

E-ALERT | Food & Drug

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FDA ISSUES NEW DIETARY INGREDIENT NOTIFICATION DRAFT GUIDANCE

On July 5, 2011, the U.S. Food and Drug Administration (“FDA”) published a draft guidance document (“the draft guidance”) intended to assist dietary supplement manufacturers and distributors in determining whether a premarket safety notification for a dietary supplement containing a new dietary ingredient (“NDI”) is necessary and in preparing such notifications (“NDI notifications”).¹ The draft guidance is written in Q&A format and it addresses: (i) how to determine whether an NDI notification is necessary; (ii) NDI notification procedures and timeframes; and (iii) the contents of an NDI notification.

Background

Since the enactment of the Dietary Supplement Health and Education Act of 1994 (“DSHEA”) on October 25, 1994, FDA has regulated dietary supplements under sections 201(ff) and 413 of the Federal Food, Drug, and Cosmetic Act (“FDCA”). Section 413, which defines the term “new dietary ingredient,” requires manufacturers or distributors of NDIs or dietary supplements that contain NDIs to submit a premarket notification to FDA at least 75 days before introducing the supplement into interstate commerce, unless the NDI and any other dietary ingredients in the supplement “have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.”² The NDI notification must contain information that forms the basis on which the manufacturer or distributor has concluded that the dietary supplement containing the NDI will reasonably be expected to be safe. If a manufacturer or distributor fails to submit the required premarket notification, the dietary supplement is deemed adulterated under section 402(f) of the FDCA. Even if a manufacturer or distributor does submit such notification, a dietary supplement containing an NDI is adulterated under section 402(f) unless there is a history of use or other evidence of safety establishing that the NDI, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.

Even though the NDI notification process has existed since the enactment of DSHEA, and FDA has issued a regulation at 21 C.F.R. § 190.6 to implement the NDI notification requirements, FDA has not previously stated its position on the definition of an NDI or the requirements for an NDI notification.

¹ Draft Guidance, available [here](#). See 76 Fed. Reg. 39111 (July 5, 2011). Section 113(b) of the Food Safety Modernization Act (“FSMA”) required FDA to publish, not later than 180 days after the date of enactment (January 4, 2011), guidance that clarifies 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 section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), the evidence needed to document the safety of an NDI, and appropriate methods for establishing the identity of an NDI. FDA has published the draft guidance to comply with section 113(b).

² FDCA § 413(a)(1).

The following discussion summarizes the FDA draft guidance. We understand that the regulated industry does not agree with many of the FDA positions and interpretations reflected in the document.

Determining Whether an NDI Notification is Necessary (pages 8-14)

Through a series of detailed hypothetical questions and answers, the draft guidance provides FDA's current thinking on how to determine whether an NDI notification is necessary. Below, we summarize highlights from this section.

What is an NDI?

An NDI is defined by statute as “a dietary ingredient that was not marketed in the United States before October 15, 1994.”³ The draft guidance states that the term “dietary ingredient” is a key component of the NDI definition. For example, the use of an ingredient in a conventional food prior to that date does *not* determine whether the ingredient is an NDI. Rather, “[w]hat matters is whether the ingredient was marketed as a dietary ingredient – meaning in or as a dietary supplement, or for use in dietary supplements – in the U.S. before October 15, 1994.”⁴ Similarly, a component of a conventional food marketed before October 15, 1994 is an NDI if a manufacturer or distributor wants to market it as a dietary ingredient. FDA states that “[t]he mere presence of a substance as a component of a conventional food that was marketed before October 15, 1994 does not establish that that substance was marketed as a dietary ingredient before that date.”⁵ FDA further emphasizes that evidence of marketing outside the U.S. is not relevant to the NDI definition; rather “[t]he only kind of marketing that is relevant to whether a dietary supplement is an NDI is marketing in the U.S. before October 15, 1994.”⁶

Establishing that a dietary ingredient was marketed prior to October 15, 1994

FDA specifies that documentation to show that a dietary ingredient is not an NDI “should consist of written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994. Examples include sales records, manufacturing records, commercial invoices, magazine advertisements, mail order catalogues, or sales brochures.”⁷ Such evidence must establish that the ingredient was marketed as a dietary ingredient for use in a dietary supplement. FDA does not recognize any authoritative lists of dietary ingredients marketed prior to October 15, 1994. Although certain trade organizations have published lists of “old dietary ingredients” or “grandfathered lists,” the guidance states that FDA will not accept the inclusion of an ingredient on any such list as proof that the ingredient is not an NDI.

