary supplement to consumers or proceed through the NDI notification process is arbitrary and inconsistent with the plain language in 21 USC § 350b 20

 E. The FDA’s interpretation of the phrase "history of use" in Section 350b(a)(2) is arbitrary, capricious, and in conflict with the statutory text..... 25

 F. The FDA's new definition of the statutory term “chemically altered” is inconsistent with Congress’s expansive interpretation of the language, which was designed to allow for more (not less) dietary ingredients to be grandfathered or sold without notifications..... 27

G.	FDA’s position concerning food additives violates the plain and intended meaning of the DSHEA.....	32
1.	Food additives are articles present in the food supply.....	32
2.	FDA Has Imposed Food Additive Standards on Dietary Supplements.....	35
H.	Nothing in the DSHEA requires each company manufacturing a dietary supplement containing an NDI to file a separate notification and the requirement that each do so is arbitrary and capricious agency action	39
I.	FDA’s new position that synthetic botanical ingredients are NDIs is arbitrary and capricious.....	42
J.	The FDA’s position concerning dietary ingredients “authorized for investigation” is inconsistent with Congressional intent.....	45
	Conclusion	46

Background of the Commenter

The Alliance for Natural Health – USA (“ANH”) is a United States division of an international, not-for-profit, non-governmental organization with headquarters in Washington, D.C. ANH is the successor to the American Association for Health Freedom, which, in turn, is the successor to the American Preventive Medical Association founded in 1992. ANH's mission objectives include the promotion of natural health and consumer access to dietary supplements. ANH has a membership of over 177,000 activists, practitioners, medical doctors, scientists, business entities, consumers, and patients who variously manufacture, sell, distribute, recommend, and consume dietary supplements. ANH represents individuals and entities within the dietary supplement industry that are adversely affected by the FDA’s NDI Guidance. Its

members must comply with FDA's interpretations of the NDI statute (21 U.S.C. § 350b, 21 C.F.R. 190.6) as they pertain to existing dietary supplements and future products. Its dietary supplement manufacturer and distributor members are directly responsible for compliance with the NDI Guidance, whether through private labeling, distributing, or manufacturing directly. The NDI Guidance would require each member of the regulated class to prepare and file 75-day premarket notifications for each new dietary ingredient subject to 21 U.S.C. § 350b(a)(2).

The NDI guidance has an adverse impact on ANH's members because it limits access to consumer dietary supplements and imposes economic hardship on members of the industry. Requirements in the FDA's guidance mandate new NDI submissions and additional testing that imposes substantial compliance costs. Thus, ANH's members suffer concrete and particularized injury resulting directly from the NDI Guidance.

COMMENTS

A. FDA violated the APA by promulgating its new NDI rules through guidance rather than through rule-making

The federal courts disfavor the creation of administrative rules through guidance documents. *See, e.g., Alaska Professional Hunters Ass'n, Inc. v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999) (“[o]nce an agency gives its regulation an interpretation, it can only change that interpretation as it would formally modify the regulation itself: through the process of notice and comment rulemaking”). Administrative law distinguishes between interpretive and legislative rules. *See Connor N. Raso, Strategic or Sincere? Analyzing Agency Use of Guidance*

Documents, 119 YALE L.J. 782 (2010). To determine whether a rule is “legislative,” the courts examine whether the rule has a “legally binding” effect on industry. See William Funk, *A Primer on Nonlegislative Rules*, 53 Admin. L. Rev. 1321, 1326 (2001). A rule that meaningfully amends the text of an underlying legislative rule is unlikely to be deemed interpretive. See *Hemp Industries Ass’n v. DEA*, 333 F.3d 1082, 1087 (9th Cir. 2003).

The distinction may be critical, as interpretive rules are more difficult to challenge through judicial review. See *Raso, supra*, at 792. Under 21 U.S.C. § 371(h), FDA guidance documents are expressly non-binding on the FDA and industry. That statutory section presents an initial hurdle for pre-enforcement challenges. Nonetheless, guidance documents are frequently held to impose binding rules on industry despite the agency’s prefatory language. See *American Hosp. Ass’n v. Bowen*, 834 F.2d 1037, 1045-46 (D.C. Cir. 1987). “Substantive rules are ones which grant rights, impose obligations, or produce other significant effects on private interests ... or which effect a change in existing law or policy.” *Id.*; *Batterton v. Marshall*, 648 F.2d 694, 701-02 (D.C. Cir. 1980); *Alcaraz v. Block*, 746 F.2d 593, 613 (1984). “[C]ourts have said that, unless a pronouncement acts prospectively, it is a binding norm. Thus ... a statement of policy may not have a present effect: a general statement of policy is one that does not impose any rights and obligations...” *American Bus Ass’n v. U.S.*, 627 F.2d 525, 529 (1980).

As explained in detail below, the NDI Guidance is not interpretive, but is instead a substantive legislative rule, because it departs from FDA’s previous standards, alters the rights of the regulated class, and imposes new and costly obligations on them. The Guidance misconstrues the plain language of the DSHEA, and revises the agency’s prior interpretation of

the NDI statutory provision, to require an enormous increase in the number of, and degree of, scientific support needed for NDI notifications.

Companies that fail to comply with the specific provisions of the NDI guidance clearly market adulterated products. The binding nature of the NDI guidance is thus apparent. The FDA should comply with the requirements of the Administrative Procedure Act, 5 U.S.C. § 551 *et al.*, by relying on formal rulemaking as prescribed by the APA rather than on unilateral issuance of a guidance to declare new rules. *See* 5 U.S.C. § 553.

B. Congress intended to preserve access to new dietary ingredients and dietary supplements generally. The NDI Guidance dramatically decreases that access by imposing costly new burdens on the regulated class

In the DSHEA legislative history, Congress explained that “FDA tried to regulate vitamins by claiming they were toxic, and therefore their potencies could be regulated.” *See* Dietary Supplement Health and Education Act of 1994, S.Rep. 103-410, 103rd Cong. 2nd Sess. 1994 (Oct. 8, 1994), *available at*, 1994 WL 562259, at *15. Congress further explained:

Beginning in the late 1970s, FDA turned from drug potency arguments to enforcement attempts utilizing the “food additive theory” to prohibit the sale of supplements which bore no claims. Essentially, the theory was that any ingredient added to a capsule or tablet rendered the resulting dietary supplement a food additive because the ingredient was added to the capsule or tablet. Under this theory, FDA could not lose, as it needed only to furnish an affidavit from one of its scientists stating that experts generally did not regard the product as safe. The actual safety of the product was never at issue. *Id.*

Congress specifically found that FDA harbored a bias against dietary supplements, concluding:

FDA has had a long history of bias against dietary supplements... Despite a voluminous scientific record indicating the potential health benefits of dietary supplements, the [FDA] has pursued a heavy-handed enforcement agenda against dietary supplements for over 30 years. The agency’s approach has forced

Congress to intervene on two previous occasions, and yet again with adoption S. 784. *See* S. Rep. 103-410, 103rd Cong., 2nd Sess. 1994, *at*, 1994 WL 562259, *13, 15.

The FDA has repeatedly attempted for decades to eliminate dietary supplements from the market. “Between 1966 and 1973 ... FDA tried to classify vitamins as over-the-counter drugs.” *Id.* *at* 15. In the late 1970s, FDA “tried to regulate vitamins by claiming they were toxic and, therefore their potencies could be regulated.” *Id.* In the 1980s, the FDA issued proposed over-the-counter drug monographs for vitamins and minerals, “implicitly placing a potency limit on vitamins and minerals.” *Id.* Also, in the late 1970s, FDA adopted a “food additive theory” to prohibit the sale of supplements because “any ingredient added to a capsule or tablet rendered the resulting dietary supplement a food additive.” *Id.* Between 1986 and 1990, the FDA permitted four “health messages” for food products but left dietary supplements with a level of proof incapable of satisfaction. *Id.* “The level of proof required for dietary supplement claims was unrealistic in that the degree of scientific consensus and clinical data required eliminated almost all existing supplement claims.” *Id.*

