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Comments of Consumers Union to the
Food and Drug Administration on the Revised Draft Guidance for Industry;
Dietary Supplements: New Dietary Ingredient Notifications and Related Issues
Docket No. FDA–2011–D–0376

Consumers Union, the policy and mobilization arm of Consumer Reports,[1] welcomes the opportunity to comment on the August 2016 draft guidance for industry issued by the Food and Drug Administration (FDA), "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues." We appreciate the agency's work to produce this revised guidance on premarket safety notifications for a new dietary ingredient (NDI) or a dietary supplement containing an NDI, which could help increase the number, quality, and utility of NDI notifications submitted.

We are very concerned that FDA oversight has not kept up with the rapid growth of the dietary supplement industry and the pace of new product introductions. Despite the approximately 85,000 dietary supplements on the market,[2] FDA has received fewer than 1,000 NDI notifications since 1994.[3] It is highly likely that there are undeclared NDIs present in hundreds, if not thousands, of dietary supplement products offered for sale today. For these products, FDA never had the opportunity to even consider safety concerns before the products reached consumers.

While far broader improvements to FDA's regulatory oversight—including statutory changes—are needed for the agency to adequately protect consumers from unsafe dietary supplements, we urge FDA to keep moving forward, in the interim, on improvements to the NDI

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[1] Consumers Union is the policy and mobilization arm of Consumer Reports, an independent, nonprofit organization that works side by side with consumers to create a fairer, safer, and healthier world. As the world's largest independent product-testing organization, Consumer Reports uses its more than 50 labs, auto test center, and survey research center to rate thousands of products and services annually. Founded in 1936, Consumer Reports has over 7 million subscribers to its magazine, website, and other publications.

[2] Weeks, J. (2015, Oct. 30), *Dietary Supplements.* CQ Researcher, 25, 913-936 (online at library.cqpress.com/cqresearcher/document.php?id=cqresrre2015103000).

[3] "FDA updates draft guidance on premarket safety notifications for dietary supplement industry," FDA (press release) (Aug. 11, 2016) (online at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm516197.htm).

notification system. After accounting for the recommendations we make in these comments, FDA should work expeditiously toward the release of strong final guidance. In addition, FDA should specify a rapid timeline to bring all products into compliance with NDI notification procedures and arrange for the removal from the marketplace of products that are adulterated under federal law.

Background

About half of U.S. adults take dietary supplements, and annual nationwide dietary supplement sales total $37 billion.[4] Consumers sometimes view dietary supplements as cheap and natural alternatives to, or substitutes for, prescription drugs.[5] Unfortunately, many consumers do not realize that supplement manufacturers routinely and legally sell their products without first having to demonstrate their safety and effectiveness. According to a 2015 nationally representative Consumer Reports survey, almost half of American adults think that supplement makers test their products for efficacy, and more than half believe that manufacturers prove their products are safe before selling them.[6]

The primary federal statute governing dietary supplements, the Dietary Supplement Health and Education Act of 1994 (DSHEA), defines the term "new dietary ingredient" as a dietary ingredient that was not marketed in the U.S. before October 15, 1994.[7] DSHEA requires the manufacturer or distributor of an NDI that has not been present in the food supply as an article used for food, or a dietary supplement that contains such an NDI, to submit a premarket notification to FDA at least 75 days before introducing the supplement into interstate commerce. This notification must provide FDA with the information on which the manufacturer or distributor is basing its conclusion that the dietary supplement containing the NDI will "reasonably be expected to be safe."[8] The statute does not specify what such a safety showing would entail, and a final rule issued by FDA in 1997 implementing the premarket notification requirements lacked specifics on this point as well.[9]

NDI notifications are critically important, designed to protect consumers from new ingredients with unknown and potentially risky effects. Yet, despite the tens of thousands of dietary supplement products on the market, and the 5,560 new dietary supplement products that come on the market every year,[10] FDA has received fewer than 1,000 NDI notifications since

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[4] Weeks, J. (2015, Oct. 30), *Dietary Supplements.* CQ Researcher, 25, 913-936 (online at library.cqpress.com/cqresearcher/document.php?id=cqresrre2015103000).

[5] "Alternative therapies," Consumer Reports (Sept. 2011) (online at www.consumerreports.org/cro/magazine-archive/2011/september/health/alternative-treatments/overview/index.htm).

[6] "Supplements Can Make You Sick," Consumer Reports (July 27, 2016) (online at www.consumerreports.org/vitamins-supplements/supplements-can-make-you-sick).

[7] 21 U.S.C. 350b(d).

[8] 21 U.S.C. 350b(a)(2).

