Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry

Draft Guidance

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For questions regarding this draft document, contact the Food and Drug Administration, Office of Dietary Supplement Programs, 5001 Campus Drive (HFS-810), College Park, MD 20740, Toll Free (855) 543-3784, or 240-402-2375.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

October 2026

Replaces revised draft guidance
issued August 2016,
March 2024 (Level 2 Revisions), and April 2024
(Level 2 Revisions)

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RESERVED – See the final guidance "New Dietary Ingredient (NDI) Notifications and Related Issues; Identity and Safety Information About the NDI: Guidance for Industry."

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Document History

Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

Under section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 350b(a)(2)), the manufacturer or distributor of a new dietary ingredient (NDI) that has not been present in the food supply as an article used for food, or a dietary supplement containing such an NDI, must submit a premarket safety notification to FDA at least 75 days before introducing the product into interstate commerce. This guidance is intended to help manufacturers and distributors of dietary ingredients and dietary supplements ("you") decide whether to submit a premarket safety notification to FDA ("we" or "us") for a product that is or contains an NDI. These premarket safety notifications are commonly referred to as NDI notifications. The guidance is also intended to help you to prepare NDI notifications that we will be able to review more efficiently and respond to more quickly.

The guidance answers frequently asked questions about NDI notifications and related issues. The major topics it addresses are:

- What qualifies as an NDI;
- When an NDI notification is required;
- What are the procedures for submitting an NDI notification;

[1] This guidance has been prepared by the Office of Dietary Supplement Programs in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

- What types of data and information FDA recommends you consider when you evaluate the safety of NDIs and dietary supplements containing an NDI; and
- What FDA recommends you include in an NDI notification.

In addition, the guidance contains questions and answers about parts of the definition of "dietary supplement"[2] that can affect whether a particular substance may be marketed as a dietary ingredient in a dietary supplement. We encourage you to consult this guidance during your safety review of dietary supplements that contain an NDI and when you prepare NDI notifications.

The guidance focuses on interpreting the FD&C Act's requirements relating to NDIs and dietary supplements that contain an NDI. It does not discuss other parts of the FD&C Act that may affect the regulatory status of a particular ingredient or product, such as provisions of the FDA Food Safety Modernization Act (FSMA)[3] that may apply to dietary ingredients and/or dietary supplements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

On October 25, 1994, the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Pub. L. 103-417) was signed into law. DSHEA amended the FD&C Act by adding, among other provisions, (1) section 201(ff) (21 U.S.C. 321(ff)), which defines the term "dietary supplement"; and (2) section 413 (21 U.S.C. 350b), which defines the term "new dietary ingredient" and requires the manufacturer or distributor of an NDI, or of the dietary supplement that contains the NDI, to submit a premarket notification to FDA at least 75 days before introducing the product into interstate commerce or delivering it for introduction into interstate commerce, unless the NDI and any other dietary ingredients in the dietary 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" (21 U.S.C. 350b(a)(1)).

The notification must contain the information, including any citation to published articles, which provides the basis on which the manufacturer or distributor of the NDI or dietary supplement (the notifier) has concluded that the dietary supplement containing the NDI will reasonably be expected to be safe (21 U.S.C. 350b(a)(2)). If the required premarket notification is not submitted to FDA, section 413(a) of the FD&C Act (21 U.S.C. 350b(a)) provides that the dietary supplement containing the NDI is deemed to be adulterated under section 402(f) of the FD&C Act (21 U.S.C.

[2] "Dietary supplement" is defined in 21 U.S.C. 321(ff). Available at: https://www.gpo.gov/fdsys/pkg/USCODE-2014-title21/pdf/USCODE-2014-title21-chap9-subchapII-sec321.pdf

[3] Pub. L. No. 111-353, 124 Stat. 3886 (2011).

342(f)). Even if the notification is submitted as required, the dietary supplement containing the 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.

To help industry comply with DSHEA, we issued a regulation in 21 CFR 190.6 (§ 190.6 or the NDI regulation) to implement the FD&C Act's premarket notification requirements for dietary supplements that contain an NDI (62 FR 49886; September 23, 1997). The NDI regulation specifies the information the manufacturer or distributor must include in its premarket NDI notification (21 CFR 190.6(b)):[4]

- The name and complete address of the manufacturer or distributor that is submitting the notification.
- The name of the NDI that is the subject of the premarket notification. For botanicals, the Latin binomial name must be given, including the author citation (the name of the scientist who gave the botanical its Latin binomial name).
- A description of the dietary supplement that contains the NDI, including:
  - the level of the NDI in the dietary supplement, and
  - 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 supplement's labeling, the ordinary conditions of use of the supplement.
- The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended in the labeling of the dietary supplement, will reasonably be expected to be safe.
- The signature of a person authorized by the manufacturer or distributor to sign the notification on its behalf.

In addition to the requirements for the content of NDI notifications, the NDI regulation establishes the administrative procedures for these notifications. Section 190.6(c) defines the filing date of a notification as the date we receive it and, consistent with section 413(a)(2) of the FD&C Act, prohibits the manufacturer or distributor of the dietary supplement that contains the NDI from introducing the product into interstate commerce, or delivering it for introduction into interstate commerce, for 75 days after the filing date (21 CFR 190.6(c)). If the manufacturer or distributor submits additional substantive information in support of the original NDI notification, § 190.6(d) provides that the date of this supplemental submission to FDA becomes the new notification filing date, and the 75-day period restarts. Consistent with section 413(a) of the FD&C Act, § 190.6(e) provides that FDA will not disclose the existence of, or the information contained in, an NDI notification for 90 days after the filing date of the notification. Section 190.6(e) further provides that after the 90th day, the entire notification, except trade secrets and confidential commercial information, will be placed on public display, as prescribed in section 413(a) of the FD&C Act. Finally, § 190.6(f) states that FDA's failure to respond to an NDI notification does not constitute a

[4] Please see question V.A.2 for a recommended template for the format and content of an NDI notification, and section VI.A for detailed recommendations on what to include in the identity section of an NDI notification.

finding by the agency that the NDI or the dietary supplement containing the NDI is safe or is not adulterated under section 402 of the FD&C Act (21 U.S.C. 342).

On January 4, 2011, the President signed into law the FDA Food Safety Modernization Act (FSMA) (Pub. L. 111-353). Section 113(b) of FSMA requires FDA to publish, not later than 180 days after the date of enactment, 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 FD&C Act, the evidence needed to document the safety of an NDI, and appropriate methods for establishing the identity of an NDI. In July 2011, we published a draft guidance to comply with section 113(b) of FSMA (see 76 FR 39111; July 5, 2011). This revised draft guidance replaces the July 2011 draft guidance.

III. Goals and Public Health Importance of the Guidance

One key goal of this guidance is to improve the rate of compliance with the NDI notification requirement. In 2012, FDA estimated that the number of dietary supplements on the market was 55,600 and that 5,560 new dietary supplement products come on the market each year.[5] This is in contrast to the approximately 4,000 products that were on the market in 1994, when DSHEA was enacted.[6] As of December 2014, we had received and completed our evaluation of just over 750 NDI notifications since the first notification was received in 1995.[7] These figures, coupled with recent concern about the presence of undeclared active ingredients in products marketed as dietary supplements, highlight the importance of submitting NDI notifications as a preventive control to ensure that consumers are not exposed to unnecessary public health risks in the form of new ingredients with unknown safety profiles.[8] To improve public understanding of the NDI notification requirement, this guidance includes an in-depth discussion of the scope of the requirement, along with detailed examples of situations in which a notification would or would not be required.

A second goal of the guidance is to improve the quality of NDI notifications. Our aim in issuing the NDI regulation in 1997 was to ensure that NDI notifications contain the information that is necessary for FDA to evaluate whether a dietary supplement containing an NDI is reasonably expected to be safe, and that aim remains the same today. After many years of experience with reviewing NDI notifications and answering questions from industry, we have concluded that a guidance on NDI issues is needed to help the dietary supplement industry understand and comply with section 413 of the FD&C Act and the NDI regulation. We hope that the additional

[5] Dietary Supplement Labeling Requirements and Recommendations Under the Dietary Supplement and Nonprescription Drug Consumer Protection Act, 77 FR 35687 (June 14, 2012).
[6] Dietary Supplement Health and Education Act of 1994, Pub. L. 103-417, § 2(12)(C), 108 Stat. 4326. Available at: http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/ucm148003.htm
[7] Memorandum to File from Fred A. Hines, Consumer Safety Officer, FDA (December 17, 2014).
[8] See, e.g., NDI Notification Response - E. coli Nissle strain (Oct. 28, 2011) Available at: https://www.regulations.gov/document?D=FDA-2012-S-1178-0014; NDI Notification Response - Human placenta extract (Apr. 6, 2011). Available at: https://www.regulations.gov/document?D=FDA-2011-S-0933-0133

explanation in this guidance will help you decide when an NDI notification is required and what that notification should contain.

DSHEA does not specify the type or amount of evidence that must be included in an NDI notification. Accordingly, this guidance explains how to submit a premarket notification and makes detailed recommendations on the type and amount of evidence to include. As set forth in more detail in the rest of this guidance, we recommend including in your NDI notification 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 your 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 your conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe.

IV. Determining Whether a New Dietary Ingredient (NDI) Notification Is Required

A. What Is a New Dietary Ingredient?

1. What do the terms "dietary ingredient" and "new dietary ingredient" mean?

As defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)), a "dietary ingredient" is any one of the following:

(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), (B), (C), (D), or (E).

An NDI is defined as a dietary ingredient that was not marketed in the U.S. before October 15, 1994 (21 U.S.C. 350b(d)). Thus, to be an NDI, a substance must be a dietary ingredient.

2. Can a substance that is not a dietary ingredient be an NDI?

No. Because "new dietary ingredient" is defined to mean a dietary ingredient that was not marketed in the U.S. before October 15, 1994, a substance cannot be a new dietary ingredient unless it is also a dietary ingredient.

3. Must I submit an NDI notification for a dietary ingredient marketed in the U.S. prior to October 15, 1994?

No. Dietary ingredients marketed prior to October 15, 1994 ("pre-DSHEA dietary ingredients") are not NDIs and, therefore, do not require an NDI notification. See questions IV.A.4, IV.A.7 and IV.A.10 for more on how FDA interprets the terms "marketed" and "dietary ingredient" in the definition of an NDI (21 U.S.C. 350b(d)).

4. Is an ingredient that was used to make a conventional food marketed before October 15, 1994, an NDI?

It depends. The use of an ingredient in a conventional food before October 15, 1994, does not determine whether the ingredient is an NDI. What matters is whether the ingredient was marketed as a dietary ingredient — meaning that it was marketed in or as a dietary supplement, or for use in a dietary supplement — in the U.S. before October 15, 1994. Therefore, an ingredient that was used to make a conventional food before October 15, 1994, is still an NDI unless the ingredient was also marketed as a dietary ingredient in the U.S. before October 15, 1994. For example, an ingredient used to color a conventional food before October 15, 1994, would be an NDI unless it was also marketed before October 15, 1994, in or as a dietary supplement, or as a dietary ingredient for use in a dietary supplement.

