

FDA Issues a Revised Draft Guidance on New Dietary Ingredients Used in Dietary Supplements

August 15, 2016

Food, Beverage, and Dietary Supplements

On August 11, 2016, FDA published its long-awaited revised draft guidance on Dietary Supplements: New Dietary Ingredient Notifications and Related Issues.¹ Like the 2011 draft it replaces, the revised draft guidance is intended to help a dietary supplement company decide (1) whether a substance is a dietary ingredient; (2) when a new dietary ingredient (NDI) notification is required before a dietary ingredient can be used; and (3) how to prepare and submit an NDI notification.

While these issues may seem technical, the stakes are high. If a company sells a substance in a dietary supplement that FDA considers either not a dietary ingredient or an NDI that needs an NDI notification, the agency may threaten or initiate enforcement against the company. For example, it might send a warning letter that can trigger consumer lawsuits, demand a product recall, or even work with DOJ to bring a criminal action.

The revised draft guidance elaborates on many of the agency's views about dietary ingredients that have vexed industry. For example, FDA continues to insist that there is no such thing as a synthetic "botanical" or a synthetic constituent of a botanical. In addition, the revised draft guidance takes the strictest position yet on whether a dietary supplement qualifies as "food" in the food supply: the agency says that dietary supplements are not food despite statutory language to the contrary. Further, FDA interprets "chemical alteration" even more broadly than before, finding chemical alteration virtually wherever it can. This means that many botanical extracts that industry may have understood to be excluded from the NDI notification requirement may now be subject to it.

While continuing to draw hard lines with its legal interpretations, the revised draft guidance does make a handful of logistical concessions to industry. Most notably, FDA offers to establish an authoritative list of ingredients that are not subject to NDI notification requirements because they were on the market before October 1994 when Congress passed the Dietary Supplement Health and Education Act (DSHEA). This authoritative pre-DSHEA list would be a safe harbor for the ingredients it includes. The revised draft guidance also allows companies to create confidential NDI master files, which NDI notifications can then reference without having to regenerate the data. Although master files should make the NDI notification process easier, an authoritative list of pre-DSHEA dietary ingredients is more likely to be a bane than a boon to

¹ The revised draft guidance is available [here](#).

industry. Any list to which FDA agrees is likely to contain few ingredients and, importantly, to omit a number of ingredients included in extant lists on which industry has relied for years.

Finally, the revised draft guidance leaves open a pathway for substances that are generally recognized as safe (GRAS). GRAS substances and direct food additives are usually dietary ingredients. Such ingredients, regardless of their chemistry, are dietary substances—one category of dietary ingredient—if they are commonly used in conventional food. They may also fall into another category of dietary ingredient, e.g., they may be a constituent of a botanical. In addition, as long as they are chemically unaltered and actually used in conventional food before they are used in dietary supplements, GRAS substances, direct food additives (when they are dietary ingredients), and ingredients marketed in conventional foods outside the United States are excluded from the NDI notification requirements. While such ingredients would still be subject to safety standards, such as the NDI adulteration provision, the exclusion from the NDI notification process is a significant advantage, largely because the historical success rate for NDI notifications has been so low (only around 20%). The NDI notification acceptance rate could potentially improve now that FDA has laid out its expectations much more clearly about the type of information and data it expects in such notifications.

Industry has until October 11, 2016 to submit comments on the revised draft guidance. We expect many companies and trade associations will chose to do so, especially to raise concerns about the agency's continued narrow reading of the definition of dietary ingredient and the exceptions from the NDI notification requirement.

When an Ingredient Is a Dietary Ingredient

An ingredient is a dietary ingredient only if it falls into one of the categories of dietary ingredients listed in the Federal Food, Drug, and Cosmetic Act (FDCA). If an ingredient does not fit into at least one of these categories, it cannot be used as a dietary ingredient in a dietary supplement. The dietary supplement ingredients that have an effect on the body must be dietary ingredients.²

The categories of dietary ingredients are listed as part of the definition of dietary supplement in section 201(ff) of the FDCA.³ A “dietary supplement” is a product that contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract or combination of any ingredient described in (A) through (E).⁴

The FDCA does not define these categories further, and there is scant legislative history on DSHEA. Like FDA's 2011 draft guidance, the revised draft guidance interprets these categories narrowly. For example, FDA has continued its hard line against synthetic botanicals. FDA's interpretations of the categories of dietary ingredients include:

² All other non-dietary ingredients used in a dietary supplement, *i.e.*, that do not have an effect on the body, must be either approved for use as food additives or color additives or generally recognized as safe (GRAS) under the intended conditions of use.