[9] FDA, *Premarket Notification for a New Ingredient,* final rule, 68 Fed. Reg. 49886 (Sept. 23, 1997).

[10] FDA, *Dietary Supplement Labeling Requirements and Recommendations Under the Dietary Supplement and Nonprescription Drug Consumer Protection Act,* 77 Fed. Reg. 35687 (June 14, 2012).

1994.[11] As Daniel Fabricant, the former director of dietary supplement programs at FDA, has said, "there is clearly a gap there, no matter how you slice it… clearly there hasn't been a lot of submitting [of NDI notifications]."[12] This gap poses health and safety risks to consumers, who, under DSHEA, are not supposed to be exposed to supplement ingredients unless the ingredients have been present in the food supply or have evidence of safety that has been submitted to FDA.

Examples of Potentially Unsafe Ingredients

The following examples support our concerns about products marketed as dietary supplements that contain ingredients, including synthetic chemicals, which have not been present in the food supply or justified as safe in a notification to FDA:

(1) *Pure, powdered caffeine:* A single teaspoon of pure, powdered caffeine is equivalent to drinking 25 eight-ounce cups of coffee, and between two and three teaspoons can be a lethal dose in adults. It is so concentrated that its suggested serving size (generally between 1/32 and 1/16 of a teaspoon) is beyond the measurement capabilities of a typical consumer. In August 2015—following the filing of a citizen petition by the non-profit group Center for Science in the Public Interest for FDA to ban the sale of pure, powdered caffeine and similar products due to the risks they pose to consumers of hospitalization, seizure, cardiac arrhythmia, and death[13]—FDA issued five letters to companies selling powdered bulk caffeine directly to the public as dietary supplements. FDA deemed the products adulterated for presenting "a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling."[14]

(2) *OSR #1:* A supplement called OSR #1, containing the industrial chemical N1,N3-bis (2-mercaptoethyl) isophthalamide, which was reportedly developed to help separate heavy metals from polluted soil, was introduced by a Kentucky company and promoted as an alternative autism treatment for children. The manufacturer failed to submit an NDI notification to FDA prior to introduction of the supplement. A senior toxicologist from FDA sent a letter to the company requesting information in June 2008, but the company had not responded as of early 2010. In the meantime, the company president said that "easily 1,000" customers had used the product. On June 17, 2010, FDA sent a letter to the company informing it that the product is illegal under the Federal Food, Drug, and Cosmetic Act.[15]

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[11] "FDA updates draft guidance on premarket safety notifications for dietary supplement industry," FDA (press release) (Aug. 11, 2016) (online at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm516197.htm).

[12] "Fabricant: Gap between NDI numbers and submissions is too big, no matter how you slice it," Nutra-Ingredients-USA.com (Oct. 13, 2011) (online at www.nutraingredients-usa.com/Regulation/Fabricant-Gap-between-NDI-numbers-and-submissions-is-too-big-no-matter-how-you-slice-it).

[13] Center for Science in the Public Interest, "Petition to Ban the Retail Distribution Of Pure and Highly Concentrated Caffeine Sold in Powder Form as a Dietary Supplement" (Dec. 9, 2014) (online at cspinet.org/resource/petition-ban-retail-distribution-pure-and-highly-concentrated-caffeine-sold-powder-form).

[14] FDA, "FDA Takes Action on Bulk Pure Powdered Caffeine Products," Constituent Update (Sept. 1, 2015) (online at www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm460097.htm).

[15] "OSR#1: Industrial Chemical or Autism Treatment?," Chicago Tribune (Jan. 17, 2010); "FDA: Autism 'Therapy' Illegal," Chicago Tribune (June 23, 2010).

(3) *Methlyl 1-D and Formadrol Extreme XL:* In May 2009, FDA seized and condemned 23,000 bottles of three dietary supplement products that contained anabolic steroids, "Methyl 1-D," "Methyl 1-D XL," and "Formadrol Extreme XL," worth an estimated $1.3 million. The supplement products were distributed by LG Sciences LLC, and marketed for use by bodybuilders on the internet and in retail stores. According to FDA's news release, "[T]he FDA determined that the products contain one or more unapproved food additives and/or new dietary ingredients for which there is inadequate information to assure that the ingredients do not present a significant or unreasonable risk of illness or injury. The FDA has no scientific information concerning the safety of the condemned products or their ingredients and, thus, cannot determine whether they represent a hazard to consumers." This release recommended that consumers who used the condemned products discuss them with medical providers, especially if they experienced any adverse events that may be related to the products' use.[16]