We recognize that the present definitions of "dietary supplement" and "dietary ingredient" were not added to the FD&C Act until after October 15, 1994, and that many products now marketed as dietary ingredients for use in dietary supplements were marketed under other product categories, such as foods for special dietary use or food additives. Therefore, we interpret "dietary ingredient" to 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. See questions IV.A.7 and IV.A.10 for more about FDA's views on the meaning of "marketing" and "dietary ingredient" in the NDI definition.

a. Is an NDI notification required for a dietary supplement containing an NDI if the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered?

No, an NDI notification would not be required in this situation because of the exception to the notification requirement for dietary supplements that contain only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered (21 U.S.C. 350b(a)(1)). See questions IV.B.4 and IV.B.5 for FDA's view on what "chemically altered" means.

Example: Ingredient X is a food additive that was approved for use to sweeten baked goods in 1993 and was marketed for that use before October 15, 1994, but was not marketed for use as a dietary ingredient in dietary supplements before that date. ABC Company wants to market a supplement that contains Ingredient X, and it plans to use the same form of Ingredient X used as a sweetener in baked goods. Ingredient X will be the only dietary ingredient in the supplement, which will be called "X-cellent." Although Ingredient X is an NDI because it was not marketed as a dietary ingredient before October 15, 1994, ABC Company is not required to submit an NDI notification for X-cellent because Ingredient X 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, and it is the only dietary ingredient in the supplement.

b. Does the adulteration standard in 21 U.S.C. 342(f)(1)(B)[9] apply to a dietary supplement containing an NDI even when an NDI notification is not required?

Yes. The adulteration standard in 21 U.S.C. 342(f)(1)(B) applies to all dietary supplements that contain an NDI, even in situations when no notification is required because the supplement contains only dietary ingredients that have been present in the food supply as articles used for food in a form in which the food has not been chemically altered. See section IV.B for more information about chemical alteration and the exception to the NDI notification requirement for certain NDIs that have been present in the food supply as conventional foods.

[9] Under 21 U.S.C. 342(f)(1)(B), a dietary supplement containing an NDI is adulterated unless there is adequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury.

5. Is a substance that was a component of a conventional food marketed before October 15, 1994, an NDI if the component was not a dietary ingredient marketed in the U.S. before October 15, 1994?

Yes, assuming the component meets the definition of a dietary ingredient. The mere presence of a substance as a component of a conventional food that was marketed before October 15, 1994, does not establish that the substance was marketed as a dietary ingredient before that date. Similarly, the fact that a minor component may have been isolated as part of an analytical chemical procedure to examine the composition of the previously marketed food before October 15, 1994, is not sufficient to establish that the component is a pre-DSHEA dietary ingredient or even that it is a dietary ingredient at all. If it is not a dietary ingredient, it is ineligible to be an NDI. If the food component fits into one of the dietary ingredient categories (for example, if it is a metabolite or extract of another dietary ingredient) but was not marketed as a dietary ingredient before October 15, 1994, it would be an NDI. On the other hand, if the substance was marketed as a dietary ingredient before that date (in addition to its marketing for conventional food use), then it is not an NDI. (See questions IV.A.4, IV.A.7, and IV.A.10 for FDA's views on the meaning of "marketing" and "dietary ingredient" in the NDI definition.)

6. Is a substance that was an ingredient in a dietary supplement marketed before October 15, 1994, an NDI?

The answer depends on whether the substance was used as a dietary ingredient or for some other purpose (e.g., excipient or processing aid) in the pre-DSHEA dietary supplement. If the substance was added to the supplement as a dietary ingredient, it is not an NDI and may be used in dietary supplements without submitting an NDI notification to FDA.

If the substance was not added to the pre-DSHEA dietary supplement as a dietary ingredient, however, the analysis becomes more complicated. If the substance was directly added to the pre-DSHEA dietary supplement, intended to become a component of the finished dietary supplement and have a technical effect in it, and was GRAS or approved as a food additive for that use, the substance would be an NDI. However, because most secondary direct food additives,[10] indirect food additives,[11] food contact substances,[12] and other indirectly added substances are not

[10] Secondary direct food additives are added during the manufacturing of a food to achieve a technical effect, but they have no technical effect in the finished food. See FDA, Food Ingredients and Packaging Terms. Available at: http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm (accessed April 22, 2015).

[11] Indirect food additives come into contact with food as part of packaging, holding, or processing, but they are not intended to be added directly to, become a component of, or have a technical effect in or on the food. Before the FDA Modernization Act of 1997, indirect food additives were approved by regulation. Now, new indirect food additives are authorized through the food contact substance notification program. In addition, indirect food additives may be authorized through the threshold of regulation exemption process in 21 CFR 170.39. See FDA, Food Ingredients and

intended to have a technical effect in or become components of the finished food (see question IV.D.4), you would first have to consider whether such a substance fits into one of the dietary ingredient categories in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)) to determine whether it is an NDI. If the substance does not fit into any of the dietary ingredient categories, it would not be either an NDI or a pre-DSHEA dietary ingredient. Rather, it could not be used as a dietary ingredient in a dietary supplement at all.

7. What does "marketing" a dietary ingredient mean?

FDA considers "marketing" a dietary ingredient to mean selling or offering the dietary ingredient for sale (1) as or in a dietary supplement, (2) in bulk as a dietary ingredient for use in dietary supplements, or (3) as an ingredient in a blend or formulation of dietary ingredients for use in dietary supplements. A dietary ingredient may be "marketed" by offering the article for sale online or at a retail establishment, listing it for sale in a catalog or price list, or through advertising or other promotion, if the promotion makes clear that the article is available for purchase. "Coming soon" advertisements would not qualify.

If a dietary supplement containing an NDI is sold before the manufacturer or distributor submits a required NDI notification or less than 75 days after the notification is submitted, the sale of the product is not evidence that the dietary supplement or NDI was lawfully marketed.

8. Is a dietary ingredient marketed outside the U.S. prior to October 15, 1994, considered to be an NDI if it was not marketed in the U.S. before that date?

Yes. Submitting documentation that the ingredient was marketed in any other country before this date does not establish that the ingredient is not an NDI. The only kind of marketing that is relevant to whether a dietary ingredient is an NDI is marketing in the U.S. before October 15, 1994.[13]

9. What documentation does FDA recommend to show that a dietary ingredient was marketed prior to October 15, 1994?

Documentation to show that a dietary ingredient is not an NDI should consist of written business records, promotional materials, or press` reports with a

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Packaging Terms. Available at: http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm (accessed April 22, 2015).

[12] A food contact substance is a substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if that use is not intended to have any technical effect in the food. 21 U.S.C. 348(h)(6).

[13] For evidence of marketing in another country as evidence of safety, especially when considering the differences in dietary consumption between countries, see question VI.B.3.

contemporaneous date prior to October 15, 1994. Examples include sales records, bills of lading, sales contracts, manufacturing records, commercial invoices, magazine advertisements, mail order catalogs, or sales brochures.

Documentation should include adequate information to establish that marketing took place in the U.S.: the identity (e.g., chemical or botanical name) of the marketed ingredient, including its form (e.g., ground herb, water extract, oil), and whether the ingredient was marketed as a dietary ingredient or for some other purpose. For example, advertising in body building magazines could be adequate evidence of marketing as a dietary ingredient. On the other hand, advertising or other references in gardening or landscaping magazines would not likely serve as adequate evidence of the marketing of a botanical or herb as a dietary ingredient.

We would also consider GRAS and food additive regulations in the *Code of Federal Regulations* as documentation that an ingredient was marketed as a dietary ingredient before October 15, 1994, if the regulation covers use of the substance as a nutrient supplement, became effective before October 15, 1994, and contains identity specifications that the ingredient meets. Although references published before October 15, 1994, such as the 1992 edition of *Herbs of Commerce*,[14] may be supportive, we are unlikely to regard a listing in *Herbs of Commerce* as being solely determinative of whether a dietary ingredient was marketed as such before October 15, 1994 because this listing may not specify necessary information such as the plant part and/or extract type. If you rely on *Herbs of Commerce* as evidence that your dietary ingredient is not an NDI, we recommend that you maintain additional documentation showing that the botanical was marketed as a dietary ingredient before October 15, 1994. The documentation should specify the plant part from which the botanical dietary ingredient was derived, and for botanical extracts it should also specify the extract type.

Affidavits attesting to recollection of when a dietary ingredient was first marketed generally would not be adequate to show that an ingredient was marketed prior to October 15, 1994, unless supported by contemporaneous written records. Because memory can be unreliable, especially when the event in question took place more than thirty years ago, we are not likely to regard such an affidavit alone, without any sort of objective, verifiable documentation from the time of marketing, as an adequate basis to establish pre-DSHEA marketing of a substance as a dietary ingredient for use in or as a dietary supplement.

[14] Moley, Timothy, Steven Foster, and Dennis Awang. *Herbs of Commerce*. Austin, TX: American Herbal Products Association, 1992.

10. Is marketing an ingredient for any use prior to October 15, 1994, sufficient to conclude that it is not an NDI?

No. FDA does not consider the marketing of an ingredient as a conventional food, as a drug, or for any other non-food use, to be evidence that an ingredient is not an NDI. Unless the ingredient was marketed as a dietary ingredient for use in or as a dietary supplement prior to October 15, 1994, it is an NDI.

11. Is there an authoritative list of dietary ingredients that were marketed prior to October 15, 1994 (a so-called "grandfathered list" or "old dietary ingredient list")?

Not currently. Some trade associations and other industry groups have compiled lists of "old dietary ingredients," [15] though FDA is unable to verify the accuracy of these lists because we have not seen documentation showing that the ingredients on such lists were marketed as dietary ingredients prior to October 15, 1994. The lists contain ingredients FDA believes are unlikely to have been marketed as dietary ingredients, like acetaminophen or pharmaceutical glaze, and mixtures that are only vaguely described, like "sterol complete premix." Moreover, the introduction to one trade association list[16] states that the association did not independently verify that the substances on the list were in use before October 15, 1994. The cover page of the list specifically states, "This list is compiled solely for reference purposes and does not constitute verification that any specific dietary ingredient was or was not marketed as a dietary supplement before October 15, 1994." The trade association's introduction to the list also states, "There is no definitive list of 'grandfathered' dietary ingredients. The best policy is for any company to maintain its own records confirming long-term use of an ingredient." Because of the uncertainty about the existence of supporting evidence, FDA does not accept the inclusion of an ingredient on an industry list of pre-DSHEA dietary ingredients as proof that the ingredient is not an NDI. However, in response to comments, we are prepared to develop an authoritative list of pre-DSHEA ingredients, based on independent and verifiable data. Because FDA does not generally have access to marketing records for dietary ingredients and dietary supplements, the documentation of pre-DSHEA marketing would have to be supplied by industry.

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[15] See, e.g., National Nutritional Foods Association, NNFA List of Dietary Supplement Ingredients In Use Before October 15, 1994 (April 26, 1996). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0012]. Available at: https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Tan%20Sheet/19/50/111212_UNPA_ODI_List.pdf

[16] Council for Responsible Nutrition, CRN List of Dietary Ingredients "Grandfathered" Under DSHEA (September 1998). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0010]. Available at: http://www.fda.gov/ohrms/dockets/dockets/05p0305/05p-0305-cr00001-04-Council-For-Responsible-Nutrition-vol1.pdf

FDA's current thinking is that the two main factors for placing an ingredient on an authoritative list of pre-DSHEA ingredients would be: (1) adequate documentation of marketing for use as or in a dietary supplement in the U.S. before October 15, 1994: and (2) a precise description of the identity of the ingredient marketed. Records offered to support an item's inclusion on the list should specify the date of marketing in the U.S. and clearly identify the ingredient marketed on that date. Documentation of an ingredient's identity should be sufficiently precise to uniquely identify the ingredient. See question IV.A.9 for the kinds of documentation FDA recommends to show that a dietary ingredient was marketed prior to October 15, 1994.