In 1993, “FDA’s efforts to ban the safe dietary supplement of black currant oil by asserting that it was an unsafe food additive were rejected ... by two unanimous United States courts of appeal.” *Id.* (citing *United States v. Two Plastic Drums-Viponte Ltd. Black Currant Oil-Traco Labs, Inc.*, 984 F.2d 814 (7th Cir. 1993); *United States v. 29 Cartons of-an Article of Food-Oakmont Investment Co.*, 987 F.2d 33 (1st Cir. 1993)). The Seventh Circuit “described the FDA’s effort as an ‘Alice in Wonderland’ approach” and the “decision by the First Circuit described FDA’s approach as ‘nonsensical.’” *Id.*

In enacting the Dietary Supplement Health and Education Act (“DSHEA”) in 1993, Senator Hatch explained that:

For more than three decades, FDA has tried to restrict severely the ability of the dietary supplement industry to sell and market its products and, consequently, the ability of consumers to buy them. The agency has repeatedly attempted to impose unnecessary and stringent standards that would leave many if not most supplement companies with no practical choice but close their doors. The institutional animosity never made sense, but it is even less logical today in light of the growing body of scientific evidence regarding the disease prevention powers of nutrients. Unfortunately, the effect of the FDA’s heavyhanded policy is that consumers are left uninformed and the Nation pays millions of dollars for health care that could have been saved through disease prevention. ... In sum, over the last 30 years, FDA has tried to prevent consumer education regarding the disease prevention properties of vitamin A, vitamin C, vitamin E, and other dietary supplements and, at times, has attempted to assert that many of these products were unsafe.

See Statement of Orrin Hatch, Proceedings and Debates of the 103rd Congress, 139 Cong. Rec. S4561-02, at S4577 (Apr. 7, 1993), *available at*, 1993 WL 102951. Within that context, Congress intended the DSHEA to preserve consumer access to dietary supplements broadly. *See* Scott Bass & Emily Marden, *The New Dietary Ingredient Safety Provision of DSHEA: A Return to Congressional Intent*, 31 Am. J.L. & Med. 285, 287 (2005) (“DSHEA was premised on an affirmation of the role of nutrition and supplements in preventative health and is firmly grounded

in Congress' recognition that consumers want information about and access to a broad range of safe products").¹

The unambiguously expressed intent of Congress must be given effect by administrative agencies. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000). "In ascertaining the plain meaning of the statute, the court must look to the particular statutory language at issue, as well as the language and design of the statute as a whole." *K Mart Corp. v. Cartier, Inc.*, 486 U.S. 281, 291-92 (1988) (collecting cases). Under *Chevron*, deference is owed to the agency's interpretation of the statute only if the regulation or rule is not in conflict with the plain language of the statute. *See United States v. Boyle*, 469 U.S. 241, 246 (1985); *Chevron, USA, Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

The NDI provision aims by the proxy of a cut-off date, October 15, 1994, to render subject to premarket notification those dietary ingredients not previously marketed in dietary supplements or otherwise not chemically altered from food sources. In interpreting 21 U.S.C. § 350b, therefore, the FDA must link rules and interpretations to the ultimate goal expressed by Congress of maximizing the availability of dietary supplements absent affirmative evidence of a

¹ FDA Commissioner David Kessler once ordered the FDA not to enforce the DSHEA in hopes that Congress would repeal the law. *See* Peter Barton Hutt, "The History & Future of the Dietary Supplement Health & Education Act," *Natural Products Insider* (Sep. 1, 2009), *available at*, <http://www.naturalproductsinsider.com/articles/2009/09/the-history-future-of-the-dietary-supplement-health-education-act.aspx>.

lack of safety. Overly burdensome regulations not rationally related to ingredient safety bear no reasonable connection to Congressional intent.

The statutory section which governs NDIs is 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:

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

(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.

The Secretary shall keep confidential any information provided under paragraph (2) for 90 days following its receipt. After the expiration of such 90 days, the Secretary shall place such information on public display, except matters in the information which are trade secrets or otherwise confidential, commercial information.

(b) **PETITION.**—Any person may file with the Secretary a petition proposing the issuance of an order prescribing the conditions under which a new dietary ingredient under its intended conditions of use will reasonably be expected to be safe. The Secretary shall make a decision on such petition within 180 days of the date the petition is filed with the Secretary. For purposes of chapter 7 of title 5, United States Code, the decision of the Secretary shall be considered final agency action.

(c) **DEFINITION.**—For purposes of this section, the term “new dietary ingredient” means a dietary ingredient that was not marketed in the United States

before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994.

See 21 U.S.C. § 350b.

C. The FDA's Assessment of Economic Burdens is a Gross Underestimation

On June 3, 2011, the FDA called for comment on Agency Information Collection Activities concerning NDI notifications generally. *See* 76 Fed. Reg. 32214 (June 3, 2011). In its public notice, the FDA solicited comment concerning, *inter alia*, the accuracy of the FDA's estimated burden on the proposed NDI notifications and methods to minimize that burden. *Id.* The FDA's original estimate was deeply flawed as Exhibit A makes clear. The FDA (1) failed to account for the cost of removing from the market dietary supplements suddenly deemed New Dietary Ingredients for the first time in the Guidance; (2) substantially underestimated the number and cost of New Dietary Ingredient submissions that must be filed to comply with the Guidance; and (3) grossly and dangerously undervalued the economic impact the Guidance will have on the dietary supplement industry and the economy as a whole. *See* Comments of Alliance for Natural Health-USA, *In re Agency Information Collection Activities; Proposed Collection; Comment Requests; Premarket Notification for a New Dietary Ingredient*, 76 Fed. Reg. 32214, Dkt. No. FDA-2011-N-0410 (Aug. 2, 2011); *see also* Exhibit A.

The FDA had erroneously determined that, on a yearly basis, "55 respondents will submit one premarket notification each and that it will take a respondent 20 hours to prepare the notification, for a total of 1,100 hours" industry-wide per year. *See* 76 Fed. Reg. at 32215. In fact, the FDA's calculation grossly undervalued the burden on industry. In related comments, the

ANH-USA demonstrated through the expert economic impact report of Emory University professor of law and economics Dr. Joanna M. Shepherd Bailey, Ph.D., that the NDI Guidance would require between 100 and 350 hours of employee time per submission. Moreover, the expected total cost in employee time to prepare the petition would in fact be between \$845 million and \$6.1 billion. *See* Comments of Alliance for Natural Health-USA, *In re Agency Information Collection Activities; Proposed Collection; Comment Requests; Premarket Notification for a New Dietary Ingredient*, 76 Fed. Reg. 32214, Dkt. No. FDA-2011-N-0410 (Aug. 2, 2011) (Exhibit B). Moreover, Dr. Shepherd Bailey determined that because dietary supplements containing NDIs not qualified for exemption under 21 U.S.C. § 350b(a)(1) and (2) may not lawfully be sold (they are adulterated by operation of law) and because FDA has greatly expanded the NDI definition, between 22,240 and 41,700 dietary supplements would likely be removed from the market at an economic loss of between \$5.6 billion and \$10.5 billion.

Costs of NDI notifications will further surpass the FDA's erroneous calculation. *Id.* Dr. Shepherd Bailey estimated the animal and human product safety studies recommended by the FDA will cost between \$450,000 to \$6.6 million per NDI notification, resulting in a cost of between \$2 billion to over \$165 billion. Moreover, based on FDA's history of rejection and denial of prior NDI submissions, Dr. Shepherd Bailey concluded that 29,190 dietary supplements currently on the market would become unlawful for sale even after the 75-day notification process. The total economic impact of those denials could shrink the dietary supplement market by between 28 and 52.5 percent, producing an annual loss for the industry of between \$7.84 billion to \$14.7 billion. In a stressed national economy, the NDI Guidance could directly result

in the loss of between 55,720 and 104,475 jobs in the dietary supplement industry. Far from a "minimal burden on industry," FDA's NDI Guidance, as ANH-USA demonstrated, will have a substantial adverse economic impact, revealing that FDA has failed to comply with the requirements of the Regulatory Flexibility Act. *See* 76 Fed. Reg. at 32214-15.

Dr. Joanna M. Shepherd Bailey also determined that the NDI Guidance would adversely affect the entire economy, concluding:

The Guidance will cause a total economic loss of \$21.2 billion-\$39.8 billion annually in the economy. It will also cause 127,598-239,247 jobs to be lost throughout the U.S. economy. Moreover, it will result in a loss of \$1.84 billion - \$3.54 billion in federal tax revenues and a loss of \$1.64 billion - \$3.07 billion in state and local tax revenues.