(4) *DMAA:* DMAA, or 1.3-dimethylamylamine, a substance used in several sports and weight loss supplements, was determined to be a synthetic chemical by Health Canada, even though it had been marketed to some customers as a natural constituent of geranium oil. The compound is considered to be a potentially powerful stimulant and was banned by the World Anti-Doping Agency in 2009. In August 2011, Health Canada declared that the product cannot be legally sold in Canada as a supplement and will now require authorization to be sold as a drug.[17] The American Herbal Products Association also concluded that the chemical is not found in geranium oil or the geranium plant, and directed its members not to label it as geranium oil or part of the geranium plant.[18]

In the U.S., a DMAA supplement called Jack3D was sold in 2011 by major retailers such as GNC, even though some segments of the supplement industry expressed serious concerns about the product's safety.[19] Supplements containing DMAA were eventually linked to the deaths of two military personnel, and banned by the U.S. military in December 2011.[20] In 2012, FDA issued warning letters to companies notifying them that products with DMAA needed to be taken off the market or reformulated to remove this substance.[21] FDA stated that there was no evidence that DMAA had been found in plants, and therefore it was not an herbal ingredient.[22] Prior to issuing its warning letters, FDA

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[16] "Dietary Supplements Worth $1.3 Million Condemned and Forfeited to the US under Consent Decree," FDA (press release) (May 11, 2009) (online at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm152358.htm).

[17] "Health Canada: DMAA is not from geranium," Nutraingredients-usa.com (Aug. 24, 2011) (online at www.nutraingredients-usa.com/Industry/Health-Canada-DMAA-is-not-from-geranium).

[18] "AHPA: If DMAA is in geranium, synthesized version is a lawful dietary ingredient," Nutraingredients-usa.com, (Apr. 30, 2012) (online at www.nutraingredients-usa.com/Regulation/AHPA-If-DMAA-is-in-geranium-synthesized-version-is-a-lawful-dietary-ingredient).

[19] *Id.*

[20] "DMAA products pulled from base shelves," Army Times (Dec. 29, 2011).

[21] FDA, "DMAA in Dietary Supplements" (July 13, 2013) (online at www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm346576.htm).

[22] "DMAA products pulled from base shelves," Army Times (Dec. 29, 2011).

received 86 adverse event reports relating to illnesses or deaths associated with DMAA.[23] Even after FDA directed manufacturers to remove DMAA from the market, DMAA supplements were still being sold as late as November 2016 by a California distributor that issued a voluntary recall order.[24]

(5) *DMBA and BMPEA:* In April 2015, FDA sent warning letters to 14 companies urging them to cease marketing 17 supplements that contained DMBA (1,3-dimethylbutylamine), an undeclared and unauthorized ingredient that reportedly raises blood pressure and may have amphetamine-like properties. DMBA has not been tested for safety or effectiveness in humans.[25] That same month, FDA also sent warning letters to five companies urging them to stop marketing eight supplements that contained BMPEA (β-methylphenethylamine), which is sometimes labeled as Acacia rigidula.[26]

Researchers at Harvard Medical School, the Netherlands Health Protection Center and NSF International found in October 2014 that DMBA is chemically related to the banned stimulant DMAA (1,3-dimethylamylamine). Because DMBA's effectiveness and safety are unknown, the researchers said it should be removed from dietary supplements.[27] In April 2015, Harvard Medical School's Dr. Pieter Cohen, who had worked on the DMBA study, and scientists from several other universities published a study identifying BMPEA in 11 of 21 bodybuilding or weight-loss supplements, appearing in such quantities that consumers following the maximum recommended amount would take in more than 90 mg of the untested product.[28] Military exchanges and GNC stores on military bases had recently stopped selling DMBA for safety concerns, and "[t]he removal marked the third time in nearly three years that fitness supplements were dropped by military retailers for safety concerns."[29]

(6) *OxyElite Pro (Aegeline/DMAA):* In 2013, 97 cases of severe hepatitis and liver failure (including one that led to death) were linked to OxyElite Pro, a weight-loss supplement containing the little-known substance aegeline.[30] Non-synthetic aegeline is an alkaloid

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[23] "DMAA is Back: DoD names 39 workout supplements to avoid," Military Times (Oct. 13, 2015) (online at www.militarytimes.com/story/military/pt365/2015/10/13/dmaa-back-dod-names-39-workout-stimulants-avoid/73674796).

[24] "DMAA Net Weight 500g by NutriVitaShop: Recall – Presence of DMAA May Pose Health Risk," FDA (Nov. 26, 2016) (online at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm530665.htm).

[25] FDA, "DMBA in Dietary Supplements" (Apr. 2015) (online at www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm444719.htm).

[26] FDA, "BMPEA in Dietary Supplements" (Apr. 2015) (online at www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm443790.htm).