Including an ingredient on FDA's list of pre-DSHEA dietary ingredients would represent our view that the evidence is adequate to conclude that the dietary ingredient in question is not "new" and, therefore, not subject to the NDI notification requirement. The mere fact that an ingredient is not on the list would *not*, however, establish that the ingredient is an NDI or that dietary supplements containing that dietary ingredient are adulterated for failure to notify. Rather, the omission of an ingredient from the list would be regarded as neutral and would not affect the ingredient's regulatory status. Whether FDA would investigate dietary ingredients not on the list to determine whether an NDI notification should have been submitted would typically depend on factors relating to public health, such as potential for risk, extent of public exposure to the ingredient, and association with adverse events.

Although only one instance of marketing as a dietary ingredient before October 15, 1994 (pre-DSHEA marketing) need be shown to establish that an ingredient is not an NDI, each dietary supplement manufacturer and distributor is responsible for determining whether each dietary ingredient in each of its dietary supplements is an NDI and ensuring that the firm complies with the NDI notification requirements, if applicable. For ingredients that are not on FDA's list of pre-DSHEA dietary ingredients, a firm could either maintain its own records of the pre-DSHEA marketing of a dietary ingredient or rely on another firm or organization's records, with that entity's permission.

12. If I change the manufacturing process for a dietary ingredient that was marketed in the U.S. prior to October 15, 1994, does that make the ingredient an NDI?

The answer depends on the extent to which the manufacturing process change affects the resulting ingredient. As discussed in a separate FDA guidance on manufacturing changes,[17] such changes may affect the identity of the food substance

[17] FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances,

or its safety and suitability for certain conditions of use. Manufacturing changes may also affect the purity of a food substance, such as the amounts of impurities and contaminants in the food substance.

Any changes in your manufacturing process that alter the identity of the ingredient will convert a previously marketed dietary ingredient into an NDI. Manufacturing changes that alter the physicochemical structure or properties, purity and impurities, or biological properties (such as bioavailability or toxicity) of the ingredient result in an NDI.[18] For example, using a solvent to prepare an extract from a pre-DSHEA dietary ingredient creates an NDI because the final extract contains only a fractionated subset of the constituent substances in the original dietary ingredient. A manufacturing change which changes the ingredient in a way that leads to alteration of the serving level or conditions of use of the product is another example of a significant change which is likely to create an NDI.

In addition, changes that alter the identity of the source material for an ingredient may create an NDI. For example, using a different part of a plant (e.g., using an extract of plant leaves where the root extract from the same plant is a pre-DSHEA dietary ingredient) would create an NDI. If the ingredient produced by the new manufacturing process is an NDI, an NDI notification is required unless the NDI 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 (see Section IV.B). On the other hand, if the manufacturing changes do not alter the identity of the ingredient (e.g., there are no changes in physicochemical structure or properties and no changes in purity, impurities or biological properties such as bioavailability or toxicity) then the regulatory status of the pre-DSHEA ingredient does not change and no NDI notification is needed.

Note that the question of whether a manufacturing change creates an NDI is different from the question of whether the manufacturing change constitutes chemical alteration, and different standards apply. The "chemically altered" standard in section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) governs only the manufacturing of dietary ingredients that have been "present in the food supply" as articles "used for food" (i.e., conventional foods and their ingredients)[19] and is applied to determine whether an NDI notification is required for a conventional food ingredient that was not marketed as a dietary ingredient before October 15, 1994. In general, a broader range of manufacturing changes would create an NDI by

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Including Food Ingredients that are Color Additives; June 2014 Available at: http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm300661.htm.

[18] FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives; June 2014 Available at: http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm300661.htm.

[19] See question IV.B.1.

changing the identity of a dietary ingredient than would "chemically alter" an article of food present in the food supply. For example, solution in water or tincture may change the composition of a pre-DSHEA dietary ingredient enough to make it an NDI for which a notification is required. However, solution in water or tincture would not constitute a "chemical alteration" of a conventional food ingredient (see questions IV.B.4 and IV.B.5), and therefore, no NDI notification would be needed when a tincture or solution in water made with a conventional food ingredient is used as a dietary ingredient.

It should also be noted that some manufacturing changes may alter the identity of the ingredient to the point that it no longer meets the definition of a dietary ingredient (see question IV.D.5). Firms planning a manufacturing change are encouraged to consult with FDA on any questions as to whether such a change would create an NDI or an ingredient that does not meet the definition of a dietary ingredient.[20]

13. Should I submit a new NDI notification if I change the manufacturing process for an NDI that is the subject of a notification for which I have received an acknowledgment without objection from FDA?

That depends on the nature of the change to the manufacturing process. If the manufacturing change does not alter the chemical or molecular composition or structure of the dietary ingredient or the specifications needed to describe the ingredient, it is not necessary to submit a second NDI notification. On the other hand, a manufacturing process change intended to produce an ingredient with particles in the 1 nm to 100 nm (approximate) nanoscale range may alter the chemical or molecular composition or structure of the NDI. In that case, the previously submitted notification for a related substance manufactured without using nanotechnology would not cover the ingredient made with the new manufacturing process, and a separate NDI notification with safety information taking into account the smaller particle size of the resulting new ingredient would then be required.

If you are planning a manufacturing change, we encourage you to consult with FDA on whether such a change would create a different NDI or a substance that is no longer a dietary ingredient.[21] (See questions IV.A.12 for additional discussion on manufacturing changes that affect the identity of an ingredient.)

[20] Contact information for the Office of Dietary Supplement Programs can be found on the title page.
[21] Contact information for the Office of Dietary Supplement Programs can be found on the title page.

B. Exception to Notification Requirement for Certain NDIs with a History of Use in Conventional Food

1. When is a notification not required for an NDI?

A notification is not required when the NDI and all other dietary ingredients in the dietary supplement have been present in the food supply as articles used for food in a form in which the food has not been chemically altered. See questions IV.B.4 and IV.B.5 for FDA's current thinking on when a dietary ingredient has been "chemically altered" from the form in which it is used in the food supply.

FDA interprets the phrase "present in the food supply" to refer to the conventional food supply. Accordingly, we interpret a dietary ingredient that has been "present in the food supply as an article used for food" to mean a conventional food or conventional food ingredient. We do not consider prior use in dietary supplements to constitute presence in the food supply. Interpreting "food supply" to include dietary supplements for purposes of this exemption from the NDI notification requirement would expand the exception to the point that it would risk swallowing the rule, as prior use in even one dietary supplement manufactured in small quantities and distributed over a small area would exempt all dietary supplements containing the NDI from the notification requirement, even if the intake level and conditions of use were much different. Moreover, such an interpretation would not make sense in light of the purpose of the NDI notification requirement, which is to ensure that dietary ingredients that have not been widely consumed receive a safety evaluation before reaching the marketplace. Because dietary supplements are generally consumed by a narrower segment of the population than conventional foods and typically have a shorter history of use than conventional food ingredients, prior use in a supplement or supplements typically provides less information about a substance's safety than prior use in conventional food. In addition, 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.

2. Am I required to submit an NDI notification for a dietary ingredient that is an NDI, but has been (a) listed or affirmed by FDA as generally recognized as safe (GRAS) for direct addition to food or (b) approved as a direct food additive in the U.S.?

No, as long as the following conditions are met. The direct food additive or GRAS substance (1) has been used in the food supply (i.e., in conventional foods) and (2) is to be used as a dietary ingredient without chemical alteration. (See questions IV.B.4 and IV.B.5 for further discussion on chemical alteration.)

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. Similarly, ingredients marketed in conventional foods outside the U.S. are exempt from the NDI notification requirement if they are not chemically altered. However, as discussed in the following question, the NDI adulteration standard still applies, and voluntary NDI notification may be advisable.

3. Does the adulteration standard in 21 U.S.C. 342(f)(1)(B) apply to an NDI that has been listed or affirmed by FDA as GRAS for direct addition to food or approved as a direct food additive in the U.S.?

Yes. The adulteration standard in section 402(f)(1)(B) of the FD&C Act (21 U.S.C. 342(f)(1)(B)) applies to all NDIs, including NDIs for which a notification is not required. In other words, if an ingredient was not marketed as a dietary ingredient in the U.S. before October 15, 1994 (see questions IV.A.4, IV.A.7 and IV.A.10), it is an NDI and the adulteration standard for NDIs applies. That standard provides that a dietary supplement containing the NDI is adulterated unless there is adequate information to provide reasonable assurance that the ingredient does not present a significant or unreasonable risk of illness or injury.

If the intake level of the NDI resulting from its use under the conditions recommended or suggested in the labeling of the dietary supplement is the same as or lower than the intake level approved in a food additive regulation or specified in a GRAS regulation and overall cumulative intake of the NDI from dietary sources is the same as or lower than the acceptable daily intake (see question VI.C.8), FDA is likely to conclude that there is adequate information to provide reasonable assurance of safety, assuming that other conditions of use remain unchanged. However, the same is not necessarily true if the intake level of the NDI in the dietary supplement is higher than that resulting from conventional food use of the NDI. For 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.

Although an NDI notification is not required for a dietary supplement that contains an NDI that has been present in the food supply as an article used for food without chemical alteration, even if the dietary supplement contains more of the NDI than is used in conventional foods, FDA recommends that you consult with us about your basis for concluding that there is adequate information to provide reasonable assurance that the use of the NDI in the dietary supplement will not present a

significant or unreasonable risk of illness or injury.[22] As with any new dietary supplement you intend to market, you should assure yourself that the product is safe under its labeled conditions of use before distributing it. To that end, it may be advisable to submit a NDI notification voluntarily when a dietary supplement contains a significantly higher level of an NDI than is used in conventional foods. FDA has reviewed and intends to continue reviewing voluntarily submitted notifications for NDIs that are exempt from the notification requirement under 21 U.S.C. 350b(a)(1) because they have been present in the food supply as articles used for food in a form in which the food has not been chemically altered.

Like higher daily intake levels, combining an NDI with other dietary ingredients could also present safety risks, as discussed in question IV.C.2 below.

4. What are examples of processes that chemically alter an article of food present in the food supply?

Below are some examples of processes that FDA would likely consider to involve chemical alteration. These processes would also be likely to affect the safety profile of a dietary ingredient. The examples below are intended only for the purpose of illustration and are not a comprehensive list of processes that result in chemical alteration. See question IV.B.5 for further discussion on chemical alteration.

- A process that makes or breaks chemical bonds, unless the bonds created by the process are reversed when the ingredient is dissolved in water (e.g., creation of a soluble salt) or during ingestion. Example: hydrolysis.

- Removal of some components of a tincture or solution in water, which changes the chemical or molecular composition or structure of the mixture. Examples: chromatography, distillation, and filtration.

