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Draft Guidance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.

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Center for Food Safety and Applied Nutrition

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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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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?

Yes. We accept notifications that cover multiple dietary supplements and include safety data for a range of doses, daily intake levels, and/or other variations in conditions of use (e.g., serving size, duration of use, frequency of intake, target population, dosage form, or different formulations of pre-DSHEA ingredients in combination with the NDI). We recommend you submit safety data up to and including the highest dose and daily intake level, but indicate any lower daily intake levels at which the NDI may be marketed and include research that evaluates statistically relevant data points, such as a range of daily intake levels, to strengthen the safety analysis. FDA has received a number of notifications that cover a range of doses and daily intake levels. These notifications are publicly available in the NDI notification docket on *www.regulations.gov*. Contact FDA's Office of Dietary Supplement Programs for more information.[27]

You may also submit a confidential "NDI master file" to FDA which contains the manufacturing, specifications and other identity information needed to completely

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

describe the ingredient. You may incorporate by reference the contents of the master file into an NDI notification. You may also authorize other firms to reference the contents of the master file in notifications describing the ingredient they obtain from you. FDA expects that most submitters will identify the contents of NDI master files and ingredient specifications as trade secrets (see question V.A.16) and will only discuss them with the firm which submitted them.

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 or master file?

Yes, if one of the following applies:

- you submitted the previous notification or master file,

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

- the person who submitted the previous notification or master file gives you written permission to rely on non-public information from that notification. If you are relying on non-public information from another firm's NDI master file or from another notification, you should provide FDA with documentation (such as a signed letter from the other notifier) showing that you are authorized to use the information, and the duration of that authorization. If the authorization does not extend to the entire master file or notification, the authorization from the previous notifier should specify the part(s) of the notification you are authorized to use.

Manufacturing processes and specifications needed to establish the identity of an NDI are usually trade secrets that are not available in the NDI docket. It should be noted that the original notifier is under no obligation to share with other manufacturers and distributors any trade secrets or confidential commercial information that were part of the basis for a safety conclusion for the original notifier's product. A written authorization to reference a notification or master file in NDI notifications does not include the right to see or copy the notification or master file unless the submitter otherwise specifies. Note that while one firm may authorize another to reference confidential safety information in a subsequent notification, that subsequent notification must demonstrate that the submitting firm understands enough about that safety information to have a basis to conclude that consumption of the NDI in the new product will reasonably be expected to be safe under the conditions of use described in its notification.

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.

Scenario 1: Ingredient Supplier A submits a notification for NDI-A1 and a master file describing its manufacturing process. Supplement Manufacturer X intends to market a single-ingredient dietary supplement containing a dietary ingredient (NDI-B1) that purports to be the same as NDI-A1, but is made by a different dietary ingredient manufacturer, Ingredient Supplier B.

Analysis: Manufacturer X should submit an NDI notification for the use of NDI-B1 in its single-ingredient dietary supplement because Supplier B has submitted no NDI notification for NDI-B1 (see question IV.C.3). However, if Manufacturer X can establish that NDI-B1 is the same as NDI-A1 and Supplier A's prior notification covers the conditions of use of NDI-A1 in Manufacturer X's single-ingredient dietary supplement, then the NDI notification for the new supplement made with NDI-B1 could simply consist of data showing that NDI-B1 is identical to NDI-A1, a reference to the safety evaluation in Supplier A's notification, and a signed authorization from Supplier A for Manufacturer X to use any non-public safety data from A's notification and the manufacturing master file. On the other hand, if Manufacturer X cannot establish that NDI-B1 is the same as NDI-A1, X's notification will have to contain safety information specific to NDI-B1 because a different NDI requires its own safety evaluation.[28]

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

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

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

1. Who is required to submit an NDI notification?

Either the manufacturer or distributor of a dietary supplement that contains an NDI, or the manufacturer or distributor of the NDI, must notify FDA at least 75 days

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

before marketing the article in the U.S., 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 (21 U.S.C. 350b(a); 21 CFR 190.6(a)). Although FDA does review notifications from manufacturers and distributors of NDIs, notifications from ingredient manufacturers do not eliminate the requirement for a notification from the manufacturer or distributor of the dietary supplement in which the NDI will be used unless the prior notification for the NDI: (1) included a description of the dietary supplement with the information required by 21 CFR 190.6(b); and (2) provided the history of use or other evidence of safety on the basis of which the notifier concluded that the dietary supplement would reasonably be expected to be safe under its labeled conditions of use. See questions IV.C.1 and IV.C.5 for more information.

2. What should be included in an NDI notification and how should it be presented?

The required elements of an NDI notification are listed in 21 CFR 190.6(b). FDA's recommendations for additional information to include are provided in the template below.

The NDI notification should be well organized to facilitate an efficient and timely FDA review. We recommend that the notification be organized by sections, with continuous and consecutive pagination throughout the notification. Each subject area should begin with a new page to facilitate division of the notification among reviewers. The page number should appear in the same general location on every page.

Recommended Template for Organizing an NDI Notification

I. Cover Letter

Consumer Safety Officer
Office of Dietary Supplement Programs (HFS-810)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Department of Health and Human Services
5001 Campus Drive
College Park, MD 20740

DEAR SIR OR MADAM:

The undersigned, _____, (*Name of the primary contact person designated by the manufacturer or distributor that is submitting the notification*) submits this NDI notification under section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act with respect to _____(*Name of the dietary*

supplement containing the NDI), which contains the following new dietary ingredient:

_____ .

[*For herbs and other botanicals, the name must include the Latin binomial name, including the author citation (21 CFR 190.6(b)(2)).*]

Additional information necessary to uniquely characterize the new dietary ingredient:

_____

- *If the NDI is a botanical or is derived from a botanical, the notification should specify the part of the botanical that is the source of the new dietary ingredient (e.g., leaf, bark, root).*
- *Examples of information sufficient to uniquely characterize an NDI that is a single molecular entity could include the common or usual name of the molecular entity, the chemical identity, the chemical structural formula as noted in ChemIDPlus Advanced, PubChem, or International Union of Pure and Applied Chemistry (IUPAC), and the Chemical Abstracts Service (CAS) registry number (if available).*
- *NDIs consisting of more than one molecule should be described in a way that accurately communicates the basic nature of the ingredient and its characterizing ingredients or components. Examples:*
    - *Bacteria should be described by Latin binomial name and strain designation.*
    - *Unusual forms of botanicals should be identified (e.g., immature apples or malted barley.)*
    - *If a botanical is grown or cultured to incorporate an unusual constituent (e.g., selenium yeast), that fact should be disclosed.*
- *If the NDI was the subject of a previous NDI notification submitted by you or by the manufacturer or distributor from which you obtain the NDI, please include the docket report number, which you can find in FDA's letter responding to the notification.*

_____

(Signature of the contact person designated by the manufacturer or distributor)
[*This signature is required by 21 CFR 190.6(b)(5) and should be the primary contact, i.e., the person who represents the notifier in any discussions with FDA and who designates any additional contact persons in the notification or in subsequent correspondence.*]

Primary Contact:

(*Typed or printed name, title, address, telephone number and, if available, email address and facsimile number of the primary contact person.*)

Additional Contacts:

(*Typed or printed name, title, address, telephone number and, if available, email address and facsimile number of each additional contact person*.)

Contact persons can be agents, employees, officers, consultants, or attorneys.

II. Table of Contents

The table of contents should consist of a listing of the sections of the notification in the order in which they appear, along with the beginning page number of each section. Each section of the notification should begin on a new page.

III. Body of the Notification

A. Administrative

1. Description of the NDI, the dietary supplement containing the NDI, and the conditions of use of the dietary supplement (see questions V.A.3, V.A.4, and VI.A.19).
2. Identification of information believed to be trade secret or confidential commercial information, including the basis for identifying the information as such (see question V.A.16)
3. Safety narrative for the dietary supplement (see question VI.C.3)

B. Attachments used to establish identity

[*Provide only the information that identifies your NDI and dietary supplement. Do not provide efficacy data unless it is included in references that also provide identity information*.]

1. Detailed description of the identity of the new dietary ingredient and the dietary supplement.
2. Manufacturing methods and practices to establish identity and safety
3. Specifications to identify dietary ingredients, other ingredients, and contaminants, including the analytical methods used to establish each.
4. Identity References

This subsection should contain reprints or photocopies of the full text of all published and unpublished identity references that have not already been included in other subsections of the Identity section.

C. Safety and Toxicology Attachments

[*Provide only the information that formed the basis for your conclusion that the dietary supplement containing the new dietary ingredient is reasonably expected to be safe. Do not provide efficacy data unless it is included in studies that also provide safety information.*]

1. Comprehensive Safety Profile for the NDI (see question VI.C.2).
2. Toxicology Studies
3. Human Studies
4. Other Studies
5. History of Use
6. Other Evidence of Safety
7. Other Safety and Toxicology References
   This subsection should contain reprints or photocopies of the full text of all published and unpublished safety and toxicology references that have not already been included in other subsections of the Safety and Toxicology section.

IV. Complete List of References

3. How should the notification describe the NDI?

Your notification should: (1) specify which of the dietary ingredient categories in section 201(ff)(1) of the FD&C Act the NDI belongs to and explain the basis for your conclusion; (2) describe the manufacturing process used to make the NDI, including process controls; (3) describe the physical properties and chemical or molecular composition and structure of the NDI; and (4) include a specification sheet (preferably in table form) that describes the critical identity and safety attributes of the NDI, including the purity and strength of the NDI and the levels and identities of any impurities and contaminants. See section VI.A for further information.