[27] "Supplements Targeted" at 47, Air Force Times (May 18, 2015).

[28] *Id.*

[29] *Id.*

[30] "The trouble with diet pills," Consumer Reports on Health (Jan. 2015).

extract from the leaves of the Asian bael tree (agele marmelos). However, USPLabs did not provide evidence for the safety of this new dietary ingredient, according to FDA.[31]

USPLabs LLC, the product's manufacturer, initiated a recall of OxyElite Pro in November 2013. The company announced the recall after receiving a letter from FDA, stating that the products have been linked to liver illnesses. FDA notified USPLabs LLC that if the company did *not* initiate a voluntary recall, the agency could by law order the company and other parties to immediately stop distributing the dietary supplements. The action marked the second time FDA has exercised its recall authority under the FDA Food Safety Modernization Act (FSMA) by sending such a letter.[32] According to an FDA Consumer Update, an earlier version of OxyElite Pro was destroyed in 2013 after being found to include the banned ingredient DMAA.[33]

Two years later, in February 2015, FDA confirmed that a new formulation of OxyElite Pro, also made by USPLabs LLC, contained hidden amounts of fluoxetine, an antidepressant that has been associated with serious side effects including suicidal thinking, abnormal bleeding, and seizures.[34]

(7) *Methylsynephrine:* In April 2016, Dr. Pieter Cohen of Harvard Medical School published a study documenting the presence of methylsynephrine in 14 different U.S. brands of dietary supplement products. Methylsynephrine, which is also known as oxilofrine and *p*-hydroxyephedrine, is a synthetic chemical similar to ephedrine that has been banned for use by athletes. According to Dr. Cohen and his co-authors: "Consumption of supplements containing oxilofrine may also pose serious health risks. For example, one brand of supplements containing oxilofrine has been linked to serious adverse events including vomiting, agitation, and cardiac arrest."[35] In response to Dr. Cohen's findings, in April 2016, FDA wrote letters to 7 companies marketing a total of eight products containing methylsynephrine. The letters stated that "methylsynephrine is a substance that does not meet the definition of a dietary ingredient." Therefore, any supplements that list it as an ingredient are considered by FDA to be misbranded, and would be removed from the marketplace.[36]

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[31] FDA, "OxyElite Pro Supplements RECALLED" at 1, Consumer Health Information (Nov. 2013) (online at www.fda.gov/downloads/forconsumers/consumerupdates/ucm375497.pdf).

[32] FDA, "USPLabs LLC recalls OxyElite Pro Dietary Supplements; Products Linked to Liver Illnesses" (Nov. 19, 2013) (online at www.fda.gov/newsevents/newsroom/pressannouncements/ucm374395.htm).

[33] FDA, "OxyElite Pro Supplements RECALLED" at 1, Consumer Health Information (Nov. 2013) (online at www.fda.gov/downloads/forconsumers/consumerupdates/ucm375497.pdf).

[34] FDA, "Public Notification: Oxy ELITE Pro Super Thermogenic contains hidden drug ingredient" (Feb. 28, 2015) (online at www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/ucm436017.htm).

[35] Cohen, P. et al. (Apr. 7, 2016) "Pharmaceutical doses of the banned stimulant oxilofrine found in dietary supplements sold in the USA," Drug Testing and Analysis (online at onlinelibrary.wiley.com/doi/10.1002/dta.1976/abstract).

[36] FDA, "Methylsynephrine in Dietary Supplements" (online at www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm493282.htm).

(8) *Intentionally Adulterated Supplements:* In addition to the previous examples, FDA has published recall notices for dozens of other dietary supplements spiked with a wide variety of prescription drugs, including sibutramine (the banned weight-loss drug); locaserin (a prescription weight-loss drug); and phenolphthalein, a laxative which animal studies have linked to an increased risk of cancer.[37] In addition, many herbal male sexual enhancement supplements have been found to be contaminated with sildenafil, the prescription drug used in Viagra. A recent study of 150 herbal sexual enhancement supplements found that 61% of them contained prescription drugs, untested "designer drugs," or over-the-counter drugs—none of which are legally permitted for use in dietary supplements. Fully 27% of the supplements were found to contain FDA-approved prescription drugs.[38]

Taken together, these recent incidents illustrate the presence of potentially unsafe ingredients in products marketed as dietary supplements and paint a disturbing picture of an uncontrolled, poorly regulated marketplace. If these manufacturers had followed appropriate procedures and had been forced to try to justify these ingredients as NDIs—when in reality many are synthetic chemicals or drugs—FDA may not have permitted them to go on sale. Instead, there have been numerous situations in which supplements with illegal ingredients go on sale, and may remain on the market for several years, before they are detected and removed by FDA, sometimes in the face of mounting adverse event reports regarding organ damage or deaths. These incidents do not inspire confidence that NDI notifications are being used effectively as a preventive safety control, or that the current safety system is functioning at anywhere near the level that consumers expect and deserve.