Exhibit A.

FDA responded to comments concerning the economic burden on August 19, 2011. *See Agency Information Collection Activities; Submission for Office Management and Budget Review; Comment Request; Premarket Notification for a New Dietary Ingredient*, 76 Fed. Reg. 51986 (Aug. 19, 2011). Standing by its original erroneous estimations, the FDA stated that it

believes that there is minimal burden on the 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 as the basis for its conclusion that a dietary supplement containing an NDI will reasonably be expected to be safe.

Id. at 51987. The agency's foregoing conclusory assertion is not a serious economic assessment of impact and fails to explain rationally why its revised standards for NDIs have no significant impact. The FDA's economic impact assessment is thus an arbitrary and capricious agency evaluation contrary to the APA and the Regulatory Flexibility Act.

In FDA's Guidance at Part III (scope of the guidance), the agency declared the aim of the guidance to be an increase in 75-day notifications under Section 350b. The FDA claimed that in 16 years, there have been an estimated 55,600 dietary supplement products on the market, and FDA has received just 700 NDI notifications. *See* NDI Guidance at III. Moreover, "the Institute of Medicine has estimated that 1,000 new dietary supplements are introduced to the market each year." *Id.* Under the FDA Guidance, most if not all of those products must satisfy the notification requirements in Section 350b before they may be lawfully marketed. Yet in its August response to economic comments, the FDA contradicted itself, stating that only 55 submissions would be required per year. FDA arrived at that number by averaging the number of submissions received over the prior three years without the guidance in place (a bogus comparison). *See* 76 Fed. Reg. at 51987. Obviously reliance on the pre-Guidance submission record grossly underestimates submissions required post-Guidance when the very purpose of the guidance is to increase submissions. At a minimum, therefore, the guidance document renders the FDA's estimated burden arbitrary and capricious.

In addition, the FDA omits the costs companies incur when determining whether products must comply with 21 U.S.C. § 350b. FDA concerns itself only with those costs directly associated with the filing and processing of an NDI notification. *See* 76 Fed. Reg. at 51987. The exclusion of preparatory and background costs, which constitute the bulk of expense for the regulated class, is arbitrary and capricious. FDA cannot fairly release a draft guidance that greatly expands the reach of Section 350b, requires extensive testing above previous requirements, substantially limits the grandfathered dietary ingredient exemption, and

substantially increases the number of NDI notifications required, without recognizing the costs companies must incur to (1) determine whether existing or new products must meet the new standards and (2) compile data necessary to meet those heightened standards.

In similar fashion, the FDA expressly disregards the provisions of the new NDI guidance when reporting to the OMB. *See* 76 Fed. Reg. at 51988. The FDA focused solely on the requirement that companies submit 75-day notifications as articulated by 21 C.F.R. § 190.6. FDA's position is impossible to reconcile with the regulatory reality companies now face. 21 C.F.R. § 190.6(a) reiterates significant portions of the statutory text in 21 U.S.C. § 350b. Section 190.6 states that:

At least 75 days before introducing or delivering for introduction to interstate commerce a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered, the manufacturer or distributor of that supplement, or of the new dietary ingredient, shall submit to the Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820), Center for Food Safety and Applied Nutrition, Food and Drug Administration ..., information including any citation to published articles that 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.

21 C.F.R. § 190.6(a). Because the FDA's NDI Guidance expands the reach of 21 C.F.R. § 190.6, the draft guidance substantively amends and modifies Section 190.6. In its August 19th response, the FDA offers no reasoned basis to disregard the obvious import of the draft guidance in its calculation of economic burden. By failing to address the new expansive reach of the NDI guidance, the FDA misled the Office of Management and Budget in its presentation of economic burdens, violating the Paperwork Reduction Act of 1995.

Indeed, had FDA been truthful and revealed the full economic impact of the NDI Guidance, as explained in Dr. Shepherd Bailey's analysis, it would undermine entirely the rather superficial notion that the Guidance is merely a non-binding interpretive, rather than a binding substantive legislative rule.

The FDA is further incorrect by assuming companies should already possess the requisite documentation to complete a 75-day NDI notification under the new NDI guidance. The FD&C Act, as amended by DSHEA, requires a manufacturer or distributor of a dietary supplement containing an NDI to possess evidence that the dietary supplement will reasonably be expected to be safe. *See* 21 U.S.C. § 350b. Section 113(b) of the FDA Food Safety Modernization Act (“FSMA”) (Public Law 111-353) requires the FDA to publish a guidance clarifying when a dietary supplement ingredient is an NDI, when the manufacturer or distributor of a dietary ingredient or dietary supplement should submit an NDI notification to FDA under 21 U.S.C. § 350b, the evidence needed to document the safety of an NDI, and appropriate methods for establishing the identity of an NDI.

FDA's NDI Guidance represents the Agency's first comprehensive interpretation of the provision and, as explained in this comment, the FDA has substantially altered the plain and intended meaning of key terms in section 350b, including the term “dietary ingredient” and “chemically altered.” Whether a company had sufficient information to fulfill its obligations under the FD&C Act before the guidance is irrelevant. The relevant inquiry is whether companies should have in their possession the heightened evidence now required by the FDA in the new guidance. Because the guidance expands the number of dietary ingredients that would

be considered "new" as opposed to "grandfathered," the conclusion that supplement companies would already possess the requisite data to fulfill a 75-day notification is a non-sequitur. The type of evidence required to prove that a dietary ingredient is grandfathered (e.g., marketing information) is different from that required to show safety (e.g., toxicology tests). Moreover, the express Guidance delineation of the kind, nature, and degree of evidence required to support an NDI notification is new and is a heightened burden of proof beyond that reflected in the statutory language, which seeks no greater proof than that which would indicate that the dietary supplement containing the dietary ingredient would "reasonably be expected to be safe."

Contrary to the plain and intended meaning of section 350b, the Guidance necessitates the filing of multiple NDI notifications for the same ingredient when used in a supplement containing other dietary ingredients that are not NDIs (Guidance at IV(C)(1)) or when the target population for the dietary supplement changes (Guidance at IV(C)(1)). Moreover, if an NDI is permitted to be marketed, FDA's allowance applies only to the manufacturer which sought permission and to no others that wish to sell the very same NDI (Guidance at IV (D)(1)). Additionally, the FDA concludes that a synthetic copy of a constituent of a botanical is not even a dietary ingredient (Guidance at IV(D)(2)). Each of these determinations constitutes a new and markedly arbitrary and capricious requirement resulting in an unnecessary diminution in the availability of safe dietary ingredients for the consuming public.

The agency's redefinition of key terms in section 350b achieves the Agency's underlying, albeit unarticulated, objective of expanding the definition of an NDI and, thus, constricting the exemption in section 350b(a)(1), thereby satisfying its aim to force the filing of more NDI

notifications. Because the Guidance greatly expands the meaning of the term “NDI,” thousands of dietary supplements in the marketplace, presumed lawful by the industry and consumed safely for years (including back to 1994), are now adulterated by operation of law under the Agency’s “current thinking,” explained in the Guidance at IV(B)(1); IV(B)(3); and IV(B)(4), and must be removed from the market. Specifically, Dr. Shepherd Bailey expects between 22,240 and 41,700 dietary supplements would be rendered adulterated under the Guidance and would have to be removed from the market costing between \$5.6 billion and \$10.5 billion.

Because FDA has expanded the data requirements necessary to comply with Section 350b and 21 C.F.R. § 190.6, and has substantially expanded the number of dietary supplements that must comply with Section 350b and 21 C.F.R. § 190.6, the agency cannot rationally conclude that companies will not be required to incur considerable costs in response. The FD&C Act imposes no existing duty on companies to maintain the specific quantitative and qualitative safety data that would be required to satisfy the FDA's new guidance document. Any requirement to maintain such information comes from the FDA’s interpretation of Section 350b of the FD&C Act, which is explained in detail for the first time in the NDI Guidance.

21 U.S.C. § 350b requires that companies maintain evidence of safety. Before the FDA issued its NDI Guidance interpreting Section 350b, however, companies were under no obligation to maintain the breadth of information now required. FDA cannot assume that companies have possessed or maintained such information in the ordinary course when there was no clear regulatory requirement to that effect before issuance of the Guidance. FDA therefore errs when it assumes the NDI Guidance or 21 C.F.R. § 190.6 would impose only minimal

burdens on industry. The Guidance imposes substantial new burdens because it expands the information FDA deems necessary to prove compliance under Section 350b.