4. How should the notification describe the dietary supplement in which the NDI will be used?

The notification should contain a description of the dietary supplement in which the NDI will be used, including: (1) the level of the NDI in the dietary supplement; (2) the identity and level of any other dietary ingredients and non-dietary ingredients (e.g., binders and fillers) in the dietary supplement; (3) a description of the manufacturing process of the dietary supplement, including process controls; (4) a specification sheet for the dietary supplement that describes its critical safety attributes; and (5) 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 of the dietary supplement, a discussion of the ordinary conditions of use

of the dietary supplement. The conditions of use should include the serving form (e.g., tablet, capsule, powder, etc.), serving size (e.g., weight or volumetric measure per serving), frequency of use (e.g., number of servings per day and interval between servings), duration of use, instructions for use, target population, excluded populations (if any), and any other restrictions on use. For purposes of FDA's review, daily lifetime use by all age groups and other populations at the highest described serving size and number of servings will be assumed, unless the notification specifies otherwise.

5. What information should not be in the NDI notification?

The notification should only contain data or information, as described in the safety narrative or comprehensive safety profile, that helps provide a basis for the safety of the NDI or the dietary supplement containing the NDI. It should not contain general or extraneous information. For example, data or information that is used primarily to substantiate a claim about the efficacy of the ingredient or supplement is not useful unless it also contains information that pertains to safety. In addition, the requirement to notify FDA within 30 days after marketing a supplement with a labeling claim described in section 403(r)(6) of the FD&C Act (21 U.S.C. 343(r)(6)) cannot be met by submitting the required information in a premarket NDI notification.[43] An NDI notification should not include published review articles about other products, or publications and websites that promote other products, unless the information in the articles or websites can be specifically linked to the NDI or dietary supplement that is the subject of the notification.

6. Should I explain how the information in the notification provides a basis to conclude that the dietary supplement in which the NDI will be used will reasonably be expected to be safe?

Yes. Your notification should include a dietary supplement safety narrative containing your objective evaluation of the history of use or other evidence of safety cited in the notification, along with an explanation of how the evidence of safety provides a basis to conclude that the dietary supplement containing the new dietary ingredient, when used under the conditions described in the notification, will reasonably be expected to be safe. See question VI.C.3 for further information.

[43] The regulation governing these notifications is 21 CFR 101.93. Please refer to this regulation for instructions on where and how to submit a notification of a dietary supplement labeling claim under 21 U.S.C. 343(r)(6). Notifications for labeling claims are not reviewed by the same staff who review NDI notifications.

7. Does FDA accept NDI notifications electronically?

Yes, you may submit an NDI notification electronically through FDA's electronic submissions gateway at https://www.access.fda.gov. You also have the option of continuing to submit paper NDI notifications for us to review.

8. When must an NDI notification be submitted?

If you are the manufacturer or distributor of a dietary supplement containing an NDI for which a notification is required (i.e., 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), you must submit your NDI notification at least 75 days before you introduce the dietary supplement into interstate commerce or deliver it for introduction into interstate commerce (21 U.S.C. 350b(a); 21 CFR 190.6(a)). If you are the manufacturer or distributor of the NDI, you must submit your NDI notification at least 75 days before you introduce the NDI into interstate commerce or deliver it for introduction into interstate commerce (21 U.S.C. 350b(a); 21 CFR 190.6(a)).

9. How many copies of an NDI notification should be submitted?

You should submit an original and one copy of the NDI notification. If the NDI notification is a paper submission, the original should be a paper document. For the copy, FDA accepts either paper or an exact copy of the original scanned into an electronic file in PDF format on a CD-ROM disk.

10. Where should an NDI notification be submitted?

Submit your NDI notification to: Consumer Safety Officer, Office of Dietary Supplement Programs (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740. You may also submit an NDI notification electronically through FDA's electronic submissions gateway at https://www.access.fda.gov.

11. How should published literature and other scientific information cited in the notification be listed?

Publications and other scientific references cited in the notification should be listed in a reference section at the end of the notification (see suggested notification format in question V.A.2). The reference section should include the reference number or short descriptor used to cite each study or publication in the body of the notification. The list of references should include unpublished work as well as publications.

12. How should unpublished scientific work be described?

The more complete the description of the data and methods in an unpublished study report, the more easily FDA reviewers will be able to evaluate whether the data support the safe use of the dietary supplement containing the NDI. Abstracts or cursory summaries of data (e.g., "a 90-day study in 5 rats failed to show any toxicity") do not provide enough detail to be useful as a basis for a safety determination.

13. Do I have to provide copies of publications cited in the notification to FDA?

Yes. All references to published information offered in support of the notification must be accompanied by reprints or photocopies of such references (21 CFR 190.6(b)(4)). You should not submit only the abstract or bibliographic citation of any publication or other material with your notification; instead, submit a photocopy or reprint of the full text. Do not submit abstracts that are the only published report of a scholarly or scientific work. Because abstracts do not contain sufficient information to judge the reliability of the scientific conclusions drawn in the study and generally do not undergo the rigorous review and editing used to evaluate other publications, they do not provide data that are useful in evaluating the safety of an NDI.

14. May I use material published in languages other than English to support the safe use of my NDI?

Yes, material written in a foreign language may be used as part of the basis for a conclusion that the NDI will reasonably be expected to be safe under the conditions of its intended use in the dietary supplement; however, the material must be accompanied by an accurate and complete English translation (21 CFR 190.6(b)(4)).

15. Should raw data be provided?

The level of detail that should be provided (raw data vs. summary) depends on how important the data in question are to the conclusion of safety and also whether the data suggest a safety problem. The more critical the data are to the overall evaluation, the more detail is needed. Data summaries (e.g., a table containing the average value and range or standard deviation for each parameter measured in a safety study or the peaks in a spectrum or chromatogram) are usually sufficient unless the data suggest that some values are outside of the acceptable range, in which case the individual values (raw data) should be provided. During review of the notification, FDA may request submission of raw data or other additional information. If the additional information is a substantive amendment, FDA will reset the filing date and start a new 75-day review period (see 21 CFR 190.6(d)).

16. How should I identify information that I believe is trade secret or

confidential commercial information?

As provided in 21 U.S.C. 350b(a)(2) and 21 CFR 190.6(e), after the 90th day after the filing date of the notification, all information in the notification will be placed on public display, except for any information that is trade secret or confidential commercial information (CCI).

We recommend that you clearly identify any information in the notification that you believe is trade secret or CCI—either by marking the information where it appears in the notification or by identifying this information in a separate document that accompanies the notification—and that you explain the basis for this belief. Likewise, if you believe there is no trade secret or CCI contained in the notification, we request that you state this in your notification.

Trade secret information may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort (21 CFR 20.61(a)). There must be a direct relationship between the trade secret and the productive process; for example, information relating to the manufacturing process (see 21 CFR 20.61(a)). Examples of trade secret information might include manufacturing methods and product composition (if different from what is declared on the label), product specifications needed to protect proprietary composition information (including proprietary analytical methods used to evaluate the product), and certificates of analysis.

CCI covers information that is related to a business or trade and is "confidential" (21 CFR 20.61(b)). In the case of information that FDA requires to be submitted, such as an NDI notification, the information is "confidential" if its disclosure is likely to cause substantial harm to the competitive position of the submitter.[44] Examples of CCI might include sales statistics, dollar volume, amount or source of income (e.g., a company's list of customers), profits or losses, expenditures (of any person, firm, partnership, corporation, or association), names of suppliers or subcontractors, or brand of equipment.

FDA believes that the following data and information contained in a notification are generally not trade secrets or CCI and, therefore, would be available for public disclosure after the 90th day after receipt of the notification by FDA:

(1) Information about history of use or other safety information related to the NDI or the dietary supplement, including both published and unpublished studies.

(2) All correspondence and written summaries of oral discussions relating to the

[44] *National Parks & Conservation Ass'n v. Morton,* 498 F.2d 765 (D.C. Cir. 1974).

notification, except specific information that is exempt from disclosure under 21 CFR 20.61.

17. What signature and contact information should I provide?

The signature of the person designated by the notifier is required by 21 CFR 190.6(b)(5). This person should be the primary contact, who represents the notifier in any discussions with FDA and who designates any additional contact persons in the notification or in subsequent correspondence. The typed or printed name, title, address, telephone number and, if available, email address and facsimile number of the primary contact person should be listed at the end of the cover letter that accompanies the notification (see suggested notification format in question V.A.2) so that FDA can reach him or her when necessary. The typed or printed names, titles, addresses, telephone numbers and, if available, email addresses and facsimile numbers of additional contact persons for the notification should be listed after the contact information for the primary contact. Contact persons can be agents, employees, officers, consultants, or attorneys for the notifier.

B. What Happens After an NDI Notification Is Submitted?

1. When is an NDI notification considered to be filed?

The date when FDA receives a complete notification is the date of filing. A complete notification is a notification that contains all the information required by 21 CFR 190.6. The date of filing is the start of the 75-day premarket review period during which the manufacturer or distributor of a dietary supplement containing an NDI may not market the dietary supplement (21 U.S.C. 350b(a)(2); 21 CFR 190.6(c)). If the notification does not meet the requirements of 21 CFR 190.6, a member of FDA's Office of Dietary Supplement Programs will contact the notifier to determine how long it will take for the notifier to provide the missing information. If the notifier can provide the information within 14 days, FDA will file the notification upon receipt of the missing information. If the notifier cannot provide the missing information within 14 days, FDA will consider the notification incomplete and will mail a letter so informing the notifier. Upon request, members of the New Dietary Ingredient Review Team will provide advice on how to prepare a notification that meets the requirements of 21 CFR 190.6.