Recommendations on Key Elements of the Guidance

As previously discussed, Consumers Union supports far broader improvements to FDA's regulatory oversight of dietary supplements than just those that appear in the NDI notification guidance. We support statutory measures that—among other changes—would require supplement manufacturers to register their products and prove they are safe before they enter the marketplace, improve dietary supplement labels, and provide FDA with expanded funding and personnel resources so that it can increase its review, investigative, inspection, and enforcement capabilities. We also support a binding rulemaking by FDA regarding NDI notifications that would include requirements for the minimum quality and quantity of evidence that manufacturers and distributors must submit with safety determinations. These measures would enable the agency to adequately protect consumers from safety risks posed by dietary supplements.

However, we understand that these steps are not the focus of FDA as it seeks comment. Therefore, in the interim, we urge FDA to keep moving forward on improvements to the current NDI notification system. We make the following comments on key elements of the revised draft

[37] "The trouble with diet pills," Consumer Reports on Health (Jan. 2015).

[38] "These Herbal Sex Supplements Really Work – But They May Also Cause Some Nasty Side Effects," Consumer Reports (Oct. 31, 2014) (online at www.consumerreports.org/cro/news/2014/10/these-herbal-sex-supplements-really-work/index.htm).

guidance, which we ask FDA to consider as it moves expeditiously toward making the guidance final.

Part III: Goals and Public Health Importance of the Guidance

Consumers Union agrees with the primary goal of the guidance: for NDI notifications to be a critically important "preventive control" to "ensure that consumers are not exposed to unnecessary public health risks in the form of new ingredients with unknown safety profiles."[39] Quite simply, if FDA does not know the safety profile of an ingredient that has not been present in the food supply, the ingredient does not belong in the dietary supplement marketplace. We also agree that an important goal of the guidance should be to improve the quality of NDI notifications, so that FDA has robust and complete information to evaluate whether a dietary supplement containing an NDI will reasonably be expected to be safe.

We further agree that an NDI notification submission should, at a minimum, include the following four core components:

- A full description of the identity and composition of the NDI and the dietary supplement in which the NDI will be marketed;
- A discussion of the basis for a conclusion that the substance is an NDI;
- A description of the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling, the ordinary conditions of use of the supplement; and
- An explanation of how the history of use or other evidence of safety in the notification justifies a conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe.

The description of conditions of use for a supplement is especially important in circumstances where the supplement is not appropriate for certain populations or for people with chronic illnesses or other conditions; or where the supplement may interact with other prescription drugs or supplements the consumer is taking. For example, St. John's Wort has been shown to lower the efficacy of birth control pills and several other drugs, including HIV/AIDS medications.[40] Other supplements can increase the likelihood and severity of drug side effects, such as glucosamine, which can interact with the blood thinner warfarin and increase the risk of bleeding.[41] Consumers may not realize they are putting themselves at risk, because supplement labels do not always warn against potentially harmful prescription drug interactions.[42]

In addition, the explanation regarding the ingredient's history of use or other evidence of safety is important both for FDA's review, but also for consumers, medical providers, and health

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[39] FDA, *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry* at 12, draft guidance (Aug. 2016) (hereinafter "August 2016 NDI guidance").

[40] "The dangers of dietary and nutritional supplements investigated," Consumer Reports (Sept. 2010) (online at www.consumerreports.org/cro/2012/05/dangerous-supplements/index.htm).

[41] *Id.*

[42] *Id.*

system researchers who rely on this information. Such safety information should be fully available to the public, so that consumers and other stakeholders can evaluate the quantity and quality of the safety evidence and make informed decisions about whether to use a particular ingredient or supplement product.

Question IV.A.4: Ingredients in pre-DSHEA conventional foods[43]

We agree with FDA's explanations in this answer, which make clear that unless an ingredient was marketed in or as a dietary supplement, or for use in a dietary supplement, prior to October 15, 1994, an NDI will be required. Also, because the present definitions of "dietary supplement" and "dietary ingredient" were not added to the FD&C Act until after October 14, 1994, we consider it reasonable for FDA to interpret that "dietary ingredient" should refer to ingredients 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.[44]

Question IV.A.8: Dietary ingredients marketed outside, but not in, the U.S. pre-DSHEA

For a dietary ingredient marketed outside the U.S. pre-DSHEA, we agree that manufacturers and distributors should submit an NDI notification if they were not marketed as a dietary ingredient in the U.S. prior to October 15, 1994. We agree that submitting documentation that the ingredient was marketed in any other country before October 15, 1994, does not establish that the ingredient is not an NDI.