³ Section 201(ff) of the FDCA is codified at 21 U.S.C. § 321(ff).

⁴ FDCA § 201(ff)(1).

- Vitamins, minerals, and amino acids can be synthetic. FDA considers them to be dietary ingredients regardless of their source.
- The term “amino acid” is restricted to an “alpha-amino carboxylic acid used as a constituent of proteins or peptides.” This interpretation, also in the 2011 draft, has been controversial. FDA acknowledges in a footnote that “amino acid” is often defined more broadly, but it insists that its interpretation is correct in the nutritional context of a dietary ingredient.
- A synthetic copy of an herb or other botanical is not a “botanical.” Likewise, FDA says that a synthetic copy of a “constituent,” “extract,” or “concentrate” of a botanical is not a dietary ingredient. Thus, FDA deems a synthetic copy of a botanical or of a constituent of a botanical to be a dietary ingredient only if it also qualifies as a “dietary substance”. This interpretation, especially as it relates to constituents, has been, and will continue to be, controversial. Particularly within the past few years, a significant number of FDA’s actions against dietary supplement companies have been directed against synthetic copies of constituents or extracts of botanicals.
- According to the revised draft guidance, the term “dietary substance” means “a substance commonly used as human food or drink,” or foods and food components that humans “eat as part of their usual diet” (emphasis added). The revised draft guidance says that a synthetic version of a botanical qualifies as a dietary substance if the synthetic version has been “used as a lawfully marketed ingredient in the conventional food supply.” FDA provides two common examples of synthetic botanicals that are dietary substances: vanillin and cinnamic acid. Other synthetic botanicals used in conventional food include caffeine, citric acid, and lycopene. FDA’s view on synthetic dietary substances was not in the 2011 draft guidance, but the agency states that it has long taken this position.
- According to FDA, “dietary substance” encompasses GRAS substances and direct food additives. It does not include food contact substances, other indirect food additives, secondary direct food additives (added to food for a technical effect but with no technical effect in the finished food), or contaminants in food.
- Probiotics and other microbial ingredients (unless they are algae or fungi which qualify as “botanicals”) do not constitute a distinct category of dietary ingredient. They can only be dietary ingredients if they are “dietary substances,” meaning that such ingredients must be used in food as GRAS substances, perhaps commonly so, before they can be used in dietary supplements.
- A “metabolite” of a botanical or of another type of dietary ingredient can be synthesized from a dietary ingredient. A metabolite is usually produced in the body after ingestion, but the same chemical could also be prepared synthetically and used as an ingredient in a dietary supplement. FDA’s definition of “metabolite” is quite restrictive, however. It requires the starting material to be a dietary ingredient and the production process to mimic the metabolic process in the body following ingestion.

If an ingredient does not fall within these categories, it cannot be a dietary ingredient, even if it was used in dietary supplements before October 1994 and even if it is safe.⁵ FDA’s narrow and

⁵ Dietary supplements also cannot contain articles approved as new drugs or licensed as a biologic, or those authorized for investigation under in IND unless (1) FDA issues a regulation allowing the article’s

controversial interpretations may put some currently used ingredients at risk of enforcement. Recent FDA warning letters addressed to dietary supplement companies cite ingredients, such as picamilon, that FDA says are not dietary ingredients.

When an NDI Notification Is Required

According to the FDCA, a company can use a dietary ingredient without submitting an NDI notification if the ingredient satisfies either of two exclusions:

1. The dietary ingredient is a “pre-DSHEA” dietary ingredient. No NDI notification is required if a dietary ingredient was “marketed” in the United States prior to October 15, 1994 (i.e., before DSHEA was enacted).⁶ The revised draft guidance calls such ingredients “pre-DSHEA” dietary ingredients, while most people in industry call them “grandfathered” or “old” dietary ingredients.
2. The dietary ingredient is an “article used for food” which has not been “chemically altered.” Specifically, under section 413(a)(1) of the FDCA, no NDI notification is required if a dietary ingredient has been “present in the food supply as an article used for food in a form in which the food has not been chemically altered.”⁷

If the ingredient satisfies neither of these two exclusions, a company must submit an NDI notification to FDA at least 75 days before first using the ingredient in a dietary supplement. Both exclusions have been controversial, as the agency has interpreted both narrowly—in the 2011 draft guidance, in warning letters, and now in the revised draft guidance.