2. What are examples of omissions that cause a notification to be incomplete?

An incomplete notification does not satisfy the notification requirement found in section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)); therefore, if the dietary supplement containing the NDI is marketed, it is deemed to be adulterated under section 402(f) of the FD&C Act (21 U.S.C. 342(f)) unless the notifier has amended the notification to supply the missing information at least 75 days before the dietary supplement is introduced or delivered for introduction into interstate commerce (21

U.S.C. 350b(a)). FDA does not evaluate safety or identity information in incomplete NDI notifications.

The following are examples of omissions that make a notification incomplete:

- Material in a language other than English that is either not translated or is translated inaccurately.
- Citations to published literature for which a full copy of the publication is not provided.
- A notification that is not signed, or contact information that is inaccurate and does not permit FDA to establish contact with the notifier.
- Submitting a copy of the notification that is not the same as the original.

3. What type of response may I expect to receive from FDA, and when?

Within 75 days after FDA files your notification, you may expect a letter acknowledging receipt of the notification and stating the date on which the notification was filed. Examples of the types of response letters FDA commonly sends include:

- Letter of acknowledgment without objection;
- Letter listing deficiencies that make the notification incomplete under 21 CFR 190.6;
- Objection letter raising safety concerns based on information in the notification or identifying gaps in the history of use or other evidence of safety; and
- Letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient under 21 U.S.C. 321(ff)(1), or the product is excluded from the definition of "dietary supplement" under 21 U.S.C. 321(ff)(2) because it is not intended for ingestion).

The letter may contain information about our review of your notification, and it may ask you to submit additional information if your notification is incomplete or raises safety or identity questions. The letter also contains a report number that identifies the notification in the FDA docket. If you provide FDA with an email address in your notification, FDA will send the response letter to that email address on the day the response letter is mailed.

VI. What to Include in an NDI Notification

A. Identity Information About the NDI and the Dietary Supplement

1. What is the purpose of including information about the identity of the NDI and the dietary supplement containing the NDI in my notification?

The purpose of including identity information in an NDI notification is to establish what the NDI is, including the category of dietary ingredient in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)) to which it belongs; to identify the other ingredients and components of the dietary supplement; and to provide the basis for FDA to evaluate the qualitative and quantitative relationship between the NDI and the substances that are the subject of the history of use or other evidence of safety in your notification (see questions VI.A.5 and VI.C.2). Without complete and accurate identity information, FDA cannot evaluate whether there is a history of use or other evidence establishing that the dietary supplement containing the NDI will reasonably be expected to be safe under your proposed conditions of use.

2. What types of identity information should I include in my NDI notification?

We recommend including the following in the identity section of your NDI notification:

- The name of the NDI, as given in the cover letter (see question V.A.2), its trade name (if different), and any other names by which the NDI is known;
- A description of the physical properties of the NDI, a description of the chemical or molecular composition or structure of the NDI, or both;
- Controls and/or acceptable ranges for batch-to-batch variability, where applicable;
- The identity and level of any impurities and contaminants that may be in the NDI or dietary supplement;
- Additional information specific to the type of dietary ingredient, as recommended in question VI.A.6 (vitamins, minerals, amino acids, constituents, metabolites, and other discrete chemical entities), VI.A.7 (salts), VI.A.8 (enzymes), VI.A.9 (covalently modified derivatives of a dietary ingredient), VI.A.11(mixtures), VI.A.12 and VI.A.13 (botanicals), VI.A.15 (extracts and concentrates), VI.A.16 (ingredients produced using fermentation), and VI.A.17 (live microbial dietary ingredients); and
- A description of the identity of the other dietary ingredients and the other ingredients in the dietary supplement product.

FDA recommends that you establish identity specifications for the NDI and for those components of the NDI and dietary supplement that are relevant to establishing the basis for the safety of the dietary supplement. Your notification should provide a detailed description of the identity specifications in table form, as recommended in question VI.A.5.

In addition, for a manufactured NDI, you should describe the manufacturing process and provide detailed information about the aspects of the manufacturing process that are relevant to safety and identity, as recommended in question VI.A.3 below.

3. How much detail should my description of the manufacturing process contain?

The description should have sufficient detail to enable FDA to understand the overall process used to make the NDI and the dietary supplement. You should identify any points in the process that you know to be relevant to the safety of the dietary supplement. Detailed descriptions of manufacturing can be limited to those portions relevant to safety and identity, if they can be identified. For example, you might establish a specification to limit mold contamination of a component used to make your NDI (e.g., aflatoxin in corn). You might also use a specification for the temperature of a key extraction step to prevent formation of a toxic byproduct and/or a specification for that byproduct in an analysis of an interim material or of the final product. You may describe the entire process and all specifications or select only those that are relevant to the identity and safety information that provides the basis for the safety of your NDI.

4. What is a specification?

A specification is a set of standards developed by the manufacturer or distributor of a material (e.g., an NDI or a dietary supplement). The specification includes standards for each of the components of the material and for the material as a whole. For the purpose of an NDI notification, the specifications should include critical safety attributes and may omit attributes not relevant to safety or identity. The specification sheet should provide a list of tests, the acceptance criteria for each test, and analytical methods used to support the acceptance criteria. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. They are used to determine whether to accept or reject the ingredient or product being analyzed. Acceptance criteria should be specific, rather than vague.

The description of the analytical methods should include a detailed set of directions that must be followed exactly for the results to be accepted for the stated purpose. The directions should cover all steps, from preparing the test sample to reporting the results of the analysis. The description of the method should be complete, whether it is proprietary or included as a publication. Details of the method, such as a description of the chromatographic column, solvent elution conditions, and the

source and authenticity of any reference standards, are integral to understanding how a method is used to identify the analyte.

A vague acceptance criterion is rarely useful. For example, it is not informative to say that a chromatogram or a spectrum "matches the reference sample" unless every peak matches (both height and location) or there is a description of which peak or peaks match and how they match (e.g., description of the acceptable variation in peak retention time and peak height or area under curve). The use of "fingerprint" analysis of complex spectra or chromatography of mixtures containing many ingredients does not require knowledge of the identity of all or even any of the peaks, but does require matching sufficient numbers of peaks across the entire spectrum or chromatogram to ensure the validity of the test result. Components that are known to be toxic can be identified by a single acceptance criterion (e.g., "less than"), but acceptance criteria for other components should be expressed as a range. The source and authenticity of analytical standards should also be documented.

5. What specifications for my process and ingredients should I include in the notification?

Manufacturers and distributors of dietary supplements must establish specifications for the components of their products (see 21 CFR 111.70(b)). The required types of component specifications include:

- An identity specification for each component;
- Component specifications necessary to ensure that specifications for the purity, strength, and composition of dietary supplements manufactured using the components are met; and
- Limits on the types of contamination that may adulterate or may lead to adulteration of the finished product.

Your notification should list and explain the role of those specifications that are relevant to the identity of the NDI and to the safe consumption of the dietary supplement containing the NDI, including how you arrived at the criteria for acceptance or rejection based on the results of each test in the specification. This might include specifications for starting materials used to make your NDI, process controls during manufacturing, and/or interim or final product specifications for the NDI or the dietary supplement. For ease of reference, we recommend listing the specifications in table form (see example in Table 2). You should describe the controls in place to maintain the strength, composition, and purity of the NDI throughout the shelf life of the product.

If you rely on history of use or other evidence of safety for materials other than your NDI, you should explain, based on the manufacturing method and specifications of

your NDI, the qualitative and quantitative relationship between your NDI and the materials used to demonstrate safety. For example, if your NDI is a mixture of polyphenolic compounds extracted from grapes, you might use information such as quantitative high performance liquid chromatography (HPLC) analysis to relate the quantity of those compounds in a serving of your ingredient to the quantity in a serving of unprocessed grapes or grape juice.

Table 2. An Example of a Specification Sheet or Table for a Dietary Ingredient

Test	Acceptance Criteria	Analytical Method (Referenced Method or In–House Method Name)
Appearance: Color/physical state	White to off white/powder	Visual, R-01545[1]
Dietary ingredient identity	Matches reference standard	HPLC, R-02030[1]
Dietary ingredient assay	a ± b mg/capsule	HPLC, R-02030[1]
Related substances: Total related substances	No more than (NMT) 0.5% of total peak area of the dietary ingredient	HPLC, R-02030[1]
Microbial limits, if applicable: Total Aerobic Microbial Count *Staphylococcus aureus* *Pseudomonas aeruginosa*	NMT 100 CFU/g Absent Absent	USP <61>
Apparent pH, 25 °C (if applicable)	4.5 to 5.5	USP <791> or in house method
Residual solvent, e.g., ethanol, acetone, hexane[2]	NMT specified limit in ppm	GC, R-01901[1]
Heavy metals	NMT 20 ppm	USP 30<231> Method II

[1] In-house analytical methods, which should be described in sufficient detail in the NDI notification for FDA to evaluate them. Use of a method published by an authoritative source (such as AOAC International or the United States Pharmacopeia (USP)) or described in a peer-reviewed journal (such as *Journal of Chromatography)* is also appropriate, as long as a reprint or copy of the publication is provided.

[2] Solvents that were used in the manufacturing process.

6. What additional information should I submit if my NDI is a discrete chemical entity (e.g., a vitamin, mineral, amino acid, or a constituent or a metabolite of another dietary ingredient)?