The effect of manufacturing changes on NDI status

If a manufacturer changes the manufacturing process for a dietary ingredient that was marketed in the U.S. prior to October 15, 1994, and the change alters the chemical composition or structure of the ingredient, FDA states that the change will most likely render the substance an NDI, triggering the NDI notification requirement. FDA encourages firms planning a manufacturing change to consult with the agency on whether the proposed change would create an NDI.

³ FDCA § 413(c).

⁴ Draft Guidance, at IV-A-3.

⁵ *Id.* at IV-A-4.

⁶ *Id.* at IV-A-7.

⁷ *Id.* at IV-A-8.

Exceptions to notification requirement for NDIs historically used in conventional food

A notification is not needed when a dietary supplement product 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 is not chemically altered. If a dietary ingredient has been listed or affirmed by FDA as generally recognized as safe (“GRAS”) for direct addition to food, self-affirmed as GRAS for direct addition to food, or approved as a direct food additive in the U.S., no notification is required as long as the substance has been used in the food supply and is to be used as an NDI *without chemical alteration*. All NDIs are nonetheless subject to the adulteration standard in section 402(f)(1)(B) of the FDCA, which requires adequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury. FDA is likely to conclude that this standard is met only if the intake level is not changed. Therefore, even though an NDI notification is not required for these products, FDA recommends that a manufacturer or distributor of this type of dietary supplement consult with the agency about the basis for concluding that such “adequate information” exists to avoid having the product deemed adulterated.

Processes that chemically alter an article of food

FDA cites the legislative history of DSHEA to explain that the following processes do *not* chemically alter an article of food that has been present in the food supply: minor loss of volatile components, dehydration, lyophilization, milling, and formation of a tincture or a solution in water, a slurry, a powder, or a solid in suspension. Dietary ingredients produced from conventional food through these methods therefore do not require NDI notifications.

By contrast, FDA states that a broad range of processes would be deemed to chemically alter an article of food, including:

- a process which makes or breaks chemical bonds such as hydrolysis or esterification
- removal of some components of a tincture or solution in water (e.g., by chromatography, distillation, or membrane filtration)
- use of solvents other than water or aqueous ethanol to make an extract, or the use of a different solvent than that used to make an old dietary ingredient or conventional food ingredient
- changing agricultural or fermentation conditions to alter the chemical compounds of the ingredient, or fermentation using a fermentation medium different from the one used to make conventional foods in the food supply; and
- use of a botanical ingredient that is at a different life stage than previously used, such as making an extract from unripe instead of ripe apples.

According to the draft guidance, NDIs produced through these processes should be the subject of an NDI notification.

Other considerations

Among the numerous other considerations that manufacturers and distributors must take into account when determining whether an NDI notification is required, the draft guidance provides the following:

- If a manufacturer or distributor has already submitted an NDI notification for a dietary supplement containing an NDI, it does not need to submit a notification for a different product containing the same NDI as long as: (1) the daily intake level recommended or suggested in the

labeling of the new supplement will be equal to or less than that specified in the prior NDI notification; (2) the new supplement does not contain other dietary ingredients that were not included in the original NDI notification; (3) the target populations (e.g., children or pregnant or lactating women) are the same or a subset of the target populations specified in the original notification; (4) all other conditions of use are the same or more restrictive (e.g., fewer intended uses, shorter duration of use) than those described in the prior NDI notification; and (5) FDA did not express safety or other concerns in response to the prior notification.