Exclusion 1, the “pre-DSHEA” exclusion, remains narrow, though some pre-DSHEA dietary ingredients may find a safe harbor

With the revised draft guidance, FDA continues to interpret narrowly the “pre-DSHEA” exclusion from the NDI notification requirement. The details of this narrow interpretation include the following:

- **To qualify as a pre-DSHEA dietary ingredient, the ingredient must have been used prior to DSHEA as a “dietary ingredient,” not merely as or in a conventional food, a drug, or any other article.** This is confusing because DSHEA added “dietary supplement” and “dietary ingredient” to the statute, so technically there was no such thing as a dietary ingredient before October 1994. Acknowledging this confusion, the revised draft guidance says that pre-DSHEA use of an ingredient counts as use as a dietary ingredient if it was marked before October 15, 1994 “for use as or in a product

use in a dietary supplement or (2) the ingredient was used as a dietary supplement or conventional food before it was approved or authorized for use as a drug. This does not necessarily mean that the article is not a dietary ingredient, just that it cannot be used in dietary supplements because of other provisions of the FDCA.

⁶ A “pre-DSHEA” dietary ingredient is excluded from the definition of a “new dietary ingredient” by section 413(d) of the FDCA. 21 U.S.C. § 350b(d) (“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.”). DSHEA was signed into law on October 25, 1994.

⁷ The “article used for food” exclusion is set forth section 413(a)(1) of the FDCA. 21 U.S.C. § 350b(a)(1).

that would now be a ‘dietary supplement’. . . and that would not also meet the definition of ‘drug.’” For example, FDA says that use of an ingredient to color conventional food before October 15, 1994 does not count as use as a dietary ingredient.

- **Not all ingredients used in dietary supplements before DSHEA count as pre-DSHEA dietary ingredients.** The revised draft guidance says that a substance is a pre-DSHEA dietary ingredient excluded from the NDI notification requirement only if it was added to a pre-DSHEA dietary supplement “as a dietary ingredient.” But excipients or other substances added for their “technical effect” are not pre-DSHEA dietary ingredients. They may not be dietary ingredients at all and if they are dietary ingredients, they are NDIs.
- **FDA specifies certain types of marketing in the United States prior to October 15, 1994 to demonstrate pre-DSHEA use as a dietary ingredient.** According to both the original and the revised draft guidance, marketing includes selling as or in a dietary supplement or as a bulk dietary ingredient for use in dietary supplements. Offers for sale online, in stores, or in advertisements or catalogs count as marketing. Documentation of such marketing can include written business records, promotional materials, and press reports. The revised draft guidance, in a new discussion that does not appear in the prior draft, says that pre-DSHEA GRAS and food additive regulations could qualify as marketing as a dietary ingredient so long as the regulation covers uses of the substance as a “nutrient supplement.” It also says that appearance in the 1992 version of *Herbs of Commerce* can be supportive but not determinative of marketing because a listing may not specify key information such as plant part or extract type. Affidavits are also inadequate on their own.
- **Changes in manufacture can turn a pre-DSHEA ingredient into an NDI.** If a change in the process used to manufacture pre-DSHEA ingredient changes the identity of the ingredient, the ingredient would become an NDI. Here the revised draft guidance goes even further than the prior draft. FDA now considers changes to the identity to include not only changes to the physiochemical structure or properties of the ingredient or changes that alter the source material (using leaves instead of roots) but also changes to the purity or biological properties (such as bioavailability or toxicity) or changes to the serving level or conditions of use of the product.

While continuing to view skeptically the lists of pre-DSHEA ingredients put together by trade associations, the revised draft guidance announces that FDA is willing to create an authoritative list of pre-DSHEA dietary ingredients, based on independent and verifiable data. FDA would base its authoritative list on (1) documentation of marketing for use as or in a dietary supplement in the United States prior to October 15, 1994 and (2) a precise description of the marketed ingredient.