The NDI Guidance prescribes costly proof requirements nowhere required by the statute, making it certain that many supplements now redefined as NDIs will remain off of the market even after manufacturers and distributors pursue the 75-day notification process. In addition to the data companies already possess, Dr. Shepherd Bailey estimates the animal and human product safety studies now demanded by the FDA will cost between \$450,000 to \$6.6 million per NDI notification, resulting in a cost of between \$2 billion to over \$165 billion. Dr. Shepherd Bailey further estimates that the regulated industry must spend between \$845 million and \$6.1 billion to prepare NDI notifications, and industry will lose between \$2.3 and \$4.3 billion after submitting NDI notifications because dietary supplements featured in notifications cannot be marketed during the 75-day statutory period. Finally, FDA's historic predisposition to reject most NDI notifications will cause even more financial loss. Based on Dr. Shepherd Bailey's review of FDA's rejection of NDI notifications for form or substance, 75-day notifications rejected by the FDA could shrink the market by 28 to 52.5 percent, amounting to an annual loss of between \$7.84 and \$14.7 billion for the industry, and a loss of between 55,700 and 104,475 workers in the industry.

In fashioning its estimate of the burdens on industry, the FDA has simply ignored the real possibility that its new guidance document will require companies to compile far more data than they may already possess. *See, e.g.*, 21 U.S.C. § 342 (adulterated food); *Id.* at § 343 (statements of nutritional support).

D. The FDA's requirement that an ingredient be specifically "marketed" as a dietary supplement to consumers or proceed through the NDI notification process is arbitrary and inconsistent with the plain language in 21 USC § 350b

FDA's position that a dietary ingredient must have been marketed to consumers as a dietary supplement or for use in dietary supplements is arbitrary and capricious, an abuse of discretion, and in contradiction to the plain meaning of the DSHEA. The agency considers "marketing" a dietary ingredient to mean "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." See NDI Guidance, at IV.A.6. Thus, the FDA is focused solely on whether the ingredient was itself marketed as a *dietary supplement*. Under this tortured view, the agency classifies all dietary ingredients contained in dietary supplements sold before October 15, 1994, but not marketed as the dietary supplement itself to be ineligible for grandfathered status. This constrained definitional approach shifts the focus from dietary ingredients to dietary supplements. It is plain from the statutory language in 21 U.S.C. § 350b(c) that Congress contemplated exemption from NDI notification requirements for dietary ingredients in the food supply where they would not be marketed as the food. To argue that dietary ingredients in dietary supplements marketed before October 15, 1994, are not grandfathered because the ingredients themselves were not marketed as supplements renders the provision inherently contradictory and reveals the new rule to be arbitrary and capricious.

The aim of Congress was not to deem unlawful dietary ingredients marketed within dietary supplements before the cut-off date but to grandfather them. The focus is on preventing new or novel ingredients for which there is no history of safe consumption from being introduced into the market, not to bar them based on a technical distinction having no bearing whatsoever on safety (that the ingredient was itself not marketed as a dietary supplement). That is an academic distinction having no substantive import to protecting consumers, but it does have a profoundly debilitating effect on the industry. That absurd distinction in the Guidance is quintessentially arbitrary and capricious and an abuse of agency discretion.

FDA's new interpretation is explained with reliance on the "grandfathered" provision of Section 350b. *See* NDI Guidance, Part IV.A.9. FDA explains that "[u]nless the ingredient was marketed as a dietary ingredient for use in a dietary supplement prior to October 15, 1994, it is an NDI." *Id.* That conclusion is a distortion of the statutory text of DSHEA. In 21 U.S.C. § 350b(c), Congress defined "new dietary ingredient" by reference to a "dietary *ingredient* that was not marketed in the United States before October 15, 1994..." (emphasis added). Congress explicitly stated that a "new dietary ingredient" was *not* a "dietary ingredient which was *marketed in* the United States before October 15, 1994." 21 U.S.C. § 350b(c). The statutory definition of "new dietary ingredient" is clear; there is no ambiguity. Congress drafted the exclusion to include dietary ingredients which were "marketed in" the United States, not "marketed as" dietary supplements. *But see Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000) (holding that, in context of IND exception in 21 U.S.C. § 321(ff)(3), use of the words "marketed as" were specific to the dietary ingredient itself).

Merriam-Webster's dictionary defines "market" as follows: "to expose for sale in a market." Used as a verb, the word "market" is synonymous with "sell." *See* Merriam Webster's Dictionary, Online Query "Market." There is simply no language in Section 350b that requires a dietary ingredient to have been "marketed as" a dietary supplement, or marketed for use in dietary supplements, in order to be grandfathered. The FDA's revision of the DSHEA is a transparent attempt to limit the class of dietary ingredients eligible for the grandfathered exclusion. Contrary to the FDA's position, the plain meaning of Section 350b(c) is that a dietary ingredient sold in the food supply before October 1994, whether as an ingredient in food or in dietary supplements, is grandfathered and excluded from the NDI provisions in Section 350b.

Perhaps Congress never included the FDA's specific language because it had little to do with the purposes of the NDI statute. The NDI statute is designed to promote safety for "new" dietary ingredients that have not been previously consumed by United States consumers. New dietary ingredients are properly marketed if "[t]here is a history of use or other evidence of safety" concerning the ingredient in the United States. *See* 21 U.S.C. § 350b(a)(2). Dietary ingredients are a broader category of "articles" consumed by humans in the food supply. Apples and oranges are nothing but compendia of dietary ingredients that have been consumed for ages. If a dietary ingredient has been present in the food supply before October 15, 1994, then Congress tacitly recognized that there would be no need to demonstrate safety for such ingredients that had been consumed, whether or not the ingredient had been specifically promoted to consumers. In short, whether the ingredient is specifically marketed to consumers has no relation to the ingredient's safety when consumed in food or dietary supplements.

Beyond legislative revisionism, the FDA's new interpretation of Section 350b(a)(1) is at odds with FDA's "marketed as" interpretation of the grandfathered provision in Section 350b(c). Section 350b(a)(1) states that a dietary supplement containing an NDI is adulterated unless

The dietary supplement contains only dietary ingredients which have been present in the food supply *as an article used for food* in a form in which the food has not been chemically altered.

See 21 U.S.C. § 350b(a)(1) (emphasis added). Section 350b(a)(1) provides an exclusion to the notification provisions in Section 350b(a)(2).

The FDA's guidance is silent on the term "articles used for food." That silence is surprising given the inconsistency in FDA's analysis of the grandfathered provision. In logic, there is no difference between a grandfathered dietary ingredient and a new dietary ingredient exempted from the NDI notification procedure. Exempted NDIs may be marketed in the same fashion as grandfathered dietary ingredients, provided they are in a form not chemically altered. The significant analysis, therefore, turns on whether an ingredient must follow the 75-day notification procedure. Under Section 350b(a)(1), no dietary supplement is subject to the notification requirements if its ingredients were "used for food in a form which the food has not been chemically altered." Whether a notification is required depends, therefore, on whether the dietary ingredient was "used for food..."

Consequently, the FDA's interpretation of the "marketed" language in Section 350b(c) is at odds with the "used for food" language in Section 350b(a)(1). In context with *new* dietary ingredients, the question is whether the ingredient was merely "present in the food supply." 21 U.S.C. § 350b(a)(1). Yet, in context with grandfathered ingredients, the question becomes

whether the ingredient was specifically *marketed to* consumers in a dietary supplement or for the ingredient itself. FDA would thus impose a *greater* burden on industry to market grandfathered ingredients than new dietary ingredients that were "used for food."

Even assuming the statutory text was in some way ambiguous, principles of statutory construction require that the provisions of a document be interpreted in a way that renders them harmonious, not contradictory. *See Erlenbaugh v. U.S.*, 409 U.S. 239, 244 (1972) (holding that statutory sections should be construed together); *Northern Natural Gas Co. v. Grounds*, 441 F.2d 704 (10th Cir. 1971). If possible, no interpretation should be adopted that renders the provision in question, or any other provision, superfluous, unlawful, or invalid. *See Planned Parenthood of Idaho, Inc. v. Wasden*, 376 F.3d 908, 928-29 (2004) ("it is a cardinal principle of statutory construction that a statute ought, upon the whole, to be so construed that, if it can be prevented, no clause, sentence, or word shall be superfluous, void, or insignificant").