Question IV.A.10: Sufficiency of marketing an ingredient for any use pre-DSHEA

We agree that "unless the ingredient was marketed as a dietary ingredient for use in or as a dietary supplement prior to October 14, 1994, it is an NDI."[45] The fact that a product was marketed as a conventional food, drug, or for any non-food use, does not establish that it is not an NDI.

Question IV.A.11: Authoritative list of "grandfathered" dietary ingredients

We understand that FDA is "prepared to develop an authoritative list of pre-DSHEA ingredients, based on independent and verifiable data."[46] When FDA develops such a list, we urge the agency to release it in draft form for public comment and inspection of the documentation and descriptions of identity provided by industry.

Question IV.A.13: Manufacturing process and the use of nanotechnology

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[43] "Pre-DSHEA" is used in these comments in a manner similar to how FDA uses the term—that is, as shorthand for "prior to October 15, 1994."

[44] August 2016 NDI guidance at 14.

[45] August 2016 NDI guidance at 19.

[46] *Id.*

We agree with FDA that if a dietary ingredient previously available on the market is now being produced and sold at the nanoscale level, an NDI notification should be submitted. For many reasons, we favor mandatory premarket safety review for any dietary supplements or drugs that contain nanoparticles. Use of nanotechnology should trigger the "new dietary ingredient" definition, because between 1 and 1,000 nanometers, materials could begin to exhibit unique properties or phenomena, including physical or chemical properties or biological effects that affect their physical, chemical, and biological behavior. These unique properties could potentially render a nanoscale ingredient more toxic than its large particle form. The issue of how such particles may be absorbed by the body and its cells needs to be very carefully considered by FDA. Smaller particles could evade the immune system, pass through the blood-brain barrier, or directly enter cells and their nuclei in a way that conventional-scale materials cannot.[47]

Question IV.B.1: "Present in the food supply" refers to the conventional food supply

We agree with FDA that prior use of an ingredient in a dietary supplement should not be interpreted to constitute presence in the food supply. Such an interpretation would yield plainly absurd results, and, as FDA states, "expand the exception to the point that it would risk swallowing the rule." We also agree that such an interpretation would not make sense in light of the overall purpose of the NDI notification requirement. However, we disagree with FDA that "substances added to conventional foods must meet the safety standards for conventional food ingredients, which are more demanding than those that apply to dietary ingredients used in dietary supplements." Substances added to food that companies market on the basis of an independent conclusion that they are generally recognized as safe (GRAS)—i.e., those substances that companies conclude are GRAS but are not the subject of a notification to FDA, such as a GRAS notice—bypass FDA's oversight altogether.

Question IV.B.2: GRAS substances and direct food additives

We strongly disagree with several aspects of FDA's answer to question IV.B.2 pertaining to GRAS substances. The August 2016 guidance, unlike the previous draft guidance, makes no explicit reference to substances that are self-affirmed to be GRAS by companies. However, we are very concerned that the guidance may still permit companies to avoid submitting an NDI notification by self-designating them GRAS.[48] A 2014 report on the contemporary GRAS system found that this loophole allows companies to self-affirm the safety of food ingredients and dub an ingredient exempt under DSHEA,[49] meaning that FDA may never review evidence on the

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[47] *See* Comments of Consumers Union on the FDA Draft Guidance for Industry; Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (Aug. 2, 2011).

[48] *See* Comments of Center for Science in the Public Interest, Consumers Union, Environmental Working Group, and the Natural Resources Defense Council on Substances that Are Generally Recognized as Safe (GRAS) (Docket No.: FDA-1997-N-0020) (Apr. 15, 2015) (online at cspinet.org/sites/default/files/attachment/GRAS%20Comment%20FINAL.pdf).

[49] Neltner, T and Maffini, M. (Apr. 2014) "Generally Recognized as Secret: Chemicals Added to Food in the United States" at 8, Natural Resources Defense Council (online at www.nrdc.org/food/files/safety-loophole-for-chemicals-in-food-report.pdf).

riskiest ingredients in either food or dietary supplements. While some terminology has changed, the GRAS system under the final rule issued by FDA on August 17, 2016, does not differ substantially in this respect.[50]

The text of question IV.B.2 pertains only to GRAS substances "listed or affirmed by FDA." Yet, in its answer to this question, FDA states: "If the NDI has been legally marketed in the U.S. as an ingredient for use in conventional food and has been introduced into the food supply as a result of such marketing, it would be exempt from the notification requirement under section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) because it has been present in the food supply as an article used for food in a form in which the food is not chemically altered."[51] This language is very similar to language used in the previous draft guidance, and it certainly does not decisively close the loophole we describe. To ensure that FDA can exercise some oversight over ingredients for which companies have made an independent conclusion of GRAS status, we strongly urge the agency to consider such ingredients NDIs. To enhance this oversight, FDA should require that notifications include all adverse information concerning a supplement that is known to the manufacturer or discoverable through a reasonable search of the literature.