You should provide sufficient information to uniquely characterize your NDI as a discrete molecular entity (or mixture of discrete molecular entities). Information that uniquely characterizes a single molecular entity should include the common or usual name of the molecular entity, the molecular formula and formula weight, the structural formula (as noted, for example, in ChemIDPlusAdvanced, PubChem, or International Union of Pure and Applied Chemistry (IUPAC)) and, if available, the Chemical Abstracts Service (CAS) registry number. For example, if the substance exists as a configurational isomer (stereoisomer), such as an enantiomer or a

geometric isomer, the isomer in question should be specified and characterized. For an enantiomer, the notification should include the correct stereoisomeric structure and the correct chemical name with the appropriate R or S designations.

Other systems of nomenclature (such as D or L for amino acids) are also appropriate as long as the name unambiguously identifies which isomer(s) are present. For a geometric isomer, the correct cis (Z) or trans (E) stereoisomeric structure and the correct chemical name should be provided. In addition, if the notification asserts that the NDI is a metabolite, you should document the basis for this assertion. For example, the notification should cite evidence showing that the level of the NDI in the human body increases with intake of a precursor constituent of food. (See definition of "metabolite" in section VII.)

Other relevant information might include:

- Specifications for your raw materials (e.g., food grade), and evidence that your raw materials conform to the specifications.
- A detailed description of each step of the production process, including:
    - Reaction conditions in the synthesis and purification process.
    - The process and quality controls used in the manufacturing process; for example, temperature, time, pH, shielding gas, etc.
    - Flow diagrams of the manufacturing process.
    - Composition: Provide the identity and quantity (including units and any ranges) for each component.
    - A description of how undesirable byproducts of manufacturing are removed. Examples of undesirable byproducts include unreacted chemical reagents, reaction byproducts, and solvents like methanol or hexane.

7. What additional chemistry information should I submit if my NDI is a salt?

You should describe the extent to which the salt will dissociate following ingestion, particularly if the history of use or other evidence of safety describes forms of the ingredient other than the salt that is the subject of the notification. Specific discussion of whether different salt forms have different toxic properties also should be included.

8. What additional chemistry information should I submit if my NDI is an enzyme?

If your NDI is an enzyme, you should describe the following in the specifications portion of the identity section of your notification:

- The analytical method used to determine enzyme activity;
- The specifications for enzyme activity in the NDI; and
- The acceptance criteria for enzyme activity and for the number of units of activity per serving of the NDI in the dietary supplement.

9. What additional chemistry information should I submit if my NDI is a covalently modified derivative of a dietary ingredient?

Covalent modification chemically alters the ingredient and changes its identity. Examples include covalent bonding of one dietary ingredient to another or exchanging a functional group (e.g., an alcohol) for another (e.g., an acid or an ester). The chemical structure of the new ingredient should be described explicitly and clearly. Before submitting an NDI notification for the new ingredient, you should consider whether it qualifies as a dietary ingredient under one of the categories in section 201(ff)(1)(A)-(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(A)-(F)) (see question IV.D.5). If not, the new ingredient cannot be an NDI because it is not a dietary ingredient.

10. What information should I submit if my notification relies on history of use or other evidence of safety for a substance or product that is similar to, but not exactly the same as, my NDI or dietary supplement?

You should use chemical, microbiological, and botanical characterizations, as appropriate, to explain how the substance or product is similar to your NDI or dietary supplement and to provide a rationale for how the safety information that is presented for the similar substance or product is relevant to the safety of your NDI or dietary supplement. Note that developing such a rationale requires knowledge of the identity (e.g., composition and strength) of the related substances that were studied or that have a history of safe use. The discussion in the notification should include the scientific rationale that supports extrapolating conclusions from a safety evaluation of the related substance or product to your NDI or dietary supplement. Otherwise, such evidence of safety may not provide a basis to conclude that your NDI or product will reasonably be expected to be safe.

11. What additional identity information should I submit if my product contains a mixture of ingredients?

You should state the identity and level of each ingredient in the dietary supplement, including both dietary ingredients and other ingredients, such as those used for a technical or functional effect in the product (e.g., binders, fillers, and color additives). You should also describe how the ingredient combination in the mixture relates to the history of safe use or other evidence of safety of the dietary supplement in which the NDI will be used. The dietary supplement safety narrative should address bioavailability of the ingredients as formulated, including use of any binders or fillers that affect bioavailability of any of the dietary ingredients in the dietary supplement.

12. What additional identity information should I submit if my NDI is a botanical or is derived from a botanical?

You must provide the Latin binomial name, including the author citation, for any ingredient that is a botanical or derived from a botanical (21 CFR 190.6(b)(2); see also 21 CFR 101.4(h)). We recommend that you also specify the part of the plant from which the ingredient is derived. You may, in addition, provide a common or usual name for your botanical ingredient. The Latin binomial name should be in accordance with internationally accepted rules on nomenclature, such as those found in the International Code of Nomenclature for algae, fungi, and plants (ICN) (formerly known as the International Code of Botanical Nomenclature). FDA recommends using the most recent edition of ICN.[45] We also recommend providing the following to help us evaluate whether your botanical ingredient is the same as or similar to botanical ingredients described in the history of use or other safety evidence in your notification:

- Description of specific tests or examinations you use to ensure correct taxonomic identity, including identification of any authenticated botanical reference materials or authoritative botanical descriptions used;
- Conditions of propagation, if they involve deliberate manipulation of propagation in a manner that is significantly different than common plant propagation and breeding practices;
- Conditions of cultivation (e.g., wild harvest, field, or greenhouse) and geographical origin of plant material, if necessary to accurately identify the NDI or relevant to your conclusion that the ingredient is reasonably expected to be safe;

[45] McNeill, J.; Barrie, F.R.; Buck, W.R. et al., editors. International Code of Nomenclature for algae, fungi, and plants (Melbourne Code) 2012 (electronic ed.). Available at: http://www.iapt-taxon.org/nomen/main.php

- Periods during which the botanical is cultivated and harvested (season or month(s) and year, age of plant, or both) and the stage of maturity of the harvested plant part;
- The part of the plant from which the ingredient is derived;
- Whether the botanical is used in a fresh or dehydrated state;
- The form in which the botanical is used (e.g., whole, chopped, cut-and-sifted, or powdered);
- A properly prepared and curated voucher of the botanical source material; and
- The full Latin binomial name (with author) of any known adulterant species that must be excluded from use in production of the NDI, and a description of how its use is excluded.

13. Should I describe the production methods for my botanical NDI?

Yes. You should describe the production methods for your botanical NDI to the extent necessary to demonstrate that the NDI is the same as or similar to the botanical materials described in information submitted as evidence of the safety of the NDI. Thus, cultivation of plants, algae, or fungi in wild or standard conditions might not require extensive explanation. However, unusual production conditions should be explained. For instance, if you culture *Saccharomyces cerevisiae* in a medium with unusually large amounts of selenium, you should describe the fermentation process, as well as the levels and types of selenium compounds in your final product. If you use traditional or molecular methods to produce a variety with novel properties, you should describe the variety in sufficient detail to demonstrate that the ingredient you derive from it is reasonably likely to be safe under the conditions of use of the dietary supplement to which the NDI will be added.

14. How should the identity section of my NDI notification deal with toxins in related plants or microorganisms?

You should identify the toxins or classes of toxins or other deleterious constituents or properties (e.g., antibiotic resistance genes in microorganisms or toxigenic properties for which the toxin is unidentified) known to be present in the same species or in a family or genus that is phylogenetically related to the NDI. You should also document the absence (or the amount, if present) of those toxins or other deleterious constituents or properties in the NDI, as well as in the substances that are the subject of the history of use or other evidence of safety presented in the notification. Identification below the species level (e.g., plant variety or strain

designation) can be relevant to the safety determination when some varieties or strains of a species are known to contain toxins.

15. How should I describe an extract or concentrate of a botanical or a dietary substance?

You should include the following in the description of your extract or concentrate:

- Overview of the manufacturing process, including a general description of each step (e.g., a flowchart), followed by a description of the method of manufacturing in sufficient detail to make clear the identity of the final product (the finished extract or concentrate) and how it is similar to and different from the starting material.

- Description and amount, expressed as a percentage or range of percentages, of all added ingredients, including all solvents used, along with specifications for residual solvents other than water in the finished NDI or dietary supplement.

- Concentration or dilution ratio, or range of concentration or dilution ratios, of the finished extract or concentrate relative to the original starting material. If the concentration or dilution ratio is based on the weight of fresh herb, rather than dried, this fact should be disclosed.

- Content, minimum content, or range of content of any marker substances, expressed as a percentage of the finished extract or concentrate, accompanied by (1) a description of whether the marker is a marker of effectiveness, toxicity, or a surrogate marker, and (2) a calculation or estimate of the relative level of each marker in the NDI compared to the original starting material.

- The names and specifications for any marker substances deemed relevant to the identity of the NDI (e.g., markers whose presence or absence is relevant to the identity of the botanical or that must occur in a particular ratio to each other to confirm identity).

- How the extract or concentrate is standardized from batch to batch.

- Measures taken to remove adulterants (e.g., nonfood solvents) that may be present due to production methods or to reduce such adulterants to within acceptable limits.

- Measures taken to control adulterants (e.g., pesticides, heavy metals, and filth) that may be present in raw materials from which the NDI is derived.

- Quantitative limits on contaminants that must be controlled to ensure the NDI's safety, if any are present in the source material or may result from the manufacturing process.

- If reagents used during processing are likely to make covalent changes to components in the mixture during processing, you should determine whether the new material is still a dietary ingredient. For example, use of a large amount of an oxidizing acid like sulfuric acid to process a botanical mixture may create a new "semi-synthetic" mixture that is no longer a mixture of components that were present in the original plant. Therefore, the mixture would no longer be a dietary ingredient.