- Use of solvents other than water or aqueous ethanol to make an extract or tincture. The official legislative history of DSHEA specifies that "solution in water" and "tincture" (solution in aqueous ethanol) are not processes that chemically alter a food.[23] However, other solvents typically alter the composition of the extract in significantly different ways, usually by extracting different types of constituents than are extracted using water and aqueous ethanol.

- High temperature baking or cooking of an ingredient that has not previously been baked or cooked, unless the process causes only minor

[22] Contact information for the Office of Dietary Supplement Programs can be found on the title page.
[23] Statement of Agreement, 140 Cong. Rec. S14801 (daily ed. Oct. 7, 1994).

loss of volatile components with no other changes to the chemical or molecular composition or structure of the ingredient.

- Changing the manufacturing method for an ingredient such that the chemical or molecular composition or structure is significantly different. Examples: changes that alter the composition of materials used to make the ingredient, use of a different solvent, or use of a chromatographic matrix instead of a passive filter.

- Application of nanotechnology that results in new or altered chemical properties of the ingredient.

- Changing agricultural or fermentation conditions to alter the chemical or molecular composition or structure of the ingredient. Examples: sprouting garlic or fermenting yeast using a medium containing large amounts of sodium selenite to create large amounts of organic selenium compounds.

- Fermentation using a fermentation medium different from the one used to make conventional foods in the food supply. Example: use of a defined commercial growth medium to produce a microorganism previously made by fermenting milk into dairy products like yogurt or cheese.

- Use of a botanical ingredient that is at a different life stage than the life stage of the botanical ingredient used as a conventional food. Examples: making an extract from unripe instead of ripe apples or using the mycelium instead of the fruiting body of a fungus.

5. What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not result in chemical alteration?

As set forth in the Congressional Statement of Agreement between the House and Senate sponsors of DSHEA, "[T]he term ''chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyoph[i]lization, milling, tincture or solution in water, slurry, a powder, or solid in suspension."[24] FDA considers this list to represent examples of manufacturing processes that do not involve chemical alteration, but not necessarily a complete list of such processes.

FDA views "chemical alteration" specifically within the context of section 413(a)(1) of the FD&C Act, which creates an exemption from the NDI notification requirement for NDIs that have been "present in the food supply" as "article[s] used for food in a form in which the food has not been chemically altered." Because this

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

exemption is for articles that are used for food and present in the food supply (conventional foods and their ingredients), it applies to ingredients that meet the safety standards for conventional foods and have a history of safe use as food. These safeguards provide some confidence that such ingredients are likely to be safe when used in dietary supplements at comparable levels, as long as they are not chemically altered from their form in conventional food.

A process that chemically alters an ingredient found in the food supply can introduce contaminants, solvents, or impurities whose safety is unknown.[25] Such a process may result in an ingredient that not only differs from the source ingredient but also has an unknown safety profile. See question IV.B.4 for further discussion on chemical alteration. A well-characterized starting material may result in no change to the identity of the material after processing, in which case an NDI notification would not be required. However, dietary supplements and dietary ingredients that are complex mixtures introduce more variability into the processing. Therefore, their identity is more likely to change during processing.

In general, FDA considers a process that does not result in chemical alteration to mean a process that: (1) involves an ingredient composed of one single raw material, or derived from a single raw material using a manufacturing process that involves only physical steps (e.g., water extraction and condensation); and (2) does not involve attempts to selectively increase the concentration of particular active ingredients or cause a chemical reaction (other than esterification) that would modify the covalent bonds of any substance in the original material. This type of process is unlikely to affect the safety profile of the ingredient in question or of dietary supplements containing the ingredient.

Some of the processes characterized as "physical modifications" in the Congressional Statement of Agreement (milling, slurry, powder, or solid in suspension) do not alter the chemical or molecular composition or structure of the ingredient. FDA views such changes as unlikely to create a change in the safety profile of an ingredient being used in conventional food. Dehydration, lyophilization, or making a tincture, solution in water, or slurry can be said to change the composition of the ingredient, but only by changing the amount of water (or ethanol, in the case of a tincture). FDA regards such a minor change in composition as extremely unlikely to change the safety profile of an ingredient used in conventional food. Similarly, a minor loss of volatile components during processing is unlikely to change the safety profile of an ingredient used in conventional food. In a typical extraction, however, the first step is solution in water or another solvent, followed by filtration to remove undissolved material.

[25] FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives; June 2014. Available at: http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm300661.htm

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 and therefore triggers the NDI notification requirement for the resulting dietary ingredient.

As industry develops new technologies and processes other than those described as physical modifications in the Congressional Statement of Agreement, we encourage you to consult with us when considering whether a notification is needed in a particular situation, as well as before submitting an NDI notification.[26] We intend to evaluate any new technology or process based on our guidance on chemical alteration as set forth in this document. We also intend to consider whether or not the technology or process would affect the safety profile of the dietary ingredient and the dietary supplement in which it is used.

We are willing to consider arguments supported by science demonstrating that particular manufacturing processes do not actually result in a chemical alteration or have any effect on the safety profile of the ingredient. In such cases, we encourage manufacturers and distributors to arrange a pre-notification meeting with FDA to discuss their basis for this belief.

C. Other Questions About When an NDI Notification Is Necessary

1. May I submit a single NDI notification that contains safety data for a range of conditions of use and covers multiple products?

RESERVED – See the final guidance "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry."

RESERVED -- See the draft guidance "New Dietary Ingredient Notification Master Files for Dietary Supplements."

[26] Contact information for the Office of Dietary Supplement Programs can be found on the title page.

RESERVED – See the final guidance "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry."

RESERVED -- See the draft guidance "New Dietary Ingredient Notification Master Files for Dietary Supplements."

If you are a dietary supplement manufacturer or distributor and either you or the manufacturer or distributor of the NDI have submitted an NDI notification that covers the conditions under which the NDI will be used in your supplement, you need not submit a new notification for the use of the NDI in that supplement. However, if you are planning to market a product that exceeds the highest daily intake level or single-serving dose for which safety information was submitted in the previous NDI notification, you should submit a new notification because the previous NDI notification does not cover the higher single-serving or daily intake level. Similarly, if the NDI is not identical to the NDI evaluated in the previous NDI notification, the dietary ingredients to be combined with the NDI in your product differ from those in the product that was the subject of the previous notification, or any other conditions under which the NDI will be used in the new product were not evaluated in the original notification, a new notification should be submitted. See questions IV.C.2 and IV.C.3.

2. If I submit an NDI notification for a dietary supplement that I manufacture or distribute and then decide to manufacture or distribute a different supplement that contains the same NDI, should I submit another NDI notification?

The answer depends on what was covered in your previous NDI notification, on how FDA responded, and on the extent to which the NDI's proposed conditions of use in your new dietary supplement differ from those evaluated in the notification. If you have already submitted an NDI notification for a dietary supplement containing an NDI, you need not submit a separate notification for a different dietary supplement containing the same NDI if the following criteria are met:

- The single-serving dose and daily intake level of the NDI specified in the labeling of the new supplement are less than or equal to the highest single-serving dose and daily intake level evaluated in your original NDI notification;

- The new supplement does not combine the NDI with other dietary ingredients that were not included in your original NDI notification;

- The target populations for the new supplement are the same as, or a subset of, the target populations specified in your original notification;

- All other conditions of use are the same as or more restrictive (e.g., lower dose and daily intake, shorter duration of use) than the conditions of use described in your prior NDI notification; and

- FDA did not express safety or other regulatory concerns in response to your prior NDI notification.

As discussed in question IV.C.1, you may submit a NDI notification that contains safety information about a range of daily intake levels and/or other conditions of use for dietary supplements containing the NDI. Once you have submitted a notification for an NDI that covers multiple conditions of use, you may market as many dietary supplements containing that NDI as you wish without submitting another notification, as long as the bulleted criteria above are met. Put another way, if the conditions of use for the dietary supplement you plan to market are within the conditions of use evaluated in your original notification and FDA did not object to that notification, you may market the supplement without submitting another notification.

However, if any of the bulleted criteria above are not met, you should submit another NDI notification. For example, suppose you want to market a dietary supplement with a higher daily intake level of the NDI than the level evaluated in your original notification. In general, the risk from a substance is likely to increase as intake increases above levels safely consumed in the past. A higher intake level of some substances could present toxicity risks to consumers. If you have not evaluated safety information for the higher daily intake level, you do not have an adequate basis on which to conclude that a dietary supplement containing the NDI at that higher level will reasonably be expected to be safe.

The same principle applies for other changes in conditions of use, such as combining the NDI with dietary ingredients other than those that were in the dietary supplement evaluated in the original NDI notification. When dietary ingredients are combined, they can interact. In some cases, these interactions can present risks to consumers. For example, adverse effects—such as low blood pressure, low heart rate, gastrointestinal distress, and in severe cases, irregular heartbeat—may occur when a new dietary ingredient with cholinesterase-inhibiting properties (such as huperzine A or galantamine) is combined with another dietary ingredient that is a cholinergic agonist (e.g., yohimbe bark extract). To have a basis to conclude that a dietary supplement that combines an NDI with one or more pre-DSHEA dietary ingredients will reasonably be expected to be safe, it is necessary to consider whether the addition of the other dietary ingredients will affect the safety of the NDI or the resulting dietary supplement.

The same analysis applies to other conditions of use that are outside the scope of the original notification. If the information in your original notification is insufficient to provide a basis to conclude that your new dietary supplement will reasonably be

expected to be safe, then the statutory requirement for the "manufacturer or distributor of the dietary ingredient or dietary supplement" to provide FDA with "information . . . 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" (21 U.S.C. 350b(a)(2)) has not been met. It is your responsibility to meet it by conducting a safety evaluation and submitting a notification with data about the safety of the NDI under the conditions of use in your proposed dietary supplement.

3. If a dietary supplement manufacturer or distributor has submitted an NDI notification prior to marketing a dietary supplement with the NDI, and I intend to market a dietary supplement containing the same NDI, should I also submit an NDI notification?

Yes. Section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)) states that a dietary supplement that contains an NDI is deemed adulterated unless, among other things, the manufacturer or distributor of the dietary ingredient or the dietary supplement submits an NDI notification at least 75 days before introducing it into interstate commerce. Note that, in situations where the NDI manufacturer or distributor has not submitted a notification, the statute deems a dietary supplement that contains the NDI to be adulterated unless the manufacturer or distributor of "the" dietary supplement (that particular dietary supplement), not "a" dietary supplement (some other dietary supplement containing the NDI) has submitted a notification. Accordingly, if the NDI manufacturer or distributor has not submitted a notification covering the conditions of the NDI's use, each manufacturer or distributor of a supplement containing the NDI must submit an NDI notification with "information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe" (21 U.S.C. 350b(a)(2)). The supplement manufacturer or distributor may meet the requirement to provide safety information either by conducting its own safety evaluation or relying on a safety evaluation conducted by another entity, such as a previously submitted NDI notification (see question IV.C.4). Once the manufacturer or distributor of the supplement has submitted an NDI notification to FDA, that firm need not submit further notifications for other supplements containing the same NDI if the conditions of use of the other supplements are within the conditions of use evaluated in the firm's original notification (see question IV.C.2).

4. When I submit an NDI notification, may I rely on data from another NDI notification RESERVED ?

Yes, if one of the following applies:

- you submitted the previous notification **RESERVED** ,

- the previous notification (or portion of a previous notification) on which you wish to rely is public, or

RESERVED -- See the draft guidance "New Dietary Ingredient Notification Master Files for Dietary Supplements."