Additionally, FDA should clarify in its final guidance with regard to NDIs that mere marketing of an ingredient should not suffice to meet the legal requirement that a substance was "present in the food supply" under 21 U.S.C. 350b(a)(1). Instead, an ingredient should be exempted from the NDI notification requirements only if it was actually "present in the food supply as an article used for food in a form in which the food is not chemically altered," as the law requires, in the U.S. and at the same intake level as in the supplement. For the purposes of 21 U.S.C. 350b(a)(1), it would be inappropriate to consider the activity of marketing an ingredient for food uses to meet the established, and plainly different, legal standard of being "present in the food supply." Just because an ingredient was marketed does not mean that it was present in the food supply.

We also strongly disagree with the statement that "…ingredients marketed in conventional foods *outside the U.S.* are exempt from the NDI notification requirement if they are not chemically altered" (emphasis added).[52] It is not necessary or prudent to exempt such ingredients from a potential NDI submission, especially because they may be ingredients that are not commonly used or consumed in the U.S. food supply, and they may not have a history of safe use, or adequate evidence to support their use as a dietary ingredient in dietary supplements.

Question IV.B.3: Application of the adulteration standard to GRAS substances and food additives

We strongly agree that an NDI notification should be submitted in cases where the intake level of the NDI in the dietary supplement is higher than that resulting from conventional food use of the NDI, and that the adulteration standard should apply unless there is adequate information to ensure that the supplement does not pose an significant or unreasonable risk of

[50] FDA, *Substances Generally Recognized as Safe,* final rule, 81 Fed. Reg. 54959 (Aug. 17, 2016).

[51] August 2016 NDI guidance at 23-24.

[52] *Id.*

illness or injury. As stated in FDA's example, "if an ingredient generally used in microgram quantities to flavor food is placed in a capsule with a serving level of hundreds of milligrams, a safety analysis would be necessary to determine the safety of the much higher intake level in the dietary supplement. In the absence of adequate information to provide reasonable assurance that the higher intake level of the NDI in the dietary supplement is safe, the dietary supplement would be adulterated."[53]

Consumers could be exposed to unnecessary safety risks when they ingest dietary supplements containing certain ingredients at higher levels than present in the food supply. Bitter orange peel, for example, has been safely used in orange marmalades; in pill form, however, bitter orange extract is more concentrated and consumed in much higher doses, and can not only interact adversely with several medications, but has also been associated with fainting, heart-rhythm disorders, heart attack, and stroke.[54] Simply recommending that companies consult with FDA does not sufficiently protect consumers in this situation. Consumers and the public interest would be best served if FDA stated that a company should submit an NDI notification in this situation, so that the potential safety implications are appropriately reviewed by FDA prior to the marketing of the product. This suggestion is consistent with the language in question IV.C.2 of the guidance, which indicates that manufacturers or distributors should submit an NDI if the daily intake level for a supplement for a new dietary ingredient is higher than for an NDI they have already submitted for an existing supplement in their product line.

Questions IV.B.4-5: Chemical alteration of an article of food

We strongly agree with the language stating that a notification should be submitted if a dietary ingredient has been chemically altered, such as using solvents other than water or ethanol to make an extract; breaking chemical bonds through hydrolysis or esterification; removing of some chemical components of a tincture or solution in water, such as through chromatography, distillation, or membrane filtration; high temperature baking or cooking; fermentation; and application of nanotechnology. Another key example is using a botanical ingredient at a different life stage. FDA is rightfully concerned about the potential alteration of the chemical composition or structure of supplement ingredients, and we strongly agree that the use of these processes should trigger an NDI notification.

Milling should generally not be included as a concern for chemical alteration, with the exception of a milling process that results in the production of particles of one micron or less, which could raise concerns similar to those for nanoscale ingredients. Therefore, if a milling process results in particles below one micron that will be used in a supplement ingredient, manufacturers should submit an NDI notification.

Questions IV.C.1-5: Other questions about when an NDI notification is necessary

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[53] August 2016 NDI guidance at 24.