FDA's "marketed as" language conflicts with the NDI statute because it renders superfluous the text in 21 U.S.C. § 350b(a)(1). The agency's "marketed as" phrase appears nowhere in the NDI statute. *See* 21 U.S.C. § 350b. Section 350b(a)(1) requires NDI notifications only for those ingredients that have not been "present in the food supply as an *article used for food* in a form in which the food has not been chemically altered." Noticeably absent from the statutory language is any requirement that the NDI be marketed as a food by itself, or marketed for its specific components. A food component when consumed with the whole food is unquestionably used as food.

E. The FDA's interpretation of the phrase "history of use" in Section 350b(a)(2) is arbitrary, capricious, and in conflict with the statutory text

Section 350b is also silent concerning the limits of the phrase "history of use or other evidence of safety," an element of 75-day NDI notifications. *See* 21 U.S.C. § 350b(a)(2). A "new" dietary ingredient cannot be marketed absent proof, through the 75-day notification, that the ingredient has a history of safe use or is expected to be safe based on scientific evidence. Under FDA's interpretation of the phrase "history of safe use," only products with a history of safe use over a period of *at least* "25 years of widespread use" can be marketed under the "safe use" category. Here, FDA's interpretation is arbitrary, capricious, and inconsistent with the statutory language. *See Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29, 43 (1983).

The FDA's 25 year minimum has again nullified, or rendered superfluous, language in the DSHEA. Enacted in 1994, the DSHEA grandfathers and exempts from the 75-day notification process in Section 350b(a)(2) all dietary ingredients that were "marketed in the United States before October 15, 1994." *See* 21 U.S.C. § 350b(c). Thus, a dietary ingredient marketed in the United States in December 1993 is grandfathered and exempted from the notification requirement. Yet, according to the FDA, a new ingredient marketed in the United States in December 2011 must possess a history of safe use beyond December 1986 to establish a so-called "history of use" sufficient under Section 350b(a)(2). Of course, such an ingredient would be grandfathered and, so, the "history of use" criteria in Section 350(b)(a)(2) would be entirely superfluous. By requiring record evidence of safe use dating beyond 25 years, the FDA has

effectively precluded application of the "history of use" criteria in Section 350b. To the extent a history of safe use is even possible or practical beyond 1994, grandfathered status would be satisfied. Statutory interpretations that render statutory text superfluous are unreasonable as a matter of law. *See Bilski v. Kappos*, 130 S.Ct. 3218, 3228-29 (2010) (citing *Corley v. United States*, 129 S.Ct. 1558, 1566 (2009)).

The FDA's newfound 25-year requirement is unsupported by any facts. FDA simply has no factual basis to conclude that Congress intended a history of safe use to require a minimum period of years, particularly a minimum period that would grossly exceed the temporal span of Section 350b(c)'s grandfathered clause. *See* NDI Guidance, Part VI(B)(9) (explaining that "the agency considers 25 years of widespread use to be the minimum to establish a history of safe use"). FDA has no factual basis to conclude that a dietary supplement marketed safely for 25 years has exhibited sufficient safety when an identical product marketed for 24 years has not. Even assuming the FDA's interpretation of Section 350b(a)(2) did not nullify the plain statutory meaning, the agency's approach is arbitrary and capricious. Without reasoned explanation, the FDA's interpretation is by definition arbitrary. *See, e.g., DeFrancesch v. Employers Mut. Cas. Co.*, 2008 WL 1930450, at *3 (E.D.La. 2008) (explaining that "[a]n 'arbitrary' act is an act 'based on random choice or personal whim, rather than any reason or system'"); *see also Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29, 43 (1983); *Burlington Truck Lines, Inc. v. U.S.*, 371 U.S. 156 (1962) ("[t]he agency must explain the evidence which is available"); *McDonnell Douglas Corp. v. U.S. Dep't of the Air Force*, 375

F.3d 1182, 1187 (D.C. Cir. 2004) (the "Court will not defer to the agency's conclusory or unsupported allegations").

A federal agency must "examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *State Farm*, 463 U.S. at 43. Here the FDA has performed no examination of relevant data, except to conclude that "little scientific literature address[es] this topic." *See* NDI Guidance, at Part VI(B)(9). FDA failed to explain how that "little scientific literature" forms the basis for the 25-year minimum history of use requirement.

F. The FDA's new definition of the statutory term "chemically altered" is inconsistent with Congress's expansive interpretation of the language, which was designed to allow for more (not less) dietary ingredients to be grandfathered or sold without notifications

The FDA's interpretation of "chemically altered" shifts the burden from FDA to manufacturers to prove products are not adulterated. 21 USC § 350b states that a dietary supplement is deemed "adulterated" unless, under Section 350b(a)(1), the ingredient was "present in the food supply as an article used for food in a form in which the food *has not been chemically altered.*" FDA then enumerates a list of common manufacturing processes that render a product "chemically altered." That list of processes includes, but is not limited to:

- Application of nanotechnology that results in new or altered properties of the ingredient (Guidance at IV.A.12; IV.B.4);
- Use of solvents other than water or aqueous ethanol (tincture) to make an extract (Guidance at IV.B.4);

- High temperature baking or cooking an ingredient that has not previously been baked or cooked, unless the process causes only minor loss of volatile components (Guidance at IV.B.4);
- Changing agricultural or fermentation conditions to alter the chemical composition of the ingredient, such as by sprouting garlic or fermenting yeast using a medium containing large amounts of sodium selenite to create large amounts of organic selenium compounds (Guidance at IV.B.4);
- Fermentation using a fermentation medium different from the one used to make a conventional food in the food supply (e.g., use of a defined commercial growth medium to produce a microorganism previously made by fermenting milk into dairy products like yogurt or cheese) (Guidance at IV.B.4); or
- Use of botanical ingredients that is at a different life stage than previously used (e.g., making an extract from unripe instead of ripe apples or using the mycellum instead of the fruiting body of a fungus) (Guidance at IV.B.4).

In short, only the most basic manufacturing methods would not chemically alter an ingredient (e.g., dehydration, lyophilization, milling). The result is to deny use of innovations that leave the biochemistry of ingredients unchanged but that involve new modalities for production. Under the NDI Guidance, many commercial-scale manufacturers will be deemed to have chemically altered products through use of common manufacturing methods. FDA would require that those manufacturers submit a 75-notification. A notification requires that companies

prove their manufacturing methods to be consistent with conventional methods sufficient to complete a 75-day notification. Indeed, a company can avoid a burdensome 75-day only by proving to FDA that the product is not "chemically altered" and, thus, not adulterated absent an NDI. That shifts FDA's burden in 21 USC 342(f) to prove adulteration, which Congress unmistakably placed on the agency. Default lists of processes which render a product "chemically altered," therefore, unlawfully shift to the manufacturer FDA's burden to prove adulteration. Congress placed the onus on FDA to show that a manufacturing methodology leads to an adulterated product. It did not require that industry prove that its products were unadulterated, proving a negative is oftentimes impossible.

Nothing in the statutory definition of "dietary supplement" or "dietary ingredient" or in any provision of the FDCA reveals that Congress intended to restrict dietary ingredients based on the "process by which the ingredient is obtained, synthesized, or otherwise processed." *See Bass & Marden, supra*, at 295. Rather, the DSHEA's emphasis is on ingredient safety. The FDA's interpretation of "chemically altered" should depend on safety. 75-day notifications should be required only where the process of "chemical alteration," by any method of manufacture, results in an output that is *chemically distinct* from the source ingredient, thereby raising a question of safety. Thus, chemical identity should be the FDA's primary concern. A product cannot be chemically altered unless the end product is molecularly distinct. The use of different solvents, baking temperatures, agricultural conditions, or extraction methods cannot implicate Congress's concerns in 21 U.S.C. § 350b(a) unless the final molecule is distinct as a result of the manufacturing process. Indeed, in the context of generic drugs, the FDA considers

bioequivalency--not safety--the primary factor. *See, e.g.*, 21 CFR Parts 314, 320; FDA, "Generic Drugs: Questions and Answers." ANDA applications are generally not required to include data to establish safety and effectiveness. FDA far exceeds Congress's intent in the DSHEA when it imposes greater obstacles on dietary supplement manufacturers than it does pharmaceutical manufacturers of generic drug products.