5. Can FDA provide examples with an explanation to help distinguish situations in which separate notifications are required for dietary supplements containing the same NDI from situations in which the same NDI notification covers multiple dietary supplements?

Two important factors you should consider when deciding whether to submit a notification for a dietary supplement containing an NDI that was the subject of a previous notification are:

1) Are the NDI's conditions of use in the second product within the conditions of use evaluated in the previous notification?

   If not, you should submit a separate notification for the second product because the safety evaluation in the previous notification did not include any consideration of the new conditions of use in the second dietary supplement and therefore cannot provide a basis to conclude that the NDI will reasonably be expected to be safe under those conditions of use.

2) Who was the previous notifier and what is that entity's relationship (e.g., same firm, supplier, or competitor) to the manufacturer or distributor who intends to market the second product?

See questions IV.C.2 and IV.C.3 and the examples below for more about how the answer to this question affects whether an NDI notification for the second product is necessary.

In each of the scenarios below, assume that FDA has acknowledged the filing of the first NDI notification and has not raised any safety or regulatory concerns in response to that notification.

RESERVED -- See the draft guidance "New Dietary Ingredient Notification Master Files for Dietary Supplements."

Scenario 2: Ingredient Supplier A submits a notification for NDI-A2. Supplier A's notification includes safety information for a dietary supplement tablet containing NDI-A2 as the sole dietary ingredient in a formulation with several non-dietary ingredients used as binders and fillers. Supplement Manufacturer X wants to use the same level of NDI-A2 in a dietary supplement tablet with NDI-A2 as the sole dietary ingredient, but in a formulation with different non-dietary ingredients used as binders and fillers.

Analysis: Manufacturer X does not need to submit an NDI notification because the only difference between Manufacturer X's product and the formulation described in

RESERVED -- See the draft guidance "New Dietary Ingredient Notification Master Files for Dietary Supplements."

Supplier A's notification is a change in non-dietary ingredients (i.e., inactive ingredients). However, Manufacturer X should evaluate whether the change affects the safety of the dietary supplement and document the basis for its conclusion before marketing the product.

Scenario 3: Ingredient Supplier A submits a notification for NDI-A3 that includes safety information for single-ingredient dietary supplement formulations containing up to 500 mg/day of the NDI. Supplement Manufacturer X is using NDI-A3 in a single-ingredient dietary supplement at a level of 250 mg/day but wants to increase the amount of NDI-A3 to 500 mg/day.

Analysis: Because Supplier A's initial notification included safety information for NDI-A3 up to 500 mg/day, Manufacturer X does not need to submit a notification for either the 250 mg/day or 500 mg/day formulation, assuming all other conditions of use are the same as those evaluated in Supplier A's notification.

Scenario 4: Ingredient Supplier A submits a notification for NDI-A4. Supplier A's notification includes safety information for a dietary supplement containing NDI-A4 in combination with vitamin A, vitamin C, sodium, calcium, and iron. Supplement Manufacturer X intends to use NDI-A4 in a dietary supplement at recommended doses and daily intake levels that do not exceed the high end of the range evaluated in Supplier A's notification. Manufacturer X's supplement will also contain some, but not all, of the vitamins and minerals included in Supplier A's notification. All other conditions of use will be the same as those evaluated in A's notification.

Analysis: Manufacturer X does not need to submit another notification because Supplier A's notification covers all the conditions of NDI-A4's use in Manufacturer X's new product.

Scenario 5: Company Q wants to market a supercritical fluid extract of *Convallaria majalis* L. The plant is on an industry list of pre-DSHEA dietary ingredients.

Analysis: Company Q must submit an NDI notification. Even though this botanical appears on an industry list of old dietary ingredients, it has historically been used only as an herbal drug, so a history of use in food has not been established. In addition, supercritical fluid extraction was not commonly used prior to 1994, and there is no evidence of extracts like this having being marketed as food prior to 1994.

Scenario 6: Company Q received an acknowledgment letter without objection in response to its NDI notification for the *Convallaria majalis* L. supplement described in Scenario 5. Now Company Q wants to market the ingredient in combination with another dietary ingredient, an extract from *Nerium oleander* L., which has been the subject of an NDI notification from one of Company Q's competitors, Company Y. Company Y received an acknowledgment letter without objection in response to its

notification. Both notifications discussed the safety of the extracts in depth and described manufacturing procedures and specifications for cardiac glycosides. The notifications also included results from clinical testing or testing in a non-rodent species appropriate for the evaluation of cardiac risk.

Analysis: Company Q must submit a new notification for the combination. A combination of two NDIs is itself an NDI. Although the notifications included in-depth discussions of the safety of the extracts, each of the plants is known to contain glycosides with potent cardiotoxic activity and it is difficult to predict the toxicity of the combination. The new notification should include a discussion of the safety of the combination, which is likely to be an in-depth discussion because both ingredients affect the same organ system. Given the overlapping toxicological endpoint and the severity of the potential toxicity, we would recommend that the new notification include results from safety testing of the combination. However, in a notification for a combination of two NDIs with no specific safety problems where each of the NDIs had been the subject of a prior notification to FDA that was acknowledged without objection, the section of the new notification discussing the safety of the combination could be brief.

6. Should I notify FDA about a microbial ingredient in my dietary supplement?

Yes, if it is an NDI that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered (21 U.S.C. 350b(a)(1)).

However, not all bacterial microorganisms are dietary ingredients, and a microorganism that is not a dietary ingredient cannot be an NDI. For example, pathogenic species of bacteria, such as *Salmonella* species or *Escherichia coli*, are not dietary ingredients even though they may have been inadvertently present in foods as contaminants. Bacteria that have never been consumed as food are unlikely to be dietary ingredients.

A bacterial microorganism is a dietary ingredient if it is a dietary substance (an intentional constituent of food) or otherwise falls within one of the dietary ingredient categories listed in 21 U.S.C. 321(ff)(1). For example, bacteria that are used to produce fermented foods that are eaten without a cooking or pasteurization step (e.g., lactic acid bacteria used to produce cheese or yogurt) could be "dietary substances for use by man to supplement the diet by increasing the total dietary intake," which are defined as dietary ingredients in section 201(ff)(1)(E) of the FD&C Act (21 U.S.C. 321(ff)(1)(E)). FDA does not have a separate regulatory category or definition for dietary ingredients consisting of live or viable microorganisms.

7. If I want to market a dietary supplement containing several pre-DSHEA

ingredients that haven't previously been marketed together, do I have to submit an NDI notification?

No. The NDI notification requirement applies only to dietary supplements that contain at least one NDI. If each of the dietary ingredients in a dietary supplement was marketed in the United States before October 15, 1994, marketing these ingredients together for the first time in the same dietary supplement does not create an NDI or trigger the NDI notification requirement.

8. Can FDA provide visual aids to help me decide whether I should submit an NDI notification?

Yes. The following table illustrates when an NDI notification is required and when the NDI adulteration standard applies. In addition, **Section VIII. Appendix: Decision Tree for NDI Notification** has a decision tree to walk you through the steps of deciding whether to submit an NDI notification.

Table 1: Definition of New Dietary Ingredient (NDI), Requirement for NDI Notification and Applicability of NDI Adulteration Standard

	New Dietary Ingredient (NDI)	NDI notification required?	NDI adulteration standard[29] applies?
A dietary ingredient that was marketed in the U.S. before October 15, 1994	No	No	No
A dietary ingredient that was NOT marketed in the U.S. before October 15, 1994, AND was present in the food supply as an article used for food which has	Yes	See a) or b)	Yes
a) not been chemically altered	Yes	No	Yes
b) been chemically altered	Yes	Yes	Yes
A dietary ingredient that was NOT marketed in the U.S. before October 15, 1994, AND was NOT present in the food supply as an article used for food.	Yes	Yes	Yes

[29] The NDI adulteration standard in 21 U.S.C. 342(f)(1)(B) provides that a dietary supplement containing an NDI is adulterated unless there is adequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury.

D. Additional Issues to Consider Before Submitting an NDI Notification

1. What is a dietary ingredient?

The definition of "dietary supplement" describes a "dietary ingredient" in 21 U.S.C. 321(ff)(1) as:

(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), (B), (C), (D), or (E).

2. May a contaminant that is found in the food supply be a dietary ingredient?

No. Although most constituents of conventional foods in the food supply would be "dietary substances" that could be used as dietary ingredients under section 201(ff)(1)(E) of the FD&C Act (21 U.S.C. 321(ff)(1)(E)), contaminants are different from other food constituents. A contaminant of food (like *Salmonella* or lead) is not a dietary substance that qualifies for use as a dietary ingredient in a dietary supplement product even if it is not harmful to health (e.g., sterilized *Salmonella*) because contaminants are not intended for ingestion, nor are they considered to be food or part of the food supply. Contaminants are consumed unintentionally and are not "dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake" (21 U.S.C. 321(ff)(1)(E)).

3. Under what circumstances does FDA consider synthetically produced substances to be dietary ingredients under the FD&C Act?

Whether a synthetically produced substance qualifies as a dietary ingredient depends on whether the substance fits into one of the categories of dietary ingredients that are defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)). In some cases, description of the category in the FD&C Act encompasses synthetically produced substances; in others, it does not. The six dietary ingredient categories are discussed in the bullets below.

- **Vitamins, Minerals, and Amino Acids (21 U.S.C. 321(ff)(1)(A), (B), (D))**

Synthetic vitamins, minerals, and amino acids qualify as dietary ingredients because vitamins, minerals, and amino acids, regardless of source, are specifically designated as dietary ingredients under sections 201(ff)(1)(A), 201(ff)(1)(B), and 201(ff)(1)(D) of the FD&C Act, respectively. Synthetic vitamins, minerals, and amino acids are recognized as dietary ingredients because a vitamin, mineral, or amino acid is defined by its nutritional function (its ability to provide nutrients to the human body), not by its state of matter like a botanical.

- **Herb or other botanical (21 U.S.C. 321(ff)(1)(C))**

Under a plain reading of the FD&C Act, a synthetic copy of an herb or other botanical does not qualify as a dietary ingredient under section 201(ff)(1)(C) of the FD&C Act. As defined in the glossary, an herb or botanical includes only plants, algae, fungi, their exudates (secretions, such as sap or resin), and their physical parts. A substance that has been synthesized in a laboratory or factory has never been part of an herb or other botanical and, therefore, is not a dietary ingredient under section 201(ff)(1)(C) of the FD&C Act.[30]

- **Dietary substance for use by man to supplement the diet by increasing the total dietary intake (21 U.S.C. 321(ff)(1)(E))**

For purposes of section 201(ff)(1)(E) of the FD&C Act, we interpret "dietary substance" in accordance with its common, usual meaning because the term is not defined in the FD&C Act or by regulation. According to *Webster's II New Riverside University Dictionary* (1994), "dietary" means "of or relating to diet" and "diet" means "an organism's usual food and drink." In conjunction with "for use by man," we interpret "dietary substance," as used in section 201(ff)(1)(E), to mean a substance commonly used as human food or drink. The rest of the definition, which specifies that the substance be for use "to supplement the diet by *increasing* the *total* dietary intake,"[31] is further evidence that "dietary substance" is intended to mean foods and food components that humans eat as part of their usual diet. One cannot increase the "total dietary intake" of something that is not part of the human diet in the first place.