[54] "The dangers of dietary and nutritional supplements investigated," Consumer Reports (Sept. 2010) (online at www.consumerreports.org/cro/2012/05/dangerous-supplements/index.htm).

In general, we agree with FDA's reasoning, and the guidelines provided in this section, for when it is necessary to submit an NDI, especially when that NDI is used in a different dosage format, or with different excipients or dietary ingredients. Also, when more than one NDI is incorporated into a supplement product, an NDI should also be submitted, as discussed in Scenario 6, because it necessitates a new safety analysis.

We also believe that the safety information submitted in connection with NDI notifications should be made fully public, so that consumers, scientists and medical providers have access to this information, and can use it in evaluating the safety profiles of particular ingredients. Because our supplement safety system relies extensively on post-marketing surveillance, the public will benefit from full and complete sharing about NDIs that could have a variety of unexpected effects, under varying conditions of use, and in potential combination with other supplements, foods, or medications.

Question IV.D.3: Synthetically produced substances

We strongly support FDA's position that synthetic herbs and botanicals do not quality as dietary ingredients under Section 201(ff)(1)(C) of the FD&C Act. We agree with FDA's statement that "A substance that has been synthesized in a laboratory or factory has never been part an herb or a botanical, and therefore, is not a dietary ingredient under section 201(ff)(1)(C) of the FD&C Act."[55]

In addition, we are very concerned about any possible exceptions to this rule that may be provided in the interpretation of Section 201(ff)(1)(E) of the FD&C Act, referenced in footnote 30 of the guidance.

> "Note, however, that if the synthetic copy has itself been used as a lawfully marketed ingredient in the conventional food supply, it may be a "dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake" and therefore qualify as a dietary ingredient under 21 U.S.C. 321(ff)(1)(E) (see next bullet in text), even though it is not an herbal or botanical dietary ingredient under 21 U.S.C. 321(ff)(1)(C)."[56]

Because the "dietary substance" category is defined in part by history of use, a synthetic copy of a botanical ingredient may qualify as a dietary ingredient under section 201(ff)(1)(E) if the synthetic copy has been used as a lawfully marketed ingredient in the conventional food supply. For example, a synthetic copy of a botanical ingredient would be a dietary ingredient under section 201(ff)(1)(E) if the synthetic copy has been used as an ingredient in the conventional food supply. Two common examples are vanillin and cinnamic acid, botanical constituents that, for economic reasons, are usually produced synthetically for use as flavorings in food.

Many consumers might be concerned to learn that artificial flavorings and synthetic copies of botanical ingredients are allowed to be used as ingredients for dietary supplements in

[55] August 2016 NDI guidance at 38.

[56] *Id.*

this category. It is not clear how many such substances would then be permitted to find their way into dietary supplements through this exception. The synthetic botanical ingredients may not have been adequately vetted for safety prior to entering the food supply. We would think that if any exceptions of this type are permitted, they should be very limited in character and publicly identified and announced.

Any exceptions of this nature should be clearly and transparently identified by FDA and the supplement manufacturers, and disclosed in product labeling. This industry broadly promotes the herbs and food ingredients in dietary supplements as coming from natural sources. At a minimum, consumers have a right to know when manufacturers are using synthetic ingredients from laboratory sources, so that they could evaluate the safety of these ingredients and make their own decisions about whether they wish to consume these products.

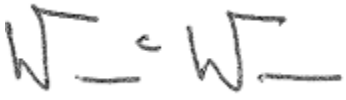
Section VI.C: Summary for the Basis for a Conclusion of Safety

Consumers Union supports FDA's recommendation for manufacturers to provide (1) a summary of both the safety of the NDI, and (2) a summary of the safety of the dietary supplement in which it will be used. If there are multiple NDIs in a proposed product, we agree that manufacturers should submit a comprehensive safety profile for each NDI, with the safety of the combination of NDIs addressed in the safety narrative. Also, manufacturers should provide information regarding the history of use or other evidence of safety for the combination of NDIs used in the dietary supplement, to ensure there is a comprehensive safety profile for that combination of ingredients, in addition to a separate profile for each NDI.

Conclusion

While there is much more that needs to be done to ensure the safety of dietary supplements, we anticipate that FDA's NDI notification guidance will provide clearer advice to companies to ensure that the appropriate NDI notifications are made, and assist the industry in complying with the requirements of DSHEA. It should also provide FDA with more complete information to determine whether a dietary supplement containing an NDI can reasonably be expected to be safe. We urge FDA to promulgate a final guidance as soon as possible, to clarify the rules of the road and ensure that appropriate NDI notifications are filed on a timely basis. Thank you for your consideration.

Respectfully submitted,



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