16. What additional information should I include if my NDI is produced using fermentation?

The notification should include information about the organism(s) and fermentation process used to culture the microorganism that produces the NDI. The safety of the fermenting organism for use in food production should be discussed. Poorly defined microbiological mixtures are acceptable if there is a long history of use in production of food (e.g., mixtures used to make dairy products like kefir or cheese) and the fermentation substrate is consistent with that history of use. The notification should describe the history of use of the fermenting organism(s) to produce food or, in the absence of such history, should thoroughly explain how the manufacturing process excludes toxins and other undesirable byproducts of fermentation from the finished NDI.

The information about the fermentation process should describe the complete media formulation, the fermentation vessel(s), the fermentation conditions, the methods used to harvest the NDI from the fermentation mixture, and any specifications for the production organism in the finished NDI, particularly if the production organism is not inactivated or removed.

You should also address methods used to ensure the integrity of the production organism, such as how you guard against contamination and genetic change. FDA is particularly concerned about contamination when fermentation occurs outside of a sterile production vessel (e.g., production of algae in ponds).

Note that the use of a major food allergen in the fermentation medium may require a separate notification or petition to the FDA if the presence of the allergen is not declared on the product label. See section 403(w) of the FD&C Act (21 U.S.C. 343(w)).

If your ingredient is an enzyme, the specifications portion of the identity section of your notification should describe the analytical method used to determine enzyme activity, the specifications for enzyme activity in the NDI, and the acceptance

criteria for enzyme activity and for the number of units of activity per serving of the NDI in the dietary supplement. Post-fermentation harvest and processing should be described, including filtration, washing, and preservation methods.

17. What additional information should I include if my NDI is a live microbial dietary ingredient?

You should include a complete description of the organism, including:

- The strain;
- Methods used to establish the identity of the strain, such as identification by internationally recognized third-party repositories (e.g., the American Type Culture Collection); and
- The relationship of the strain to the strain(s) of the same species used to establish the history of use or other evidence of safety for the NDI.

The use of scientific names (Latin binomial name with author citation) is required for botanical ingredients (21 CFR 190.6(b)(2)) and is recommended for bacteria. For bacteria, FDA recommends using the Bacteriological Code (1990 Revision),[46] validated lists of names in the International Journal of Systematic and Evolutionary Microbiology, and public lists of prokaryotic nomenclature (e.g., Prokaryotic Nomenclature Up-to-Date[47] or the List of Prokaryotic Names with Standing in Nomenclature[48]). FDA will pay particularly close attention to the proper identification of organisms from genera or species that do not have a long history of food use and to those from genera, like *Bacillus* and *Streptococcus*, which contain both species with long histories of food use and species known to contain human pathogens.

FDA regards all members of a species that contains human pathogens as potentially harmful to human health and, therefore, inappropriate for use as dietary ingredients, because of the absence of a consensus that there are valid scientific ways to distinguish between pathogenic and non-pathogenic members of a single species or to prevent horizontal transfer of genes for pathogenic traits between members of the

[46] Lapage, S. P.; Sneath, P. H. A.; Lessel, E. F.; Skerman, V. B. D.; Seeliger, H. P. R.; Clark, W. A., editors. International Code of Nomenclature of Bacteria (Bacteriological Code), 1990 Revision. Washington (DC): American Society for Microbiology Press; 1992.

[47] Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures, Prokaryotic Nomenclature Up-to-Date. Available at: http://www.dsmz.de/bacterial-diversity/prokaryotic-nomenclature-up-to-date/prokariotic-nomenclature-up-to-date.html [Note that content on this website is updated frequently. Use the search function in the embedded link to retrieve the current validated name of a bacterial organism.]

[48] Parte, A.C., editor. List of Prokaryotic Names with Standing in Nomenclature (LPSN) Database. Available at: http://www.bacterio.net/. [Note that content on this website is updated frequently. Use the search function in the embedded link to retrieve the current validated name of a bacterial organism.]

same bacterial species. Examples of species that should not be used in dietary supplements include *Escherichia coli*, *Enterococcus faecalis*, and *Enterococcus faecium*.

FDA considers each strain of a bacterial or yeast species to be a separate ingredient. You should explain how your strain was obtained and how it varies from other members of the same species. If your strain was genetically modified using either random mutagenesis or bioengineering, you should describe the process used and how you characterized the properties of the new strain.

FDA also considers the manufacturing process, including the fermentation, as an intrinsic part of the identity of an ingredient that is viable at the time of ingestion. We recommend that the fermentation and other parts of the manufacturing process relevant to safety and identity be described in detail in your notification, as recommended in questions VI.A.3 and VI.A.16.

FDA will pay particular attention to the viability of microorganisms in the NDI. The per-serving level of a viable microorganism depends on both the mass (in grams) and the viability (e.g., number of colony-forming units) of the organism in the final product. The composition of the growth medium and the fermentation conditions of the organism are also relevant to the safety of the product, particularly when they alter the form of the organism (e.g., spore vs. vegetative) or the composition of the ingredient (e.g., when the ingredient includes both the organism and the growth medium). The notification should explain the relevance of safety information presented about other strains from the same species.

18. What information should I provide in my notification if the labeling of the NDI or dietary supplement containing the NDI will include an expiration date or "use by" date?

The expiration or "use by" date should be based on appropriate supportive stability data showing that (1) no new degradants will form during the labeled shelf life of the product under the conditions of storage specified in the notification, if any, or under normal storage conditions; and (2) the NDI or dietary supplement will continue to meet the critical safety attributes of identity, strength, and purity through its labeled expiration or "use by" date. You should provide these supportive data in the notification.

19. What information should I submit to describe the conditions of use that I intend to recommend or suggest in the labeling of my dietary supplement?

Your notification must describe the conditions of use that will be recommended or suggested in the labeling of your dietary supplement or, if no conditions of use will be recommended or suggested in the supplement labeling, the ordinary conditions of use of the supplement (21 CFR 190.6(b)(2)(ii)). Conditions of use include the dose

(serving size), serving form (e.g., capsule or powder)), frequency of use (e.g., number of servings per day and interval between servings), duration of use, instructions for use, target population, other dietary ingredients in the dietary supplement, and any restrictions on use, such as excluded populations.

For purposes of review, daily lifetime use by all age groups and other populations at the highest recommended serving size will be assumed unless the notification specifies that the labeling will contain restrictions on conditions of use (e.g., excluded populations or frequency and duration of intake). Population restrictions could include exclusion of children, pregnant or lactating women, or sensitive individuals who should not consume the product. Allergen warnings are an example of a population restriction on conditions of use. The conditions of use to be recommended or suggested in the labeling of the dietary supplement(s) containing the NDI should be described prominently in the administrative section near the beginning of the notification (see question V.A.2).

B. History of Use or Other Evidence of Safety

1. What safety information is required to support an NDI notification?

You must provide the information that forms the basis on which you have concluded that a dietary supplement containing the NDI will reasonably be expected to be safe under the supplement's labeled conditions of use (21 U.S.C. 350b(a)(2)). In general, this information should include an adequate history of safe use, safety studies, or both.

For dietary supplements that contain dietary ingredients or other components in addition to the NDI, the notification should include safety information for the finished product as well as for the NDI because it is not possible to conclude that the dietary supplement containing the NDI will reasonably be expected to be safe without considering the safety of these other components. As discussed in section VI.C, FDA recommends including a comprehensive safety profile for the NDI and a safety narrative for the dietary supplement in NDI notifications (see questions VI.C.1 through VI.C.3).

2. Should I submit both a history of safe use and safety testing data for the NDI?

It depends. A notification should provide evidence of a history of safe use; other evidence of safety, including clinical testing, animal testing, or both; or some combination of history of use and other evidence of safety. The submitted data should provide the basis for a conclusion that there is a reasonable expectation of safety under the proposed conditions of use of the dietary supplement containing the NDI.

FDA expects that when history of use evidence alone is adequate to support the safety of the NDI in the supplement, notifiers will prefer to use that route. Compared to the cost and time needed to conduct clinical or animal toxicology studies, it is generally less expensive and faster to gather historical information and to conduct chemistry studies to establish the identity of the historically used materials.

Submitting clinical studies, animal studies, or both, in addition to history of use data, would be appropriate when the history of use evidence contains gaps or when the proposed conditions of use for the NDI differ from the historical conditions of use.

3. What data and information should I submit to substantiate an NDI's history of safe use?

A history of safe use can be substantiated by providing evidence that the substance was safely consumed as a food or dietary supplement or as a component of a more complex mixture (e.g., calcium in milk or beta-glucan in oatmeal) at levels equal to or higher than those that would be consumed by someone taking the NDI-containing supplement under the proposed conditions of use. This history of use could be from the United States or another country, as long as the substance was consumed as a food, dietary supplement, or, in the case of foreign history of use, category of product comparable to a dietary supplement in the U.S.

Elements that FDA recommends to substantiate that an NDI has a history of safe use include: (1) a characterization and comparison of the identity of the NDI and the historically consumed article; and (2) an explanation of how the compositions of the two are related. That is, the composition and other identifying characteristics of the NDI and the historically consumed article should be characterized in sufficient detail to demonstrate that safe use of the historically consumed article is relevant to the safety of the NDI and provides a basis to conclude that the supplement in which the NDI will be marketed will reasonably be expected to be safe under the proposed conditions of use. If the NDI's history of use was as a component of a more complex mixture, you should demonstrate how the NDI is qualitatively and quantitatively related to the historically consumed component. If the NDI is itself a mixture of dietary ingredients, you should demonstrate how the component dietary ingredients in the NDI are related to historically consumed ingredients or components.