Despite Congressional intent, the FDA's strict interpretation of the phrase "chemically altered" stifles innovation and promotes an unworkable scheme, thus constituting arbitrary and capricious agency action and an abuse of discretion. The FDA presently possesses authority to act against adulterated dietary supplements that present safety risks. *See* 21 U.S.C. § 342(a). Under the NDI Guidance, innovations in manufacturing processes that enhance safety or purity of products would render the resulting ingredients new dietary ingredients, even in instances where the biochemical identity of the ingredient resulting from the new processes is the very same as that resulting from historic processes. Thus, widespread use of a novel manufacturing technology would effectively eliminate the category of grandfathered dietary ingredients. *See* NDI Guidance at Part IV.B. Innovation will thus be retarded or prevented altogether through this arbitrary imposition of agency proscriptive power.

Because the FDA's interpretation of the NDI statute compels 75-day notices for every *dietary supplement* which includes an NDI, no global notification could satisfy all products made from new procedures.

The result is a legal requirement that companies submit a new 75-day notification for every dietary supplement manufactured using a novel methodology, whether or not the end

ingredient was nutritionally equivalent to the original grandfathered ingredient, or presented any new safety risks. The FDA should not create legal impediments to innovation and compel reliance on outdated technologies. The promotion of innovation should be a crucial factor in FDA's approach. *See* Robert D. Atkinson & Daniel D. Castro, *A National Technology Agenda for the New Administration*, 11 YALE J.L. & TECH. 190 (2009) (stating that "an increasing number of economists have come to see technological innovation as the key to higher standards of living"). The executive branch should promote innovation as part of its economic agenda. To accomplish that, the agencies need to "establish robust policies that encourage innovation on the supply side, by supporting science, technology, engineering, and mathematics education and research, and on the demand side, by creating the conditions and incentives to spur more innovation." *Id.*; *see also* Stuart Minor Benjamin, *Fixing Innovation Policy: A Structural Perspective*, 77 GEO. WASH. L. REV. 1, 8 (2008) (explaining that the promotion of innovation is essential to fostering education, political, and social development). The FDA's NDI Guidance is thus a step backwards in economic policy.

Finally, the NDI Guidance promotes an unworkable standard that cannot be coherently or consistently enforced. The Supreme Court has addressed "unworkable" standards in the context of the doctrine of stare decisis. *See* Lauren Vicki Stark, *The Unworkable Unworkability Test*, 80 N.Y.U. L. REV. 1665, 1671 (2005). Federal courts must examine whether precedent can be interpreted and applied in a workable fashion. An "unworkable" standard is one that creates "inherent confusion" in the law. *See Patterson v. McLean Credit Union*, 491 U.S. 164, 173 (1989). Precedent is "unworkable" when courts cannot apply it coherently or consistently. *See*

Hudson v. United States, 522 U.S. 93, 102 (1997); Stark, *supra*, at 1672. Similarly, in the administrative context, agencies must enact standards that can be predictably enforced in a consistent and coherent fashion. See *U.S. v. Transp. Union v. Lewis*, 711 F.2d 233, 242 (D.C. Cir. 1983) (holding that an agency is entitled to no deference under the APA for statutory constructions that an agency itself has not or could not adhere to).

FDA provides no guidance concerning the acceptable degree of "chemical alteration," if any. Chemical alteration is by itself a term subject to considerable variation in definition. Accordingly, decisions regarding whether a process has resulted in chemical alteration would result in uneven enforcement. Uncertain of whether FDA will regard any particular process as begetting new dietary ingredients, companies can only ensure compliance with federal regulations by submitting NDI notifications in every instance. The influx of NDI notifications and the agency's ad hoc decisions concerning chemical alteration creates an unworkable regulatory regime that unnecessarily burdens the agency and industry. By requiring that NDI notifications be submitted for each dietary supplement, by each company, the FDA has enacted an unworkable and inherently irrational scheme lacking objective enforcement standards.

G. FDA's position concerning food additives violates the plain and intended meaning of the DSHEA

1. Food additives are articles present in the food supply

FDA's Guidance states that a substance present in a pre-DSHEA dietary supplement or in the food supply *as a food additive* rather than as a *dietary ingredient* is an NDI if marketed as a dietary ingredient. See NDI Guidance at Part IV.A.5. FDA explains that "if [a] substance was

present in the pre-DSHEA dietary supplement as a food additive rather than 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, then it would be an NDI." *Id.* FDA's position concerns "components" of dietary supplements that were marketed in the United States before October 15, 1994. In other words, although a dietary ingredient was present in the food supply as a component of a dietary supplement, even if the ingredient had been used as a food additive and the ingredient met FDA's more rigorous GRAS standard as a food additive, the ingredient would still be classified as a new dietary ingredient subject to 21 U.S.C. § 350b.

This position is arbitrary and capricious because it conflicts with historical precedent and imputes the narrow "marketed as" language to restrict lawfully sold food additives. Presence in the food supply is the operative analysis, not whether an additive has been specifically marketed within a dietary supplement. That point notwithstanding, the FDA's decision to label certain food additives as "new" ingredients ignores the central purpose of the NDI statute: safety. *See generally*, 21 U.S.C. §350b.

The statutory burden imposed on food additives is more stringent than statutory provisions governing dietary ingredients. Food additives must be generally recognized as safe (GRAS) as determined by the FDA through premarket approval. Under FDA's food additive regulations, the burden on industry to show general recognition of safety is high; high enough for Congress to expressly bar the FDA from employing the food additive standards in the dietary supplement context. Congress's emphasis in the DSHEA was to improve access to dietary supplements by preventing the FDA from classifying them as food additives. *See S. Rep. 103-*

410, 1994 WL 562259, *32 (Oct. 8, 1994) (explaining that "Supplements are not drugs or food additives"); 139 Cong. Rec. E919-03, 1993 WL 103003, at *E920 (April 7, 1993). Through the DSHEA, Congress rejected FDA attempts to regulate dietary supplements through food additive regulations. In 1994, Congress observed that

Beginning in the late 1970s, FDA turned from drug potency arguments to enforcement attempts utilizing the "food additive theory" to prohibit the sale of supplements which bore no claims. Essentially, the theory was that any ingredient added to a capsule or tablet rendered the resulting dietary supplement a food additive because the ingredient was added to the capsule or tablet. Under this theory, FDA could not lose, as it needed only to furnish an affidavit from one of its scientists stating that experts generally did not regard the product as safe. The actual safety of the product was never at issue.

See S.Rep. 103-410, 1994 WL 562259, at *14. The same concerns are raised by the new NDI Guidance if FDA can require essentially the same threshold showing of safety for NDIs as it would food additives. If the focus is on safety, prior satisfaction of the heightened food additive standard ought to meet the NDI standards.

If a dietary ingredient was present in the food supply as a food additive then, *a fortiori*, it should be considered (1) safe for consumption and (2) present in the food supply. Failing to accept food additives as articles present in the food supply is a semantic distinction unsupported by logic. It is arbitrary and capricious agency action and an abuse of discretion. Food additives that were determined GRAS and ingested by consumers as part of a pre-DSHEA dietary supplement are grandfathered ingredients.

2. *FDA Has Imposed Food Additive Standards on Dietary Supplements*

In the NDI Guidance the FDA has projected its food additive standards onto new dietary ingredients. The result is a de facto pre-market approval process for new dietary ingredients that requires industry to produce equivalent data that would be required to achieve GRAS status.

The FDA's guidance broadly defines NDIs so that almost every new ingredient will be subject to the NDI regulations. If the safety standards are equivalent to food additives, then the NDI Guidance comes at considerable cost for industry. In 1994, Congress determined that "[t]he cost to a manufacturer to prepare a food additive petition can run to \$2 million." *See* S.Rep. 103-410, 1994 WL 562259, at *19 (Oct. 8, 1994). Congress made those findings as it prohibited FDA from imposing food additive standards on dietary supplements. *Id.*

FDA now demands extensive documentation in association with 75-day premarket notifications. FDA's ability to reject notifications on procedural grounds (e.g., that required information is lacking) combined with the substantial data requirements akin to food additive GRAS-affirmance, imposes a substantial burden to market entry that is directly analogous to the FDA's food additive regulations. FDA states that "[a]n incomplete notification does not satisfy the notification requirement found in section 413(a)(2) of the FD&C Act, and therefore, if the dietary supplement containing the NDI is marketed, it is deemed to be adulterated.." *See* NDI Guidance, at Part V(B)(2). FDA even suggests that human clinical studies would be required in some instances to prove safety. *Id.* at Section VI(B)(37). In short, the FDA has required that manufacturers produce the same data in a 75-day notification as would be required in a GRAS submission. This is in direct conflict with the legislative history of DSHEA.