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

[30] 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).

[31] 21 U.S.C. 321(ff)(1)(E) (emphasis added).

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.

- **Concentrate, metabolite, constituent, extract, or combination of another dietary ingredient described in clause (A), (B), (C), (D), or (E) (21 U.S.C. 321(ff)(1)(F))**

A "constituent" is an article that is a physical part of a whole and can be isolated from the whole. A synthetic copy of a constituent of a botanical was never part of the botanical. Therefore, the synthetic copy is not a "constituent" of the botanical and does not qualify as a dietary ingredient under section 201(ff)(1)(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(F)), even if the synthetic copy is chemically identical to a constituent of a plant.[32]

By the same principle, an extract made from a synthetic copy of one or more constituents of a botanical is not an "extract" of the botanical under section 201(ff)(1)(F) of the FD&C Act because the constituents were never part of the botanical and therefore could not be extracted from the botanical. Similarly, a synthetic copy of a botanical concentrate is not a concentrate of a botanical because, by definition, a "concentrate" is an article that has been reduced in volume or bulk by removal of liquid. To make a concentrate of a botanical, one must start by extracting the desired constituents from the botanical with a solvent and then concentrate the constituents by reducing the amount of solvent (e.g., by boiling the extract). If synthetic material that was never actually in the botanical is used as the starting point for a concentrate, the final product will be a concentrate of the synthetic material, not a concentrate of the botanical.

For more than a decade, FDA has consistently interpreted section 201(ff)(1)(F) of the FD&C Act as not including synthetic copies of botanical constituents, extracts, or concentrates. [33] Such a substance may in some cases, however, qualify as a

[32] See, e.g., Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 FR 6788, 6793 (Feb. 11, 2004).

[33] This interpretation dates back to at least 2001, and the dietary supplement industry has been aware of it since that time. See Letter from Dennis E. Baker, Associate Director for Regulatory Affairs, FDA, to Laura M. Nagel, Deputy Assistant Administrator, Office of Diversion Control, DEA (June 21, 2001) Available at: http://odspracticum.od.nih.gov/2011/readinglists/dea_ephedrine_letter.pdf; Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated, *supra* note 32; Natural Products Insider, Consumer Group Asks FDA to Seize Synthetic Ephedrine 'Supplements' (Feb. 1, 2002) Available at: http://www.naturalproductsinsider.com/news/2002/02/consumer-group-asks-fda-to-seize-synthetic-ephedri.aspx; Citizen Petition 2004P-0169 from Coalition to Preserve DSHEA (Apr. 8, 2004), Docket No. 2004P-0169 (asking FDA to reconsider position that botanical dietary ingredient category excludes synthetic equivalents) Available at: http://www.fda.gov/ohrms/dockets/dailys/04/apr04/040804/04p-0169-cp00001-vol1.pdf; Letter from Michael M.

dietary ingredient under another provision of section 201(ff)(1). For example, there are synthetically produced substances in the food supply that are dietary ingredients under section 201(ff)(1)(E) because they are "dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake" (see discussion in preceding bullet). A synthetic copy of a botanical constituent (e.g., vanillin synthesized from lignins) or an extract made from a synthetic copy of a botanical constituent (e.g., artificial vanilla extract) would qualify as a dietary ingredient under section 201(ff)(1)(E) if used as a food ingredient.

A metabolite that has been synthesized from another dietary ingredient would be a dietary ingredient under section 201(ff)(1)(F) and could be used as a dietary ingredient in a dietary supplement. Although the definition of a metabolite[34] requires human ingestion of the dietary ingredient to increase the production or flux of the metabolite in the human body, it does not require the metabolism to actually take place in a human being during the manufacture of a dietary ingredient. A metabolite may be synthetically produced, provided that the starting material is a dietary ingredient and the production process mimics the metabolic process in the body following ingestion.

4. Are food contact substances and other indirect food additives dietary ingredients? What about secondary direct food additives?

These substances generally do not qualify as dietary ingredients by virtue of their use as food additives. Although food contact substances[35] and other indirect food additives[36] may be present in the food supply because they migrate into certain foods from packaging or other articles that contact the food, their presence in these foods is merely incidental. A substance that migrates into a food during manufacturing or storage is not a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" (21 U.S.C. 321(ff)(1)(E)) because it is not consumed as a component of the diet, but merely as a byproduct of its use in articles that contact food. However, if such a substance falls under one of the other

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Landa, Acting Director, Center for Food Safety and Applied Nutrition, FDA, to Marc Ullman, Ullman, Shapiro & Ullman, LLP, responding to Citizen Petition FDA-2009-P-0298 from OVOS Natural Health Inc. (Feb. 23, 2011) Available at: https://www.regulations.gov/document?D=FDA-2009-P-0298-0008.

[34] See section VII, "Metabolite."

[35] A food contact substance is a substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if that use is not intended to have any technical effect in the food. 21 U.S.C. 348(h)(6).

[36] Indirect food additives come into contact with food as part of packaging, holding, or processing, but they are not intended to be added directly to, become a component of, or have a technical effect in or on the food. Before the FDA Modernization Act of 1997, indirect food additives were approved by regulation. Now, additional indirect food additives are authorized through the food contact substance notification program. In addition, indirect food additives may be authorized through the threshold of regulation exemption process in 21 CFR 170.39. See FDA, Food Ingredients and Packaging Terms. Available at: http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm (accessed April 22, 2015).

dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act, it could be a dietary ingredient.

For similar reasons, secondary direct food additives generally do not qualify as dietary ingredients through their use in food manufacturing. Secondary direct food additives are added during the manufacturing of a food to achieve a technical effect (e.g., controlling the growth of microbes), but they have no technical effect in the finished food. Generally, secondary direct food additives are used as processing aids, and often they also meet the definition of a food contact substance.[37] Although they may remain in the food after processing, they are generally present in the finished food only at trace levels, if at all. Like indirect additives, secondary direct food additives are not consumed as components of the diet, but are only incidentally present, if at all, in the finished food as byproducts of processing. Accordingly, they are not "dietary substances for use by man to supplement the diet by increasing the total dietary intake." However, as with indirect additives, a secondary direct food additive could be a dietary ingredient if it belongs to one of the other dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act.

5. If I alter the chemical structure of a dietary ingredient, is the new substance still a dietary ingredient?

It depends. Altering the chemical structure of a dietary ingredient (e.g., creation of new stereoisomers, addition of new chemical groups as in esterification) creates a new substance that is different from the original dietary ingredient. The new substance is not considered to be a dietary ingredient merely because it has been altered from a substance that is a dietary ingredient and, therefore, is in some way related to the dietary ingredient.

In some cases, however, the new substance may independently qualify for one of the dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act. For example, taurine is the end product of the metabolism of the amino acid cysteine. It is thus a metabolite of an amino acid and fits one of the definitions of a dietary ingredient (see 21 U.S.C. 321(ff)(1)(D), (F)). The enzymatic or synthetic processing of cysteine or any other dietary ingredient would be an appropriate method for the manufacture of a metabolite of a dietary ingredient like taurine for use in a dietary supplement. See questions IV.B.4 and IV.B.5 for additional discussion on chemical alteration.

6. In what forms may a dietary supplement containing my NDI be sold?

The FD&C Act specifically provides for dietary supplements to be in tablet, capsule, powder, softgel, gelcap, or liquid form (21 U.S.C. 321(ff)(2)(A)(i), 350(c)(1)(B)(i)).

[37] See FDA, Food Ingredients and Packaging Terms. Available at: http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm (accessed April 22, 2015).

In addition, the statute permits dietary supplements in other forms as long as the product is intended for ingestion, is not represented as conventional food, and is not represented for use as a sole item of a meal or of the diet (21 U.S.C. 321(ff)(2), 350(c)(1)(B)(ii)).

7. When FDA reviews an NDI notification, does the agency consider whether the prohibition in section 301(ll) of the FD&C Act applies to the use of the NDI in a dietary supplement?

No. Section 301(ll) of the FD&C Act (21 U.S.C. 331(ll)) prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under 21 U.S.C. 355, a biological product licensed under 42 U.S.C. 262, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. When reviewing NDI notifications, FDA's current practice is not to consider whether section 301(ll) or any of its exemptions apply to the NDI. Accordingly, a "no objection" response to an NDI notification should not be construed to be a statement that a dietary supplement containing the NDI, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll) of the FD&C Act.

8. May an ingredient that has not been marketed as a food or as a dietary supplement, but has been approved as a new drug or licensed as a biologic, be used as an NDI in a dietary supplement?

No, unless FDA issues a regulation, after notice and comment, finding that the ingredient, when used as or in a dietary supplement, would be lawful under the FD&C Act. A regulation of this type may be requested by filing a citizen petition under 21 CFR 10.30, but none has been issued to date. Absent such a regulation, an ingredient that has been approved as a new drug or licensed as a biologic can be a dietary ingredient for use in a dietary supplement if, and only if, prior to such approval or licensing, the ingredient was marketed as a dietary supplement or as a food.

9. May I use an ingredient in a dietary supplement if it has been clinically tested as a drug but has not been approved as a drug in the U.S.?

It depends on whether the ingredient was authorized for investigation in clinical trials under an investigational new drug application (IND), whether the date the IND went into effect was before or after the date the ingredient was first marketed as a food or as a dietary supplement, whether the clinical trials were "substantial clinical investigations," and whether their existence was made public. The general rule is that an article that was 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.

FDA can create an exception to this prohibition by regulation, but only if the agency finds that the use of the article in dietary supplements would be lawful. To date, no such regulations have been issued. The appropriate mechanism to request such a regulation is to file a citizen petition under 21 CFR 10.30.

10. How do I determine whether a dietary ingredient is an article that is approved or authorized for investigation as a new drug?

Either an entire product or a component of the product, such as an active ingredient, may be "an article that is approved as a new drug" or an article "authorized for investigation as a new drug" within the meaning of section 201(ff)(3)(B) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)).[38] For example, assume that Substance A, which is a constituent of a plant and has never been marketed as an article of food or as a dietary supplement, is a botanical dietary ingredient under section 201(ff)(1)(C) of the FD&C Act. A drug company is studying a salt of Substance A, "Substance A hydrochloride," as an investigational new drug under an IND. In this situation, the relevant article for purposes of whether Substance A can be used in a dietary supplement is not Substance A hydrochloride, but Substance A itself, because Substance A is the active moiety[39] that is being studied for its possible therapeutic action. Any compound that delivers Substance A is excluded from being used in a dietary supplement.[40]

11. May a dietary ingredient that was authorized for investigation as a new drug in the past be used as an NDI in a dietary supplement if the IND was withdrawn or the ingredient is no longer being investigated as a new drug?

It depends on the facts of the particular situation (see answer to IV.D.9 above), but withdrawal of the IND and cessation of clinical trials of the ingredient's use as a new drug make no difference in whether the ingredient may be used in a dietary supplement. The dietary supplement category does not include an article authorized for investigation as a new drug or biologic for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such authorization marketed as a dietary supplement or as a food, unless FDA has issued a regulation

[38] *Pharmanex v. Shalala*, 221 F.3d 1151, 1154-1160 (10th Cir. 2000).