- If another manufacturer or distributor has already submitted a notification for a particular NDI, and a new party intends to market a dietary supplement containing the same NDI, that party must also submit an NDI notification. FDA takes this position because the statute places the obligation for submitting an NDI notification on *each* manufacturer or distributor.
- A manufacturer or distributor must notify FDA about a microbial ingredient in a dietary supplement if it is an NDI that has not been present in the food supply as an article of food in a form in which the food has not been chemically altered.
- A contaminant that is found in the food supply is not a dietary ingredient. Although most constituents of conventional foods in the food supply would be “dietary substances” that could qualify as dietary ingredients, contaminants are not intended for ingestion, nor are they considered to be food or part of the food supply.
- A synthetic copy of a constituent or extract of an herb or other botanical is not a dietary ingredient. Because a synthetic copy of a constituent of a botanical was “never part of the botanical,” it cannot be a “constituent” of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FDCA.⁸ The draft guidance does not address other synthetic ingredients.
- Food contact substances and other indirect food additives usually cannot be dietary ingredients.
- If a manufacturer alters the chemical structure of a dietary ingredient, the new substance could (rarely) still be a dietary ingredient. For example, “in rare instances, the new substance may independently qualify for one of the dietary ingredient categories listed in section 201(ff)(1) of the [FDCA].”⁹
- As a general rule, an article that has been authorized for investigation as a new drug or as a biologic before being marketed as a food or as a dietary supplement cannot be marketed as a dietary supplement if substantial clinical investigations of the article have begun and the existence of such investigations has been made public. This holds true even if the investigational new drug application (“IND”) has been withdrawn or the ingredient is no longer being studied. A party may, however, manufacture and sell a dietary supplement containing a dietary ingredient that was marketed as a food or dietary supplement *before* it was approved as a drug, licensed as a biologic, or authorized for investigation under an IND.

NDI Notification Procedures and Timeframes (pages 14-20)

In this section of the draft guidance, FDA provides detailed instructions on the procedures governing the submission of an NDI notification. FDA has created a template for organizing an NDI notification to help “facilitate an efficient and timely FDA review.”¹⁰ FDA recommends the use of its sample form (attached to the draft guidance as Appendix B) because “it provides a checklist of the information

⁸ In this answer and elsewhere, the FDA position fails to recognize section 201(ff)(1)(E) (“a dietary substance for use by man to supplement the diet by increasing the total dietary intake”) as an independent category of dietary ingredients.

⁹ Draft Guidance, at IV-D-4.

¹⁰ *Id.* at V-A-2.

FDA finds most useful in evaluating notifications and organizes the information in a format consistent with the agency's current electronic review system."¹¹ Although FDA cannot accept NDI notifications electronically at the present time, the agency is making plans to convert to an electronic submission system in the future.

Although FDA's NDI notification regulation requires manufacturers or distributors to submit an original and two copies of the NDI notification to the agency, FDA "no longer needs the second copy and does not intend to enforce that part of the requirement."¹² Therefore, the original and only one copy of the NDI notification should be submitted.

All references to published information offered in support of an NDI notification must be accompanied by reprints or photocopies of such references. A manufacturer or distributor should not submit only the abstract or bibliographic citation of any publication or other material with a notification; rather, the full text must be included. If a manufacturer or distributor relies on material written in a foreign language in its submission, that material must be accompanied by an accurate and complete English translation.

After the 90th day following the notification's filing date, FDA will place all information in the notification on public display, except for any that is trade secret or confidential commercial information ("CCI"). FDA recommends that the submitter clearly identify any such trade secret or CCI, either by marking the information where it appears in the notification or identifying this information in a separate document that accompanies the notification. The submitter should also provide an explanation for the basis of this belief. Similarly, if the submitter believes there is *no* trade secret or CCI contained in the notification, FDA requests that the submitter state this in the notification. Examples of trade secrets might include manufacturing methods and product composition, product specifications needed to protect proprietary composition information, and certificates of analysis. Examples of CCI might include sales statistics, dollar volume, amount or source of income, profits or losses, expenditures, and names of suppliers or subcontractors or brands of equipment.

FDA considers the date when it receives a complete notification to be the date of filing. Within 75 days thereafter, the manufacturer or distributor may expect a letter acknowledging receipt of the notification and stating the date on which the notification was filed. Examples of the types of response letters FDA commonly sends include, but are not limited to: (1) letter of acknowledgement without objection; (2) letter listing deficiencies that make the notification incomplete under 21 C.F.R. § 190.6; (3) objection letter raising safety concerns based on information in the notification or identifying gaps in the history of use or other evidence of safety; and (4) letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient under FDCA § 201(ff)(1), or the product is excluded from the definition of "dietary supplement" under FDCA § 201(ff)(2) because it is not intended for ingestion).

Contents of an NDI Notification (pages 20-40)

This is the most extensive section of the draft guidance, providing information about how manufacturers or distributors should describe the identity of the NDI and dietary supplement and detailing the types of evidence that may support the history of use and evidence of safety of the product.

¹¹ *Id.*

¹² *Id.* at V-A-9.