A comparison of the food additive and dietary ingredient standards reveals little difference in FDA's approach to safety determinations. Section five of the NDI guidance explains (1) what should be included in an NDI notification and (2) how the information should be presented. *See* NDI Guidance at Part V(A)(2). The body of a 75-day notification must include information in three parts (A) administrative information, (B) attachments used to establish identity, and (C) safety and toxicology. Even on their face, the three sections of the 75-day NDI notification are the same sections required by the food additive petition. Parts five and six of the food additive petition require information regarding identity, administrative information, and safety and toxicological information. *See* FDA Food Additive Petition, Parts V, VI(1), VI(4)). Although the food additive petition also requires information regarding environmental impact, completion of a food additive petition would require the same information submitted in an NDI notification.

The types of information required to prove safety and establish identity are the same. The NDI guidance lists the following information as necessary to prove identity: a description of the manufacturing process, the physical and chemical composition, specifications, and analytical methods. *See* NDI Guidance, Section VI(2). Food additive petition require information concerning manufacturing methods, specifications, empirical and structural formula, and the composition of the mixture. *See* FDA Guidance for Industry: *Recommendations for submission of chemical and technological data for direct food additive and GRAS food ingredient petitions*, at III(A), (B), (C) (March 2009) (hereinafter "Food Additive Guidance"). NDI notifications must provide specification information including: critical safety attributes, testing, acceptance criteria

for each test, and analytical methods used to support acceptance criteria including detailed directions that must be followed for acceptable results. *See* NDI Guidance at Part VI(4). Specification information in a food additive petition must include identification tests for the substance, an assay (test/analysis) for the substance, the limits for the product and the test. *See* FDA Additive Guidance, *supra*, at III(C). The scope of an NDI notification and food additive petition are congruous and, thus, companies are incurring the same informational burdens under both regulatory schemes.

Companies marketing new dietary ingredients must show a reasonable assurance of safety. According to the FDA, nothing in the statute constrains the agency from imposing food additive data requirements, whether through express regulation or at the enforcement level. *See* NDI Guidance, at Section III (explaining that since the "DSHEA does not specify the type or amount of evidence that must be included in an NDI notification," the FDA provided the guidance to explain the reach of Section 350b). However, the qualitative and quantitative evidence that must be included in the NDI notification is substantially similar to that needed to support a food additive petition or to affirm a food ingredient as GRAS. Consider the information needed to complete two new sections of the 75-day NDI notification: (1) Comprehensive Safety Profile, and (2) Safety Narrative.

The NDI notification should include a Comprehensive Safety Profile (CSP) for the NDI. That CSP must provide objective summaries of all available human and animal toxicological information and any other information relevant to the safety assessment of the NDI. *See* NDI Guidance, at V(C)(2). According to FDA:

The information in the NDI Comprehensive Safety Profile should substantiate the safe use of the NDI in humans under the proposed conditions of use described in the notification. A history of use discussion in the NDI Comprehensive Safety Profile should document the identity and historical uses of the NDI, including the amount, frequency, and duration of the historical uses, as well as a description of the size and characteristics of the population that consumed the NDI. To the extent that test articles or materials described in the history of use and other evidence of safety are not identical to the NDI, the similarities and differences should be described, and the applicability of the study to the safety evaluation of the NDI should be explained.

Id.

If the NDI notification relies on safety studies then the CSP must compare the ingredients tested in the studies with the specific NDI. The guidance also requires the industry to submit a Safety Narrative. *See* NDI Guidance, at Section V(C)(3). FDA states that:

The Safety Narrative should include a concise summary of the scientific basis for the conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe when used under the conditions recommended or suggested in the supplement's labeling. It should explain how the various pieces of data and information fit together to form the basis for your conclusions about the safety of the dietary supplement.

Id.

The type of information needed to complete the Comprehensive Safety Profile and the Safety Narrative raises the standard of safety from merely showing that there a reasonable assurance of safety to providing proof that there is near absolute certainty of safety. By comparison, food additive petitions should contain "evidence of a substantial history of consumption of the substance by a significant number of consumers," and a showing that "there is a reasonable certainty that the substance is not harmful under the intended conditions of use." *See* FDA Guidance, Submission of a GRAS Notice, at Part (c)(4)(ii). There is in FDA's NDI

Guidance no practical distinction between the food additive burden ("reasonable certainty that the substance is not harmful"), the 21 U.S.C. § 350b dietary ingredient burden ("reasonable expectation of safety"), and the data required to support either determination. The phrase "reasonable expectation of safety" is less rigorous than the "reasonable certainty" standard for food additives. Accordingly, the NDI Guidance's comprehensive approach to dietary ingredient safety erects a de facto premarket system that is inconsistent with Congressional intent.

H. Nothing in the DSHEA requires each company manufacturing a dietary supplement containing an NDI to file a separate notification and the requirement that each do so is arbitrary and capricious agency action

FDA must allow companies to file abbreviated NDI notifications. As discussed above, the FDA believes any process that would “alter the chemical composition or structure of the ingredient” makes the ingredient an NDI. FDA also states that new NDIs must be submitted for identical ingredients if manufacturing processes differ so that the final ingredient is smaller in size, molecular complexion, dosage, etc. The FDA further states that companies cannot rely on existing NDIs but, rather, must submit new notifications for each NDI ingredient they market even if the very same ingredient has been the subject of an NDI notification to FDA that elicited no rejection by FDA. *See* NDI Guidance, at Part III.C.2. The FDA must adopt regulations or discuss abbreviated NDI applications that make subtle changes to existing NDI filings.

FDA's policy prohibiting companies from relying on existing NDI notifications filed by other companies or the same company is arbitrary and capricious and an abuse of discretion. It is a costly and wholly arbitrary imposition of agency power and, thus, also an abuse of discretion. Forcing the submission of multiple NDIs concerning the same dietary ingredient only burdens

the industry without any rational relationship to the safety of the “new” ingredient. Even in the drug context, companies are entitled to seek approval of generics by demonstrating bioequivalence. *See generally*, 21 CFR Parts 314, 320.

The FDA is duty bound to choose regulatory paths that present the least burden on small business. *See* 5 U.S.C. § 604(a)(6) (requiring that administrative agencies take steps to minimize economic burdens on small business entities). Indeed, the agency ought to impose regulatory schemes that achieve Congressional intent efficiently without resulting in undue expenditure of taxpayer dollars. *See, e.g., Mattingly by Mattingly v. Heckler*, 784 F.2d 258, 270 (7th Cir. 1986) (holding that Indiana state Medicaid decision would require thousands of individualized fact-finding procedures that would unnecessarily tax federal government's limited funds for such administrative procedures and would be a needless waste of taxpayer dollars); *see also Cassman v. U.S.*, 31 Fed. Cl. 121, 129 (1994) (explaining that, in the absence of clear Congressional intent to do otherwise, the Court should spare taxpayers and agencies unnecessary administrative burden).

The FDA’s interpretation writes out the exception in 21 U.S.C. § 350(b)(a)(1), which exempts an ingredient if it is “present in the food supply as an article used for food in a form in which the food has not been chemically altered.” Dietary supplements are a subclass of foods. *See Alliance for Natural Health U.S. v. Sebelius*, 775 F.Supp. 2d 114, 116-17 (D.D.C. 2011) (“[s]ince DSHEA's enactment, dietary supplements have remained generally regulated as a subset of foods”). 21 U.S.C. § 350b(a)(1) exempts from certain adulteration provisions of 21 U.S.C. § 342 dietary supplements that contain “only dietary ingredients which have been present

in the food supply as an article used for food in a form in which the food has not been chemically altered.” FDA cannot now suggest that dietary ingredients or dietary supplements are not “foods.” To do so would impose a circumscribed definition of “food” intended to limit access to ingredients.