[39] Under 21 CFR 316.3(b)(2), "active moiety" means "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." See also 21 CFR 314.108(a).

[40] Letter from Michael A. Chappell, Acting Associate Commissioner of Regulatory Affairs, FDA, to Kathleen M. Sanzo, Morgan, Lewis & Bockius LLP, responding to Citizen Petition 2005P-0259 from Biostratum, Inc (Jan. 12, 2009). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0004].

finding that the article would be lawful under the FD&C Act (21 U.S.C. 321(ff)((3)(B)(ii)). "Authorized for investigation" means that the article is the subject of an IND that has gone into effect (see 21 CFR 312.40).

12. May I 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?

Yes, in this situation the dietary ingredient may be used in dietary supplements. In considering whether a substance has been "marketed as a dietary supplement or as a food," FDA looks for evidence of one of the following:

1. Evidence that the substance itself was sold or offered for sale in the U.S. as a dietary supplement, dietary ingredient for use in dietary supplements, or conventional food. For example, a catalog listing a product identified as a "Substance A supplement" would establish the marketing of Substance A as a dietary supplement. Similarly, business records documenting that a substance was sold or offered for wholesale or retail sale for use as an ingredient in a conventional food would establish the marketing of the substance as a food.

2. Evidence that the substance was a component of a food or dietary supplement that was sold or offered for sale in the U.S., and that a manufacturer or distributor of the food or dietary supplement marketed it for the content of the substance by, for example, making claims about the substance or otherwise highlighting its presence in the product.[41] For example, in *Pharmanex v. Shalala*, the firm marketed lovastatin, a component of its red yeast rice product Cholestin, by promoting the lovastatin content of Cholestin.[42] Merely showing that the substance was present as a component in a marketed food would not be enough to show that the substance was "marketed," however.

V. NDI Notification Procedures and Timeframes

A. Procedure for Submitting an NDI notification

RESERVED – See the final guidance "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry."

[41] *See Pharmanex v. Shalala*, 2001 WL 741419, at *4 & n.5 (D. Utah March 30, 2001).
[42] *Id.* at *3.

RESERVED – See the final guidance "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry."

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B. What Happens After an NDI Notification Is Submitted?

RESERVED – See the final guidance "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry."

RESERVED – See the final guidance "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry."

VI. What to Include in an NDI Notification

A. Identity Information About the NDI and the Dietary Supplement

RESERVED – See the final guidance "New Dietary Ingredient (NDI) Notifications and Related Issues; Identity and Safety Information About the NDI: Guidance for Industry."

RESERVED – See the final guidance "New Dietary Ingredient (NDI) Notifications and Related Issues; Identity and Safety Information About the NDI: Guidance for Industry."

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B. History of Use or Other Evidence of Safety

RESERVED – See the final guidance "New Dietary Ingredient (NDI) Notifications and Related Issues; Identity and Safety Information About the NDI: Guidance for Industry."

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C. Summary of the Basis for Your Conclusion of Safety

RESERVED – See the final guidance "New Dietary Ingredient (NDI) Notifications and Related Issues; Identity and Safety Information About the NDI: Guidance for Industry."

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VII. Definitions

The following definitions represent FDA's current thinking on the meaning of the terms below in the context of the new dietary ingredient provisions of the FD&C Act and regulations. The definitions are intended for use only in that context and may not be appropriate in other contexts.[72]

Acceptable daily intake (ADI): The daily intake of a substance that, during the human lifetime, appears to be without appreciable risk on the basis of all known facts at the time.[73] In the context of an NDI notification, the ADI of an NDI or dietary supplement is calculated as the ratio of the NOAEL to the total safety factor (determined from the studies submitted in the notification).

Amino acid: An alpha-amino carboxylic acid used as a constituent of proteins or peptides.[74]

Botanical or herbal: A plant, alga, or fungus; a part of a plant, alga, or fungus (e.g., bark, leaves, stems, roots, flowers, fruits, seeds, berries, or parts thereof); or an exudate (secretion) of a plant, alga, or fungus.

Botanical raw material: Whole or physically processed (e.g., cleaned, frozen, dried, or sliced) parts of a single species of plant or a fresh or processed alga or fungus.

Chemically altered: See questions IV.B.4 and IV.B.5.

[72] For example, FDA recognizes that "amino acid" can be defined differently in non-nutritional contexts than in the definition in this section.

[73] Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

[74] Letter from Michael M. Landa, Acting Director, Center for Food Safety and Applied Nutrition, FDA, to Marc Ullman, Ullman, Shapiro & Ullman, LLP, responding to Citizen Petition FDA-2009-P-0298 from OVOS Natural Health Inc. (Feb. 23, 2011). Docket No. FDA-2009-P-0298 [Document ID: FDA-2009-P-0298-0008]. Available at: http://www.regulations.gov/#!documentDetail;D=FDA-2009-P-0298-0008

Chronic: Chronic exposure is exposure for more than 3 months. Periods of daily use interspersed with periods of non-use would be considered chronic exposure. In the context of toxicology studies, the term "chronic" generally refers to studies with at least 1 year of repeated dosing. Repeated exposure is divided into 3 categories: subacute, subchronic, and chronic. Subacute exposure refers to repeated exposure to a substance for 1 month or less, subchronic for 1 to 3 months, and chronic for longer than subchronic.[75]

Component: A substance that is part of a mixture. Includes substances that cannot be isolated from the whole, as well as those that can. Once isolated, a component of a mixture is also a constituent (see definition below).

Concentrate: An article in which constituents are more concentrated than in the original. An herbal concentrate is an extract from which all or most of the solvent has been removed, reducing the product to a solid, semi-solid, or syrupy form. The solvent and the process by which the concentrate is made are part of the definition of the concentrate.

Configurational isomer: See **Stereoisomers**.

Constituent: An article that is a physical part of the whole and can be isolated from the whole.

Dietary ingredient: A dietary ingredient is (A) a vitamin, (B) a mineral, (C) an herb or other botanical, (D) an amino acid, (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in (A) through (E).[76]

Dietary substance: A substance that is commonly used as human food or drink.

Dietary supplement: See definition in 21 U.S.C. 321(ff).

Enantiomers: Mirror-image isomers (optical isomers) that generally have similar chemical and physical properties, but different biological properties in a chiral environment.

Estimated daily intake (EDI): For purposes of an NDI notification, the EDI is the highest possible total daily intake level (in mg/day or mg/kg/day) of an NDI, as determined from the proposed conditions of use in the notification and any background exposure from other dietary sources. It is the maximum amount that would be consumed based on the conditions of use proposed in the notification, taking into account cumulative exposure from other dietary sources. The EDI should not be higher than the ADI.

Extract: A product consisting of a solvent (menstruum) combined with a dietary substance or botanical biomass by a process that physically separates constituents from the dietary substance or botanical and dissolves them into the solvent. The extract can be further concentrated through drying to a dry powder or semi-solid form.

[75] Curtis D. Klaassen, ed. Casarett and Doull's Toxicology: The Basic Science of Poisons. 8th Edition. Chapter 2: General Principles of Toxicology. McGraw-Hill Education, 2013.
[76] 21 U.S.C. 321(ff)(1).

Formulation: A formula that (1) lists the identity and quantity of each dietary ingredient and other ingredients (formulation aids) of a dietary supplement, and (2) describes the administered form (e.g., powder, liquid, capsule, etc.).

Geometric isomers: Compounds that have the same molecular formula, but differ from each other in the way that the atoms are oriented in space, and therefore have different chemical, physical, and biological properties (unless interconverted in the gut).

Ingestion: Taking an article, such as a dietary supplement or other food, into the stomach and gastrointestinal tract by swallowing.

Live microbial dietary ingredient: A single-celled prokaryotic or eukaryotic microorganism that is intended to be viable at the point of ingestion.

Margin of safety: A measure of how close the estimated daily intake (EDI) is to the level that has been shown to have no adverse effect in animal or human studies (the NOAEL). It is calculated as the ratio of the NOAEL to the highest total daily intake level (EDI) of the NDI or dietary supplement, as determined from the proposed conditions of use in the NDI notification, and is usually expressed in terms of fold change (e.g., a ten-fold margin of safety).

Marketed: See question IV.A.7**.**

RESERVED -- See the draft guidance "New Dietary Ingredient Notification Master Files for Dietary Supplements."

Maximum tolerated dose (MTD): The highest dose that causes no more than a 10 percent reduction in body weight and does not produce mortality, clinical signs of toxicity, or pathologic lesions that would be predicted to shorten the natural life span of an experimental animal for any reason other than the induction of neoplasms.[77]

Metabolite: A metabolite is a product of metabolism. In the dietary supplement context, a metabolite of a dietary ingredient is a molecular intermediate that incorporates structural elements of the ingested dietary ingredient and whose flux or net production in the human body increases on ingestion of the dietary ingredient. A metabolite can be part of (or an intermediate of) the catabolic or metabolic pathway of a dietary ingredient.

[77] Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

FDA considers X to be a metabolite of Y if ingestion of Y by humans results in net production of/increased flux of X, incorporating structural elements of Y.[78]

Mineral: A substance of defined chemical composition which provides a form or source of inorganic elements to the diet. An element is one of a class of substances that cannot be separated into simpler substances by chemical means. Examples: calcium, iodine, and zinc.

Nanomaterial, nanotechnology: FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. In the absence of a formal definition, when considering whether an FDA-regulated product, including dietary ingredients, contains nanomaterials or otherwise involves the application of nanotechnology, FDA intends to ask: (1) Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); and (2) Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to 1 micrometer (1,000 nm).[79]

New dietary ingredient: A dietary ingredient that was not marketed in the U.S. before October 15, 1994.[80]

No-Observable-Effect Level (NOEL): The highest dose or total daily intake level at which no effects (beneficial, neutral, or adverse) are observed in a properly designed and executed toxicological study.

No-Observed-Adverse-Effect Level (NOAEL): The highest dose or total daily intake level that did not elicit an adverse effect in a properly designed and executed toxicological study. [81]

Pre-DSHEA dietary ingredient: A dietary ingredient that was marketed in the U.S. before October 15, 1994.

Safety factor or **uncertainty factor**: A multiplier used to account for uncertainty about the extent to which data gathered in one context can be used to predict the safety of a substance in other contexts. For example, safety factors attempt to account for differences between animals and humans (uncertainty factor of interspecies variation), differences in sensitivity among humans (uncertainty factor of intraspecies variation), and extrapolation of subchronic to chronic data (uncertainty factor of extrapolated data from subchronic to chronic). Safety factors can be combined multiplicatively to account for multiple sources of uncertainty. Safety factors are used in calculating an acceptable daily intake (ADI) for various FDA-regulated products, including color additives, food additives, and new animal drugs. See questions VI.C.5 and VI.C.7.

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[78] *See* Hardy, Constance J. (Executive Secretary, Dietary Supplements Subcommittee of the FDA Food Advisory Committee). Summary Minutes of March 25, 2003 Meeting of the Dietary Supplements Subcommittee; College Park, MD; dated June 3, 2003. Available at: http://www.fda.gov/ohrms/dockets/ac/03/minutes/3942m1.pdf.

[79] *See* FDA, Office of the Commissioner. Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology; June 2014. Available at: www.fda.gov/downloads/regulatoryinformation/guidances/ucm401695.pdf

[80] 21 U.S.C. 350b(d).