In addition, (a) the dose (per-serving intake) and total daily intake; (b) duration of use; (c) frequency of intake; and (d) any additional information that describes the conditions of use of the historically consumed material should be provided. For example, if consumption is not uniform within the population, you should provide information about the mean and high (e.g., 90th percentile) exposure levels. Finally, the size and relevant characteristics of the consuming population (e.g., everyone vs. limitations based on age, gender, or health status) should be discussed.

For these data to demonstrate a history of safe use, the intake level for the historically consumed article should be the same as or higher than the anticipated intake level of the NDI in the dietary supplement, based on the conditions of use described in the NDI notification. For example, information showing that a steroid hormone is present in nanogram amounts in a serving of milk or beef—foods that have a long history of safe use— would not support the safety of a highly concentrated bovine extract that contains the steroid hormone in milligram amounts. In contrast, consumption of cow's milk could be used to support the safety of a specific protein purified from milk at a serving level equal to or lower than the amount of the protein found in an 8 ounce serving of milk.

As another example, if your NDI is an oil made from a plant or fish and you can show that the oil consists only of a mixture of fatty acids, each of which you can identify and demonstrate to be widely consumed at higher levels in conventional foods, you may be able to conclude that the dietary supplement containing the NDI will reasonably be expected to be safe based on compositional information alone.

The safety assessment should describe and discuss situations in which the conditions of use and composition of the NDI differ from the documented conditions of use and composition of the historically consumed substance (e.g., when the NDI is derived from a plant variety bred to produce an additional constituent or to remove a toxic constituent). When the historical usage differs substantially from the proposed use of the NDI, additional supportive data may be needed. Examples of differences in an NDI's proposed use that might necessitate further supportive data include:

- Higher dosage;
- Different route of administration (e.g., an article that has a history of safe use in sublingual form and is now intended for ingestion as an NDI);
- Longer duration of use;
- Other changes that increase exposure to potential toxic effects; and
- Any other difference that raises new safety issues, such as a change in target population (see definition in section VII).

4. What documentation of an NDI's history of use should I submit?

Documentation of an NDI's history of safe use in food could include published data and information, such as peer-reviewed scientific literature, reports from authoritative bodies, survey data on food or nutrient composition and consumption, advertisements or other published promotional material describing the composition of products, published agricultural or food production data, or cookbooks or other published recipes documenting the use of an ingredient to prepare conventional

foods. Documentation of history of use could also include trade secret or confidential commercial information, such as proprietary survey or consumption data, product sales data, and compositional analyses.

5. Am I required to submit a comprehensive survey of every historical use of the NDI?

No, only the data and information on which your reasonable expectation of safety is based are required. For example, if you have documentation that soybeans have a history of safe use in a large population in Asia, data describing lower historical consumption in the U.S. or Europe is not necessary to support the safety of an NDI that is a constituent of soybeans.

6. How do I determine whether historical use was "daily chronic" or "intermittent"?

Daily chronic use of the historically consumed material refers to ingestion at least once a day, every day, for at least three months in a row. Daily chronic use includes long-term use. Intermittent use, for purposes of this guidance, means less than daily chronic use and can be either daily and finite in duration or non-daily and lifetime in duration. An example of intermittent use is the use of seasonal fruit for less than 90 days.

7. Should I estimate the intake of historically consumed materials related to my NDI if I am relying on those related materials to establish a history of safe use, and should this estimate be included in my NDI notification?

Yes to both questions. If your conclusion that the dietary supplement containing your NDI will reasonably be expected to be safe is based on a history of safe use of materials other than the NDI itself, you should estimate the historical intake of the materials that you determine to be relevant (see question VI.A.10) and include this information in your NDI notification. In developing these estimates, you should take into account the complete pattern of intake, including dose, duration, and frequency of intake, as well as the size of the population known to have consumed the substance. The distribution of intake within the population (e.g., the mean and 90^{th} percentile amounts consumed) is also important.

8. Where may I find information on how to estimate consumer intake?

For references and information on methods of estimating consumer intake of food ingredients, including dietary ingredients in dietary supplements, refer to

"Estimating Dietary Intake of Substances in Food"[49]; section III.G, "Intake Estimate," in "Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions"[50]; and "Principles and Methods for the Risk Assessment of Chemicals in Food."[51] FDA is also aware of the existence of extensive analyses of consumption of specific conventional foods, especially in the U.S., in proprietary databases. Because these proprietary databases contain food categories much narrower than those described in public databases, they may be helpful in estimating consumer intake of a food constituent that becomes an NDI for use in a dietary supplement.

9. How is the reliability of history of use data evaluated?

One important component of reliability is the length of an ingredient's history of use. A description of the population consuming the ingredient and the ways in which they use it is also important. Finally, the number of consumers who used the ingredient and the frequency of consumption are at least as important as the number of years over which the ingredient has been used. FDA considers 25 years of widespread use to be the minimum to establish a history of safe use.[52] Because there is little scientific literature addressing this topic, we cannot make more specific recommendations at this time.

10. Should I cite the history of use of an NDI in traditional medicine?

It depends on how much information is available about the use of the NDI in traditional medicine and how similar the traditional medicine use is to the proposed use in a dietary supplement. The history of use of an NDI in traditional medicine can help to establish a reasonable expectation of safety for the NDI's use in a dietary supplement. However, because differences in composition, conditions of use, and target population often limit the relevance of a safe history of use in traditional

[49] FDA, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry: Estimating Dietary Intake of Substances in Food; August 2006. Available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm

[50] FDA, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions; March 2006; revised March 2009. Available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm124917.htm

[51] Principles and Methods for the Risk Assessment of Chemicals in Food. Environmental Health Criteria 240. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. 2009. Available at: http://whqlibdoc.who.int/ehc/WHO_EHC_240_4_eng_Chapter1.pdf

[52] See, e.g., the definition proposed in the European Union: "'[H]istory of safe food use in a third country' means that the safety of the food in question is confirmed with compositional data and from experience of use and continued use for at least 25 years in the customary diet of a large part of the population of a country." *Official Journal of the European Union* C 122 E (May 11, 2010); p. 38-57.

medicine to the safety of an NDI in a dietary supplement, additional safety information is almost always needed.

As previously described, it is important to document the size and characteristics of the population that consumed the NDI in or as a traditional medicine, as well as conditions of use, such as dose, duration, and frequency (see questions VI.B.3 and VI.B.7). In addition, if the medicinal product was consumed under the supervision of a trained practitioner of traditional medicine, it is important to document safety-related restrictions on use within the written or oral tradition. Often, traditional medicinal products are chemically and compositionally very different from the NDI that is the subject of the NDI notification. Therefore, it is important to document and explain how any information about a substance's history of safe use in traditional medicine is qualitatively and quantitatively related to the NDI that is the subject of the notification and its proposed conditions of use.

11. Does FDA recommend submitting additional animal and human studies to supplement evidence of a history of safe use by humans?

It depends on the situation. Data on history of use in humans should be the first evidence considered in evaluating the safety of an NDI.

When the NDI has been previously consumed by humans, additional animal or human safety data are seldom needed if (1) the proposed use level is similar to or less than the levels safely consumed by humans in the past; and (2) the population expected to consume the NDI is the same as, or a subset of, the population that safely consumed the substance in the past. In many cases, no additional animal or human safety data are needed because the NDI is reasonably expected to be safe based on a large margin of safety between the level shown to cause no observed adverse effects in humans and the intake level that would result from the proposed use of the NDI in the dietary supplement, or based on longstanding and widespread use of the ingredient as a constituent of conventional food at or below the intake level that would result from the proposed use of the NDI in the dietary supplement.

When the historical use differs significantly from the proposed use of the NDI in a dietary supplement, however, additional supportive data are usually needed. Examples of differences in proposed use that would ordinarily necessitate further supportive data include higher dosage than the historical use, different route of administration, longer duration of use, other changes that increase exposure to potential toxic effects, and any other differences that raise new safety concerns (e.g., a different target population). These examples are based on the general principle that the risk of a substance is likely to increase as intake increases above levels safely consumed in the past. When historical use of an NDI differs significantly from the proposed dietary supplement use, FDA encourages you to submit additional animal studies, human studies, or both. Such studies should be designed to address gaps in the history of use evidence.

12. What factors are helpful in evaluating whether to submit animal or human safety studies in addition to history of use data?

Generally, the best way to determine whether history of use data provides a basis for a reasonable expectation that a dietary supplement containing an NDI will be safe is to compare the conditions of use proposed in the NDI notification with the documented historical conditions of safe use. The following are examples of situations where FDA would typically recommend that history of use data be supplemented with additional animal or human safety studies:

- Higher proposed per-serving intake level or total daily intake level.
- Longer proposed duration of consumption than historically reported (e.g., notification states that NDI will be marketed with labeling that recommends or implies continuous daily use for improved digestive function, but the history of safe use involves only infrequent, short-term use for indigestion).
- Different proposed route of administration (e.g., data about historical use of a substance as a poultice or by injection ordinarily would not be sufficient to support the safety of an NDI for use in a dietary supplement, which by definition is intended for ingestion).
- A change from historical use that might increase potential toxic effects (e.g., the NDI will be sold as capsules of a ground leaf, but the form historically used was a tea made from the plant's roots).
- A change in the target population (e.g., history of safe use has been established in adults, but NDI will be used in a dietary supplement marketed for use by young children).

13. Should I use toxicology or clinical studies published by others, or unpublished studies I have performed, if those studies used test articles that are similar but not identical to the NDI or the dietary supplement containing the NDI?

FDA generally recommends that the test article used in safety studies be identical to the NDI or the dietary supplement that is the subject of your notification. However, in the absence of safety data on the NDI or supplement itself, it may be useful to provide data on the safety of a related substance or product.