Unlike the industry lists, the authoritative list would be a safe harbor: FDA would not subject ingredients on the list to the NDI notification requirement. FDA acknowledges that an ingredient not appearing on the list could still be a pre-DSHEA ingredient, but warns that it could investigate the NDI status of ingredients not on the list if it perceived the ingredient as a threat to public health, such as when the ingredient is associated with adverse events. In other words, FDA would continue its policy of pursuing or threatening enforcement when an ingredient captures the agency’s attention, often by making the news.

Exclusion 2, the exclusion for any “article used for food” and not “chemically altered” remains restricted to food additives, GRAS substances, and ingredients marketed in conventional foods outside the United States

Under section 413(a)(1) of the FDCA, no NDI notification is required for a dietary supplement containing an NDI if 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.”

In the revised draft guidance, FDA interprets this language to apply only to “a conventional food or conventional food ingredient.” Specifically, the agency says that direct food additives and substances listed or affirmed by FDA as GRAS are excluded from the NDI notification requirement so long as the form used as a dietary ingredient is not “chemically altered” from the form used in the food supply. In addition, ingredients marketed in conventional foods outside of the United States are excluded if not chemically altered. This exclusion applies “even if the dietary supplement contains more of the NDI than is used in conventional foods.” The revised draft guidance is notably silent on whether an article has been “used for food” if it has been present in the food supply only as a “constituent” of other foods. In at least one warning letter, FDA took the controversial position that a constituent itself must be used for food to qualify under the “article used for food” exclusion.⁸

FDA’s interpretation of the “article used for food” exclusion allows for ingredients to be lawfully used in food (most often as GRAS substances) and then used in dietary supplements without needing an NDI notification. Although some critics have called this a “loophole,” it has limits. The ingredients must actually be used in food to qualify under this exclusion: merely affirming something as GRAS without actually using it in conventional food would not count. The ingredients would also be subject to the NDI adulteration standard,⁹ though presumably they would satisfy this standard if they are GRAS or approved food additives.

Citing the official legislative history of DSHEA,¹⁰ FDA acknowledges that the following physical processes do not chemically alter a food: “minor loss of volatile components, dehydration, lyoph[i]lization, milling, tincture or solution in water, slurry, a powder, or solid in suspension.” Beyond these, however, FDA sees chemical alterations in many physical and chemical processes.

In a section that was not in the previous draft of the guidance, the agency suggests that it is likely to see alteration in any process that “attempts to selectively increase the concentration of

⁸ FDA Warning Letter to Star Scientific (Dec. 20, 2013) (“To the best of FDA’s knowledge, there is no information demonstrating that anatabine has been present in the food supply as an article used for food in a form in which the food has not been chemically altered. Although anatabine is present as an inherent constituent of foods such as cauliflower, eggplant, potatoes, and tomatoes, FDA is not aware of any information indicating that anatabine itself is an article used for food. In the absence of such information, anatabine is a new dietary ingredient subject to the premarket notification requirement in section 413(a)(2) of the Act.”).

⁹ The NDI adulteration standard, set forth in 402(f)(1)(B) of the FDCA, states that a dietary supplement shall be deemed adulterated if it contains a “new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.” 21 U.S.C. § 342(f)(1)(B).

¹⁰ Statement of Agreement, 140 Cong. Rec. S14801 (daily ed. Oct. 7, 1994).

particular active ingredients or cause a chemical reaction (other than esterification) that would modify the covalent bonds of any substance in the original material.” It appears that this new section may be an attempt to prevent any extracts from qualifying under the “article used for food” exclusion unless the extracts themselves are used as conventional foods. The agency explains that in a typical extraction the first step is to create a solution in water or another solvent followed by filtration to remove undissolved material. FDA characterizes this filtration as chemical alteration: “This is a much larger change in the composition of the ingredient. FDA generally regards extraction that includes a filtration step or that involves the use of a solvent other than water or alcohol (aqueous ethanol) as a process that chemically alters the source ingredient” This new interpretation may be surprising to many in the dietary supplement industry, as it means that FDA may consider many of the botanical extracts currently on the market, even when made by extraction with water or ethanol only, to be NDIs. We believe the agency can expect comments about its novel take on extraction and the removal of undissolved materials.