[81] Adapted from Hayes, A. Wallace, editor. Principles and Methods of Toxicology. 5th ed. New York: Informa Healthcare USA, Inc; 2008.

Salt of a dietary ingredient: Salts are composed of cations (positively charged ions) bound to anions (negatively charged ions). The salt of a dietary ingredient is a neutral compound that is formed by the union of an acid or a base with a counter ion and that dissociates to the starting ingredients after ingestion.

Stereoisomers: Stereoisomers are molecules that are identical in atomic composition and bonding, but differ in the three-dimensional arrangement of the atoms.

Subchronic: Refers to toxicological studies that are 1 to 3 months in duration.

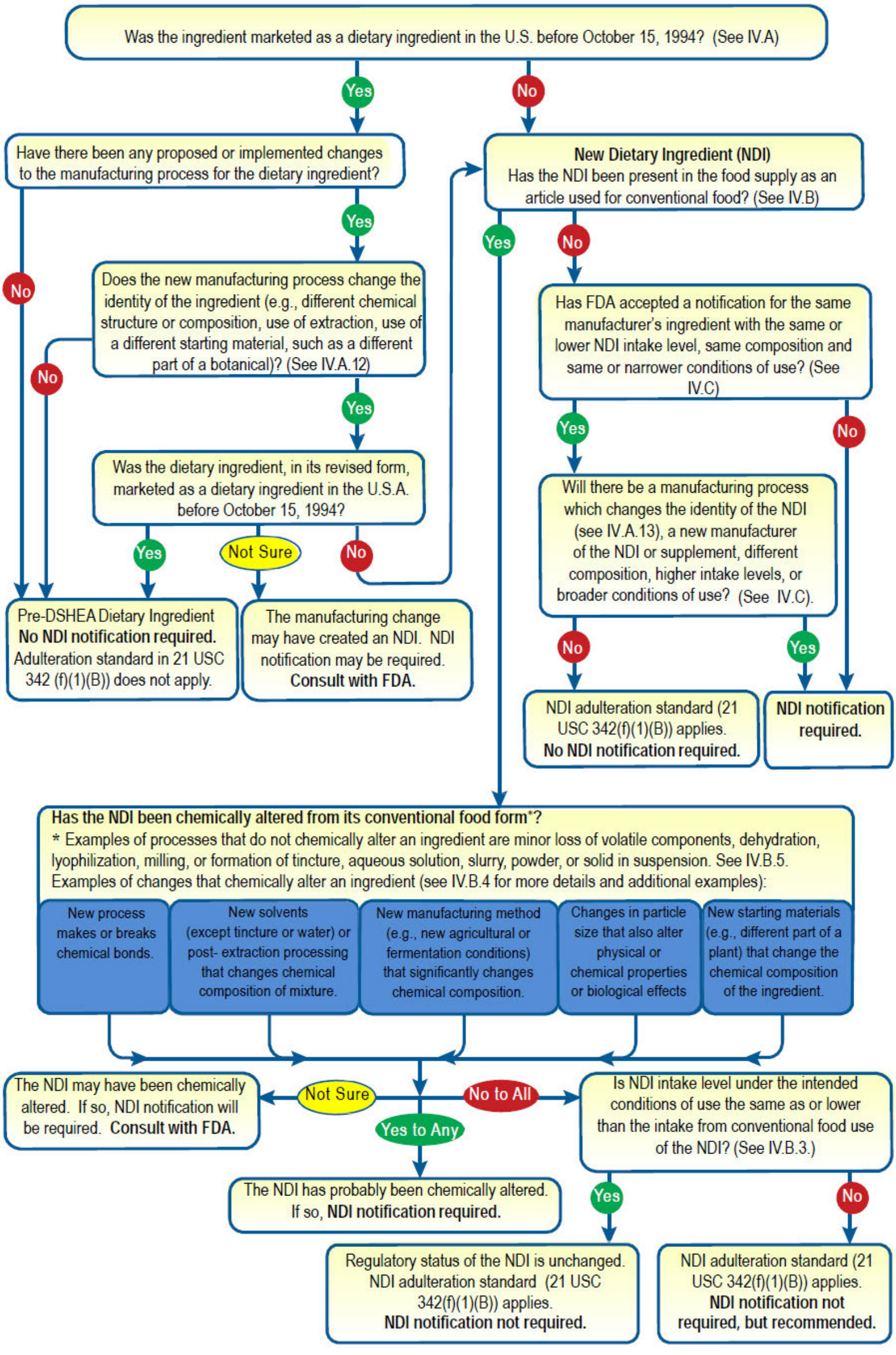
Target Population: The target population for a dietary supplement means the population group or groups (defined by sex, age, and/or health status) that a manufacturer or distributor identifies (e.g., in product labeling, promotional materials, or in an NDI notification) as those for whom the product is appropriate or recommended. Examples of target populations include adults, children 14 and over, and women going through menopause.

Tincture: An aqueous alcoholic solution (e.g., an aqueous alcoholic extract of leaves or other plant material). A tincture is characterized by the ratio of the weight of the dried botanical to the volume or weight of the finished product. A 1:5 ratio is 1 part botanical to 5 parts solution.

Uncertainty factor: See **Safety factor**.

Vitamin: An organic substance that is a minor component of foods, is essential for normal physiological functions (e.g., maintenance, growth, or development), is normally not produced endogenously (within the body) in amounts adequate to meet normal physiologic needs, and which causes, by its absence or underutilization, a clinically defined deficiency syndrome

VIII.Appendix: Decision Tree for NDI Notification



VIII.Appendix: Decision Tree for NDI Notification

Text description of the Decision Tree for NDI Notification to Determine When a Dietary Ingredient Requires a New Dietary Ingredient Notification Before Marketing

1. Was the dietary ingredient marketed in the U.S. before October 15, 1994? (See IV.A). If yes, go to 2. If no, go to 7.
2. Have there been any proposed or implemented changes to the manufacturing process for the dietary ingredient? If yes, go to 3. If no, go to 5.
3. Does the new manufacturing process change the identity of the ingredient (e.g., different chemical structure or composition, use of extraction, use of a different starting material, such as a different part of a botanical)? (See IV.A.12) If yes, go to 4. If no, go to 5.
4. Was the dietary ingredient, in its revised form, marketed as a dietary ingredient in the U.S.A. before October 15, 1994? If yes, go to 5. If not sure, go to 6. If no, go to 7.
5. Pre-DSHEA Dietary Ingredient. **No NDI notification required.** Adulteration standard in 21 USC 342 (f)(1)(B) does not apply.
6. The manufacturing change may have created an NDI. NDI notification may be required. **Consult with FDA.**
7. **New Dietary Ingredient (NDI)**. Has the NDI been present in the food supply as an article used for food? (See IV.B) If yes, go to11. If no, go to 8.
8. Has FDA accepted a notification for the same manufacturer's ingredient with the same or lower NDI intake level, same composition, and same or narrower conditions of use? (See IV.C) If yes, go to 9. If no, go to 17.
9. Will there be a manufacturing process which changes the identity of the NDI (see IV.A.13), a new manufacturer of the NDI or supplement, different composition, higher intake levels, or broader conditions of use? (See IV.C) If yes, go to17. If no, go to 10.
10. NDI adulteration standard (21 USC 342(f)(1)(B)) applies. **No NDI notification required**.
11. **Has the NDI been chemically altered from its conventional food form*?**
    *Examples of processes that do not chemically alter an ingredient are minor loss of volatile components, dehydration, lyophilization, milling, or formation of tincture, aqueous solution, slurry, powder, or solid in suspension. See IV.B.5. Examples of changes that chemically alter an ingredient (see IV.B.4 for more details and additional examples):
    - 11. A. New process makes or breaks chemical bonds. If yes to 11 A, B, C, D or E, go to 12. If not sure to 11 A, B, C, D and E, go to 13. If no to 11 A, B, C, D and E, go to 14.
    - 11. B. New solvents (except tincture or water) or post- extraction processing that changes chemical composition of mixture. If yes to 11 A, B, C, D or E, go to 12. If not sure to 11 A, B, C, D and E, go to 13. If no to 11 A, B, C, D and E, go to 14.
    - 11. C. New manufacturing method (e.g., new agricultural or fermentation conditions) that significantly changes chemical composition. If yes to 11 A, B, C, D or E, go to 12. If not sure to 11 A, B, C, D and E, go to 13. If no to 11 A, B, C, D and E, go to 14.
    - 11. D. Changes in particle size that also alter physical and chemical properties or biological effects. If yes to 11 A, B, C, D or E, go to 12. If not sure to 11 A, B,C, D and E, go to 13. If no to 11 A, B, C, D and E, go to 14.

VIII.Appendix: Decision Tree for NDI Notification

11. E. New starting materials (e.g., different part of a plant) that change the chemical composition of the ingredient. If yes to 11 A, B, C, D or E, go to 12. If not sure to 11 A, B, C, D and E, go to 13. If no to 11 A, B, C, D and E, go to 14.
12. The NDI has probably been chemically altered. If so, **NDI notification required.**
13. The NDI may have been chemically altered. If so, NDI notification will be required. **Consult with FDA.**
14. Is NDI the intake level under the intended conditions of use, the same as, or lower than the intake from conventional food use of the NDI? (See IV.B.3) If yes, go to 15. If no, go to 16.
15. Regulatory status of the NDI is unchanged. NDI adulteration standard (21 USC 342(f)(1)(B)) applies. **NDI notification not required.**
16. NDI adulteration standard (21 USC 342(f)(1)(B)) applies. **NDI notification not required, but recommended.**
17. **NDI notification required.**

Document History

- **July 2011-- Original version of the draft guidance was issued.**
- **August 2016 -- 2016 Revised Draft Guidance was issued.**
- **March 2024 -- Level 2 Revisions. Final guidance entitled, "Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry" replaces from the 2016 Revised Draft Guidance the following:**
  - **Question IV.C.1 (first paragraph of the response) with Question III.B**
  - **Section V.A with Section III**
  - **Section V.B with Section IV**
- **April 2024 -- Level 2 Revisions. Draft guidance entitled, "New Dietary Ingredient Notification Master Files for Dietary Supplements" replaces from the 2016 Revised Draft Guidance the following:**
  - **Question IV.C.1 (second paragraph of the response)**
  - **Question IV.C.4 (parts of the question and response that relate to master files)**
  - **Question IV.C.5 (Scenario 1)**
  - **Section VII, Master File definition**
- **October 2026 – Level 2 Revisions. Final guidance entitled, "New Dietary Ingredient (NDI) Notifications and Related Issues; Identity and Safety Information About the NDI: Guidance for Industry" replaces from the 2016 Revised Draft Guidance the following:**
  - **Section VI.A with Section IV**
  - **Questions VI.B.1, VI.C.1, and VI.C.3 with Section V**
  - **Questions VI.B.2-VI.B.10 with Section VI**
  - **Questions VI.B.11-19, VI.B.21, VI.B.22, VI.B.23, VI.B.25, VI.B.28, VI.B.29, VI.B.31-33, VI.B.35-VI.B.39, VI.C.4 with Section VII**
  - **Questions VI.B.40, VI.B,41, VI.B.42 with Section VIII**
  - **Questions VI.C.5, VI.C.6, VII.C.7, VIII.C.8 with Section IX**
  - **Table 3 with Appendix A**