For example, if the NDI is a component of another substance for which safety studies are available, it may be helpful to submit data from those studies, accompanied by an explanation of why the data on the related substance support the safety of your NDI. Data from a study involving the oral administration of the dried

ground root of a plant could be relevant to the safety of an NDI that is an isopropanol extract of the same root if you document that the components of the isopropanol extract were present at the same or lower levels in the ground root fed to the study subjects. The safety of an ester ingredient can be inferred if you can provide data to demonstrate that the ingredient is rapidly hydrolyzed in the stomach or intestine into an acid and an alcohol, and that the acid and the alcohol each have a long history of safe use in food.

The more different the composition of the test article in a study is from that of the NDI, however, the more difficult it will be to argue that the study is relevant.

14. Are there scenarios in which FDA considers additional safety data unnecessary if the proposed use of the NDI leads to intake levels that are the same as or less than the levels consumed historically?

Yes. When the proposed use of the NDI leads to intake levels that are the same as or less than the levels for which there is a documented history of safe use, additional safety data are not needed if the dietary supplement containing the NDI is intended for (1) daily chronic use, and the documented historical use data support safe daily chronic use in the same population or a broader population; (2) intermittent use, and the documented historical use data support safe intermittent use in the same population or a broader population; or (3) intermittent use, and the documented historical use data support safe daily chronic use in the same population or a broader population. In other circumstances, we recommend submitting additional safety data as shown in Table 3 and discussed in the following six questions. (See Table 3: Safety Testing Recommendations Matrix.)

15. What types of data does FDA recommend to assess safety if the dietary supplement containing the NDI is intended for daily chronic use, the NDI has a documented history of safe intermittent use, and the proposed use of the NDI leads to intake levels that are the same as or less than the levels consumed historically?

(1) A three-study genetic toxicity (genetox) battery (bacterial mutagenesis, in vitro cytogenetics, and in vivo mammalian test) that includes a test for gene mutations in bacteria, either an in vitro mouse lymphoma thymidine kinase+/- gene mutation assay (preferred) or another suitable in vitro test with cytogenetic evaluation of chromosomal damage using mammalian cells, and an in vivo test for chromosomal damage using mammalian hematopoietic cells;
(2) A 14-day range-finding oral study to establish a maximum tolerated dose (MTD) in an appropriate animal model;
(3) A 90-day subchronic oral study (see questions VI.B.6 and VI.B.28-30) in the same species as the range-finding study to establish an MTD and a No Observed Adverse Effect Level (NOAEL) for use in calculating the margin of safety;
(4) A multi-generation rodent reproductive study (minimum of two generations) (see

note at end of list); and
(5) A teratology study (rodent or non-rodent) (see note at end of list).

Note: The rodent reproductive study and the teratology study are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, or children 13 and younger. (See Table 3: Safety Testing Recommendations Matrix.)

16. What types of data does FDA recommend to assess safety if the dietary supplement containing the NDI is intended for daily chronic use, the NDI has a documented history of safe daily chronic use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?

(1) A two-study genetox battery (bacterial mutagenesis and in vitro cytogenetics) that includes a test for gene mutations in bacteria, either an in vitro mouse lymphoma thymidine kinase+/- gene mutation assay (preferred) or another suitable in vitro test with cytogenetic evaluation of chromosomal damage using mammalian cells;
(2) A 14-day range-finding oral study to establish an MTD in an appropriate animal model;
(3) A 90-day subchronic oral study (same species as the range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety;
(4) A repeat-dose tolerability study in humans (30-90 day duration);
(5) A one-year chronic toxicity study in an appropriate animal model or a two-year carcinogenesis study in rodents;
(6) A one-generation rodent reproductive study (see note at end of list); and
(7) A teratology study (rodent or non-rodent) (see note at end of list).

Note: The rodent reproductive study and the teratology study are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, or children 13 and younger. (See Table 3: Safety Testing Recommendations Matrix.)

17. What types of data does FDA recommend to assess safety if the dietary supplement containing the NDI is intended for daily chronic use, the NDI has a documented history of safe intermittent use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?

(1) A three-study genetox battery as described in question VI.B.15;
(2) 14-day range-finding oral studies to establish an MTD in at least two appropriate species, at least one of which is non-rodent;
(3) Two 90-day subchronic oral studies (one for each species for which there is a range-finding study) to establish an MTD and a NOAEL for use in calculating the

margin of safety;
(4) A one-year chronic toxicity study in an appropriate animal model or a two-year carcinogenesis study in rodents;
(5) A repeat-dose tolerability study in humans (30-90 day duration);
(6) A multi-generation rodent reproductive study (minimum of two generations) (see note at end of list); and
(7) A teratology study (rodent or non-rodent) (see note at end of list).

Note: The rodent reproductive study and the teratology study are generally not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, or children 13 and younger. (See Table 3: Safety Testing Recommendations Matrix.)

18. What types of data does FDA recommend to assess safety if the dietary supplement containing the NDI is intended for intermittent use, the NDI has a documented history of safe intermittent use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?

(1) A two-study genetox battery (bacterial mutagenesis and in vitro cytogenetics) as described in question VI.B.16;
(2) A 14-day range-finding oral study to establish an MTD in an appropriate animal model
(3) A 90-day subchronic oral study (same species as the range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety
(4) A single-dose or repeat-dose tolerability study in humans and/or an absorption, distribution, metabolism, and excretion (ADME) study in animals, humans, or both;
(5) A one-generation rodent reproductive study (see note at end of list);
(6) A teratology study (rodent or non-rodent) (see note at end of list).

Note: The rodent reproductive study and the teratology study are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, or children 13 and younger. (See Table 3: Safety Testing Recommendations Matrix.)

19. What types of data does FDA recommend to assess safety if the dietary supplement containing the NDI is intended for intermittent use, the NDI has a documented history of safe daily chronic use, and the proposed use of the NDI leads to intake levels that are greater than the levels consumed historically?

(1) A two-study genetox battery as described in question VI.B.16;
(2) A 14-day range-finding oral study to establish an MTD in an appropriate animal model;
(3) A 90-day subchronic oral study (same species as the range-finding study) to

establish an MTD and a NOAEL for use in calculating the margin of safety;
(4) A single-dose or repeat-dose tolerability study in humans and/or an ADME study in animals, humans, or both; and
(5) A teratology study (rodent or non-rodent) (see note at end of list).

Note: The teratology study is not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, or children 13 and younger. (See Table 3: Safety Testing Recommendations Matrix.)

20. What types of data does FDA recommend to assess safety if there is no history of use of the NDI that can be relied on to provide evidence of safe use in dietary supplements?

(1) A three-study genetox battery as described in question VI.B.15;
(2) 14-day range-finding oral studies to establish an MTD in at least two appropriate species, at least one of which is non-rodent;
(3) Two 90-day subchronic oral studies (one for each species for which there is a range-finding study) to establish an MTD and a NOAEL for use in calculating the margin of safety (see footnote "‡" in Table 3: Safety Testing Recommendations Matrix);
(4) A repeat-dose tolerability study in humans and/or an ADME study in animals, humans, or both (30-90 day duration);
(5) A one-year chronic toxicity study or a two-year carcinogenesis study in at least two animal species, if the proposed use is either intermittent or daily chronic;
(6) A multi-generation rodent reproductive study (minimum of two generations) (see note at end of list); and
(7) A teratology study (rodent or non-rodent) (see note at end of list).

Note: The rodent reproductive study and the teratology study are not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, or children 13 and younger.

Based on the nature of the NDI and the results of other testing, special studies (e.g., carcinogenicity, ADME) may be needed to provide a reasonable expectation of safety. Other nonclinical studies to assess immunotoxicity and neurotoxicity should be conducted on a case-by-case basis, as appropriate. (See Table 3: Safety Testing Recommendations Matrix.)

Table 3: Safety Testing Recommendations Matrix

Documented Historical Use	Proposed Use of the NDI	Two-Study Genetic Toxicity Battery[1]	Three-Study Genetic Toxicity Battery[1]	14-Day Range-Finding Oral Study in Animals	90-Day Subchronic Oral Study in Animals[3]	One-Generation Rodent Reproductive Study [2]	Multi-Generation Rodent Reproductive Study[2]	Teratology Study in Animals[2]	One-Year Chronic Toxicity or Two-Year Carcinogenesis Study in Animals*	Single-Dose Tolerability and/or ADME Study in Animals and/or Humans*	Repeat-Dose Tolerability and/or ADME Study in Animals and/or Humans*
Daily Chronic	**Intermittent: Less Than** Historical Use (see question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
Daily Chronic	**Intermittent: Greater Than** Historical Use (see question VI.B.19)	**X**		**X**	**X**			**X**		**X**	
Daily Chronic	**Daily Chronic: Less Than** Historical Use (see question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
Daily Chronic	**Daily Chronic: Greater Than** Historical Use (see question VI.B.16)	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**
Intermittent	**Intermittent: Less Than** Historical Use (see question VI.B.14)	Documented history of use should be sufficient as evidence of safety.									
Intermittent	**Intermittent: Greater Than** Historical Use (see question VI.B.18)	**X**		**X**	**X**	**X**		**X**		**X**	

Documented Historical Use	Proposed Use of the NDI	Two-Study Genetic Toxicity Battery[1]	Three-Study Genetic Toxicity Battery[1]	14-Day Range-Finding Oral Study in Animals	90-Day Subchronic Oral Study in Animals[3]	One-Generation Rodent Reproductive Study [2]	Multi-Generation Rodent Reproductive Study[2]	Teratology Study in Animals[2]	One-Year Chronic Toxicity or Two-Year Carcinogenesis Study in Animals*	Single-Dose Tolerability and/or ADME Study in Animals and/or Humans*	Repeat-Dose Tolerability and/or ADME Study in Animals and/or Humans*
Intermittent	**Daily Chronic: Less Than** Historical Use (see questionVI.B.15)		**X**	**X**	**X**		**X**	**X**			
Intermittent	**Daily Chronic: Greater Than** Historical Use (see question VI.B.17)		**X**	**X**	**X** [3]		**X**	**X**	**X** [3]		**X**
No History	**Daily Chronic** (see question VI.B.20)		**X**	**X**	**X** [3]		**X**	**X**	**X** [3]		**X**
No History	**Intermittent** (see question VI.B.20)		**X**	**X**	**X** [3]		**X**	**X**	**X** [3]		**X**

1 Genetic toxicity batteries are described in questions VI.B.15 and VI.B.16.

2 Reproductive and teratology testing is not needed if the product is labeled as not for use by women of childbearing age, pregnant or lactating women, and children 13 and younger.