An article present in a dietary supplement is assuredly in the food supply. If an ingredient proceeds through a 75-day notification without objection, and is marketed as a dietary supplement (which is arguably in the food supply), then the ingredient would fall under Section 350b(a)(1) and be exempt from future 75-day notifications. Having proceeded through a 75-day notification, and been “present in the food supply as an article used for food,” an ingredient subject to a prior 75-day notification would exempt future such ingredients from the notification requirement. Thus, *one* 75-day notification is appropriate for all subsequent sales of that dietary ingredient. FDA cannot show anything in the statute that supports the notion that separate NDI notifications are required by each company.

FDA’s position on separate NDI notifications thus violates the plain and intended meaning of the DSHEA. FDA states that a separate NDI notification is required if “the new supplement [has] other dietary ingredients that were not included in your original NDI notification.” *See* NDI Guidance, at Part IV.C.1. But that analysis focuses on the *dietary supplement*, not the dietary ingredients. The DSHEA (21 U.S.C. § 350b) included no such provision for multiple-ingredient products. The law concerned the safety of the specific dietary ingredients. Thus, here again, the FDA entirely disregards the import of 21 U.S.C. § 350b(a)(1). For the same reason companies must be entitled to rely on prior-filed 75-day notifications,

dietary ingredients previously established through the notification system should be exempted from future notices, regardless of the other ingredients present in the finished supplement. Note well that the food exemption applies, regardless of what other dietary ingredients are present in the particular food.

I. FDA’s new position that synthetic botanical ingredients are NDIs is arbitrary and capricious

FDA states that “synthetic cop[ies] of a constituent or extract of an herb or other botanical” are not dietary ingredients because the synthetic copy “was never part of the botanical and thus cannot be a ‘constituent’ of the botanical that qualifies as a dietary ingredient...” That interpretation completely ignores key components of the definition of "dietary ingredients" in 21 U.S.C. § 321(ff)(1). To achieve its intended result, the FDA misconstrues the definitions of “dietary ingredient” and “dietary substance” in a fashion that plainly contradicts Congress’s intent.

Section 321(ff)(1) defines a dietary supplement as:

A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- A vitamin;
- A mineral;
- An herb or other botanical;
- An amino acid;

- A dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- A concentrate, metabolite, constituent, extract, or combination of any ingredient described [above].

In its NDI Guidance, the FDA states that “a synthetic copy of a constituent of a botanical was never part of the botanical and thus cannot be a ‘constituent’ of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FDCA.” *See* NDI Guidance, at Part IV.D.2. Of course, in so finding, the FDA completely disregards the remaining sections of 21 USC 201(ff)(1), which would include “a *dietary substance* for use by man to supplement the diet by increasing the total dietary intake.” (emphasis added). To ban synthetic ingredients, the FDA escapes that provision by defining *in the NDI guidance* document the terms “dietary ingredient” and “dietary substance.”

FDA states that a “dietary ingredient” is “(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 (A) through (E).” *See* NDI Guidance, at Part VII (definitions). In other words, according to FDA, “dietary supplement” is the same as “dietary ingredient.” As explained below, that assumption is wholly incorrect. Second, the FDA defines “dietary substance” to avoid the possibility that a synthetic herbal ingredient could meet the definition. FDA defines “dietary substance” as “a substance that is commonly used as human

food or drink.” *See* NDI Guidance, at Part VII. In other words, FDA appears to define “dietary substance” to be conventional food.

FDA’s second assumption is troublesome, given that the DSHEA expressly excludes “conventional foods” from the definition of dietary supplement. *See* 21 U.S.C. § 321(ff)(2)(B). So the term “dietary substance” as used in Section 321(ff)(1)(E) cannot be equivalent to a substance “commonly used as food or drink” without directly conflicting with Section 321(ff)(2)(B) which excludes products “represented for use as a conventional food...” For FDA, there is quite literally no rational reason, other than an overt desire to ban synthetic ingredients, that can justify this misinterpretation of statutory language. FDA’s definition of “dietary substance” in its guidance simply cannot be reconciled with 21 USC § 321(ff)(2)(B).

Even more troubling, however, is the FDA’s deliberate attempt to merge the definition of “dietary ingredient” with that of “dietary supplement.” The two definitions are clearly distinct. The definition of “dietary supplement” in 21 U.S.C. § 321(ff)(1) was intended to be broad enough to include various dietary ingredients. Dietary ingredients comprise a much broader class of products, some of which might meet the definitions in Section 321(ff)(1). Congress defined dietary supplements through a subclass of possible dietary ingredients. *See* 21 U.S.C. § 321(ff)(1) (a dietary supplement is a product that "contains one or more *of the following dietary ingredients*"). While the short list of dietary ingredients in Section 321(ff)(1)(A)-(F) are undeniably "dietary ingredients" identified by Congress, there is no basis to conclude that the list identifies *all* possible dietary ingredients.

Nonetheless, as explained above, even assuming that “dietary ingredient” and “dietary supplement” were synonymous, Congress gave no indication that the catchall phrase “dietary substance for use by man to supplement the diet” would include only naturally occurring ingredients. The FDA’s decision against synthetic botanicals is simply without legislative basis and is an arbitrary and capricious distinction wrought from an abuse of discretion.

Moreover, the FDA has provided no reasoned basis to conclude that synthetic botanicals present a heightened safety risk, the only relevant consideration in a Section 350b analysis. Because safety is the primary focus of the NDI statutes, the FDA’s approach would fail on safety grounds alone. In fact, the FDA has recognized the “equivalence of marketed natural and synthetic vitamins and minerals by providing that ‘the Secretary may not establish maximum limits on the potency of any synthetic or natural vitamin or mineral.’” *See Soltis, supra*, at 27 (quoting 21 U.S.C. § 350(a)(1)(A)). In food labeling regulations the FDA specifically prohibits labeling statements that claim natural is better than synthetic. *See* 21 C.F.R. § 101.9(k)(4) (stating that food is misbranded if its label “represents, suggests, or implies ... [t]hat a natural vitamin in a food is superior to an added or synthetic vitamin”). Therefore, any position that synthetic dietary ingredients present a distinct safety concern is contradicted.

J. The FDA’s position concerning dietary ingredients “authorized for investigation” is inconsistent with Congressional intent

In the guidance, FDA states for the first time that a dietary ingredient is forever barred from the market if ever subject to investigation, even if the IND is later withdrawn or the investigation discontinued. *See* NDI Guidance, Part IV(D)(10).

FDA argues that the plain meaning of the statute (Section 321(ff)(3)(B)), when read in conjunction with 21 USC 321(ff)(3)(A), prohibits from the market ingredients that are either drugs or are *on their way to becoming drugs*. The FDA's interpretation creates a substantial incentive for companies to prevent access to future ingredients by submitting IND requests. This is particularly troublesome considering the FDA imposes very low burdens on IND investigations. Investigators must provide basic evidence of safety (not difficult for dietary ingredients). FDA has no pre-investigative approval system. Investigators may begin after a 30-day waiting period. Thus, ironically, a drug company could wait until a company submits a 75-day premarket notification before filing and making public an IND (and the investigation would begin before the dietary supplement company could market the product lawfully). We have no indication whether FDA would give priority to the dietary supplement, or hold that the dietary supplement is barred because the IND investigation began before the dietary ingredient was "marketed" lawfully to consumers. The FDA must clarify in its guidance document that the filing date of an NDI notification serves as the measuring date for any claim under 21 U.S.C. § 321(ff)(3)(A) or (B).

Conclusion

Because the FDA has greatly underestimated the adverse economic impact of its Guidance, it has failed to comply with the requirements of the Regulatory Flexibility Act. FDA has not undertaken a serious, good faith effort to determine the economic impact of each recommended requirement contained in its Guidance. Indeed, the economic burden imposed by the Guidance is extraordinary, particularly in the midst of a national recession, and will cost the

dietary supplement industry billions of dollars in revenues and will increase unemployment by over 100,000 Americans. For the reasons explained in detail above, the FDA NDI Guidance exceeds the limits of the agency's statutory authority; the NDI Guidance contradicts the plain and intended meaning of the NDI statutory provision; and the NDI Guidance is arbitrary and capricious and abuse of agency discretion. ANH-USA therefore urges the FDA to withdraw the NDI Guidance at the earliest possible moment.

Sincerely,

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