Identity information about the NDI and the dietary supplement

The draft guidance clarifies that the purpose of including identify information in an NDI notification is “to establish what the NDI is, including the category of dietary ingredient in section 201(ff)(1) of the [FDCA] to which it belongs; to identify the other ingredients and components of the dietary supplement; and to provide the basis for FDA to evaluate the qualitative and quantitative relationship between the ingredients in the dietary supplement and the substances that are described in the history of use or other evidence of safety provided in [the] notification.”¹³

Manufacturers or distributors are encouraged to describe the manufacturing process, the physical and chemical composition of the NDI, controls for batch-to-batch variability, and the identity and level of any impurities and contaminants that may be in the NDI. The description should have sufficient detail to enable FDA to understand the overall process used to make the NDI and the dietary supplement.

If an NDI is a discrete chemical entity – such as a vitamin, mineral, amino acid, or a constituent or a metabolite of another dietary ingredient – the manufacturer or distributor should provide FDA with sufficient information to uniquely characterize the ingredient as a discrete molecular entity (or mixture of discrete molecular entities).

If there is a history of use or other evidence of safety for a substance or product that is similar to, but not exactly the same as, a manufacturer’s or distributor’s NDI or dietary supplement, the submitter of the NDI notification should use “chemical, microbiological, and botanical characterizations, as appropriate, to explain how the substance or product is similar to [its] NDI or dietary supplement and...provide a rationale for how the safety information that is presented for the similar substance or product is relevant to the safety of [the] NDI or dietary supplement.”¹⁴

History of use or other evidence of safety

The guidance states that a manufacturer or distributor “must provide the information that forms the basis on which [it] has concluded that a dietary supplement containing the NDI will reasonably be expected to be safe under the supplement’s labeled conditions of use....In general, this information should include an adequate history of safe use, safety studies, or both.”¹⁵

To substantiate an NDI’s history of safe use, FDA recommends that manufacturers or distributors provide “evidence that the substance was safely consumed as a food or dietary supplement or as a component of a more complex mixture...at levels equal to or higher than those that would be consumed by someone taking the NDI-containing supplement under the proposed conditions of use.”¹⁶ FDA considers many types of documentation potentially relevant to show an NDI’s history of safe use in food, such as published data and information, advertisements or other published promotional material describing the composition of products, published agricultural or food production data, or cookbooks or other published recipes documenting the use of an ingredient to prepare conventional foods.

A manufacturer or distributor is not required to submit a comprehensive survey of every historical use of the NDI; rather, only the data and information on which its reasonable expectation of safety is based are required.

¹³ *Id.* at VI-A-1.

¹⁴ *Id.* at VI-A-9.

¹⁵ *Id.* at VI-B-1.

¹⁶ *Id.* at VI-B-3.

In this section of the draft guidance, FDA provides specific information on how manufacturers or distributors may evaluate the data establishing a history of safe use, including definitions of “daily” versus “intermittent” use or “chronic” versus “sub-chronic” use in different scenarios, as well as factors influencing the need for additional animal or human studies to support evidence of a history of safe use.

FDA cites potentially useful guidelines for safety testing, and provides its thinking on specific issues relevant to protocol selection, toxicity testing concerns, and human studies. If an NDI contains nanomaterials or otherwise involves the application of nanotechnology, FDA recommends that the manufacturer or distributor contact the agency prior to submitting an NDI notification because “there is little scientific literature discussing the safety of nanomaterials in dietary supplements.”¹⁷

FDA recommends that the discussion of the history of use and other evidence of safety in an NDI notification should include two separate safety profiles:

- a comprehensive safety profile evaluating the safety of the NDI; and
- a dietary supplement “Safety Narrative” explaining why the information in the notification provides a basis to conclude that the dietary supplement that contains the NDI will reasonably be expected to be safe when used under the conditions recommended or suggested in its labeling.

The draft guidance concludes with a detailed discussion of the information that the manufacturer or distributor should include in these safety profiles.

As many of the positions FDA has taken in draft guidance are different from the way in which stakeholders have long interpreted the NDI provisions of DSHEA, interested parties should review the draft guidance carefully and consider submitting comments to FDA. Written comments should be submitted by October 3, 2011 in order to ensure that the agency will consider them before beginning work on the final version of the guidance.

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¹⁷ *Id.* at VI-B-43.