Unlike the prior draft of the guidance, this revised draft explicitly excludes dietary supplements from the terms “food” and “food supply” used in section 413(a)(1) of the FDCA. It says, “We do not consider prior use in dietary supplements to constitute presence in the food supply.” According to the revised draft guidance, FDA interprets “food” in this way to avoid the situation where “prior use in even one dietary supplement manufactured in small quantities and distributed over a small area would exempt all dietary supplements containing the NDI from the notification requirement, even if the intake level and conditions of use were much different.”

The concern about FDA’s interpretation of “food” is that it is inconsistent with a plain reading of both the FDCA and DSHEA. In particular, section 201(ff) of the FDCA states that “a dietary supplement shall be deemed to be a food” except for certain provisions not relevant to this analysis. DSHEA added sections 201(ff) and section 413(a)(1) to the FDCA simultaneously, which is a further reason why they should be interpreted together. It is clear that Congress meant dietary supplements to be considered “food” under nearly all of the FDCA including section 413, and that it knew how to exclude dietary supplements from particular provisions when it wished to do so.

Finally, the revised draft guidance emphasizes that the NDI adulteration standard applies to all NDIs, even those excluded from the NDI notification requirement because they are present in the food supply. To help ensure compliance with the adulteration standard, the revised draft guidance encourages companies to voluntarily submit NDI notifications when a dietary supplement contains a significantly higher level of an NDI than is used in conventional food.

What an NDI Notification Should Contain

One of the biggest changes from the prior draft is that the revised draft guidance contains much more detail about what should be included in an NDI notification. While FDA continues to take the position that NDI notification must be submitted for nearly every dietary supplement that uses an NDI, and not just for the NDI itself, the revised draft guidance also contains several concessions to the industry:

- It allows notifications that will cover multiple dietary supplements and covers a range of doses and daily intakes.

- It allows for the submission of a confidential “NDI master file,” which would contain manufacturing, specifications, and other information describing the ingredient. This master file can then be incorporated by reference in NDI notifications, including by other companies (with permission of the holder of the NDI master file). In practice, ingredient suppliers will likely seek to create NDI master files, and then grant their customers, the dietary supplement companies, right of reference to the master files.
- It exempts companies from the need to submit NDI notifications for a new dietary supplement that contains the same NDI covered by the same company’s prior submission, provided certain criteria are met. Notably, however, it does not exempt companies from submitting an NDI covered by an earlier notification submitted by another company. In addition, if the new dietary supplement contains ingredients that were not mentioned in the original NDI notification, FDA says that an NDI notification would be required because FDA fears that the ingredients could interact to create a safety concern. FDA posits several such scenarios to help companies determine whether their prior NDI notifications cover new dietary supplements.

The revised draft guidance also contains practical and non-controversial details about the NDI notification. For example, it must be submitted to FDA at least 75 days before the ingredient is introduced in interstate commerce, as section 413(a)(2) of the FDCA requires.¹¹ The NDI notification should contain data explaining why the manufacturer or distributor reasonably expects the NDI to be safe for its intended use.¹² FDA recommends that it include the following:

- 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 the sponsor’s 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 the sponsor’s conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe.

Comment Period

FDA requests comments on the revised draft guidance by October 11, 2016. There is a lot to analyze in the revised draft guidance. Some of FDA’s controversial interpretations appear entrenched, such as its view on synthetic versions of botanicals. We expect FDA to receive many new comments on this topic, but believe such comments are unlikely to change the agency’s view.

¹¹ 21 U.S.C. § 350b(a)(2).

¹² *Id.* (the NDI notification should contain “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”).

Food, Beverage, and Dietary Supplements

Other interpretations the draft guidance reflects are new, and FDA may be more willing to change them. These new interpretations include the agency's insistence that a dietary supplement is not food in the food supply. Others include its novel view that extraction constitutes chemical alteration if undissolved materials are removed.

Finally, in the *Federal Register* notice announcing the revised draft guidance, FDA solicits feedback on three topics: (1) the processes that turn a pre-DSHEA dietary ingredient into an NDI; (2) the processes that "chemically alter" an ingredient; and (3) recommendations for methods of compiling data for the creation of an authoritative list of pre-DSHEA dietary ingredients. These first two topics are areas in which the interpretation articulated in the revised draft guidance is even more restrictive than earlier iterations.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Beverage, and Dietary Supplements practice:

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