3 In general, if there is no history of use, two species should be used for 90-day subchronic studies. In addition, the one-year chronic toxicity study or two-year carcinogenesis study should be done in two species. However, the one-year chronic toxicity study, two-year carcinogenesis study, or second subchronic study may not be necessary in some cases based on the amount and type of historical use data or the duration of use of the NDI, if significantly shorter than lifetime daily use. For example, if the proposed use of the NDI is for 30 days or less, then a 28-day animal study might be sufficient under certain circumstances (e.g., live microbial NDI).

*Special studies (such as one-year chronic toxicity studies in animals; two-year carcinogenicity studies in animals; and ADME, bioavailability, and tolerability studies in animals, humans, or both) should be conducted on a case-by-case basis, as appropriate, if the toxicology data or the identity of the NDI raises a special safety concern.

21. Am I required to use only FDA-published safety test protocols?

No. You should use your own judgment in selecting among FDA's protocols and other internationally recognized safety testing protocols and testing batteries developed for other types of products when you choose safety testing protocols for your NDI or the dietary supplement to which your NDI will be added. Regardless of the protocols used, you should cite the source for each protocol and why the protocol or the battery of protocols you chose is appropriate for the safety endpoints that are being investigated.

The NDI safety standard is different than the standard for food additives, drugs, and other FDA-regulated products. Recommendations in guidance documents that are tailored to the safety assessment needs of other FDA-regulated products may not always be appropriate for dietary ingredients or dietary supplements. You should compile scientific evidence that provides a basis to conclude that the NDI that is the subject of your notification will reasonably be expected to be safe when used under the conditions recommended or suggested in the labeling of the dietary supplement described in the notification.

22. What are some sources of safety testing protocols that can be used in testing NDIs and dietary supplements?

Useful guidelines for safety testing include:

- OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects, published by the Organization for Economic Co-operation and Development[53];
- Harmonized Test Guidelines, published by the Office of Chemical Safety and Pollution Prevention of the U.S. Environmental Protection Agency (EPA)[54]; and
- Principles and Methods for the Risk Assessment of Chemicals in Food, published jointly by the Food and Agriculture Organization of the United Nations and the World Health Organization.[55]

23. What is the appropriate highest dose of an NDI to use in animal and human safety studies?

To maximize the chance that toxicity associated with the test article can be detected, the highest dose (commonly referred to as the "top dose") in animal studies should be the maximum

[53] Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects. Available at: http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm.

[54] U.S. Environmental Protection Agency (EPA), Office of Chemical Safety and Pollution Prevention (OCSPP). OCSPP Harmonized Test Guidelines; September 2015. Available at: https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances.

[55] Principles and Methods for the Risk Assessment of Chemicals in Food. Environmental Health Criteria 240. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. 2009. Available at: http://whqlibdoc.who.int/ehc/WHO_EHC_240_4_eng_Chapter1.pdf.

tolerated dose (MTD) (see definition in section VII). Lower doses are used to establish the dose-response relationship and the no-effect dose (see question VI.C.4 for information on the latter). Shorter-term studies are needed to estimate the MTD for longer studies; for example, the results of a 14-day study must be known before the dose for a 90-day study can be determined.

Considering a broad range of biological information is essential to pick the correct top dose or MTD. For example, data concerning changes in body and organ weight and clinically significant alterations in hematological, urinary, neurological, and clinical chemistry parameters, in combination with more definitive toxic, gross, or histopathologic endpoints, can be used to estimate the MTD. FDA intends to consider whether the test article was tested at the MTD as a major factor in evaluating the adequacy of studies submitted in an NDI notification. The studies should include a description of the process used to select the MTD for the study, if it is not readily apparent.

Please note that it is not scientifically valid to select doses for tests based on information unrelated to the toxicity of the test article. For example, the highest dose should not be selected so as to provide a pre-determined margin of safety over the maximum expected human consumption of the test article, assuming that the results of testing at that dose will be negative.

FDA recognizes that there may be limitations on using a top dose. For example, limits on top doses can be based on animal handling considerations, such as the amount that can be safely administered by gavage or the amount in feed that still permits proper nutrition. The top dose in clinical studies should be governed by safety considerations, as determined by an Institutional Review Board. However, within the limits of safety, the top dose in clinical studies should be as high as feasible. At a minimum, the top dose or total daily intake level in a clinical trial of an NDI should be as high as the top dose or total daily intake level of the NDI under the conditions of use proposed in the notification. Preferably, the highest total daily intake level in the trial should be higher than the highest total daily intake level of the NDI proposed in the notification.

24. What should I do to justify the use of a particular protocol?

You should cite an authoritative source for the protocol and explain how information generated by the study using the protocol supports the safety of the dietary supplement in which the NDI will be used. If you decide to deviate from a standard or published protocol, you should explain why you altered the protocol and how the alteration affects the relevance of the study results to the safety of your product.

25. How will I identify a potential hazard using a standard genetic toxicity test, and what should I do after identifying a potential genetic toxicity hazard?

A positive finding in one or more of the standard genetic toxicity tests constitutes a clear but non-quantitative identification of a potential hazard. Positive results in genetic toxicity tests may necessitate additional safety testing, such as an evaluation of carcinogenicity from two-year or

lifetime chronic toxicity assays. General guidance on following up positive results in genetic toxicity testing can be found in the scientific literature on this topic.[56]

26. Should the NDI notification discuss the history of use or other evidence of safety that forms the basis for my conclusion that a genotoxic dietary ingredient can reasonably be expected to be safe?

Yes, your NDI notification should discuss this history of use or other evidence of safety. You should conduct a risk assessment to determine whether the genetic toxicity of the NDI prevents the dietary supplement from being reasonably expected to be safe under the proposed conditions of use.

27. Where can I find good examples of genotoxicity protocols that can be used in conducting animal and human studies on NDIs?

The sources cited in the answer to question VI.B.22 contain test guidelines and testing batteries for evaluating genetic toxicity.

28. What is the purpose of a subchronic oral toxicity study?

When properly conducted (e.g., with doses selected based on shorter term repeat-dose studies), subchronic oral toxicity studies are used to identify the maximum tolerated dose (MTD) of a substance, as well as the substance's No Observed Adverse Effect Level (NOAEL). Toxicity data and the NOAEL identified by the subchronic oral study are used (1) to predict the organ toxicity or other types of toxicity that are likely to be associated with human or animal consumption of unsafe quantities of the test article; (2) to determine the need for and design of additional animal studies, such as specialized toxicity studies and chronic toxicity studies; and (3) to assess the safety of short-term repeat-dose exposure to the test article, either for consumers or for participants in clinical trials.

29. What is the appropriate duration for a subchronic oral toxicity study?

Subchronic oral toxicity studies are generally conducted for 90 days (3 months). Protocols described as lasting 12 or 13 weeks are considered equivalent. Subchronic toxicity studies provide information on the possible health hazards likely to arise from repeated exposure to a substance over a three-month period.

30. Where can I find more information and examples of a subchronic oral toxicity study?

We recommend referring to the OECD Guidelines for the Testing of Chemicals. Protocols for rodent studies are in OECD Guideline 408, "Repeated Dose 90-day Oral Toxicity Study in

[56] Dearfield KL, Thybaud V, Cimino MC, Custer L, Czich A, Harvey JS, *et al*. Follow-up actions from positive results of in vitro genetic toxicity testing. Environ Mol Mutagen. 2011 Apr; 52(3):177-204.

Rodents."[57] Protocols for non-rodent studies are in OECD Guideline 409, "Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents."[58] The appropriate animal species and study design may vary depending on the safety questions associated with the NDI being studied.

31. What is the purpose of reproductive toxicity and teratology studies?

The purpose of reproductive toxicity studies is to provide information regarding the effects of a dietary ingredient on all aspects of reproduction, including sexual behavior, spermatogenic and estrus cycles, gonadal function, fertility, parturition (giving birth), lactation, and prenatal development. The purpose of teratology studies is to provide information on whether the test article causes congenital malformations in the offspring of a test animal. The purpose of multi-generation reproductive studies is to provide growth and reproductive function data regarding the effects of the test article on male and female offspring of test animals and on the growth and reproductive function of their offspring in the subsequent generation(s).

32. Should I include a discussion of the reproductive and teratology studies in my NDI notification?

Yes. FDA recommends that you provide a summary and a detailed discussion of the results of each reproductive and teratology study in the comprehensive safety profile for the NDI (see question VI.C.2).

33. Should I identify the "No Observed Adverse Effect Level" (NOAEL) for all test substance-related changes in both reproductive and teratology test endpoints?

Yes. You should identify the NOAEL for parental animals and their offspring in each generation in reproductive studies, including teratology studies. In addition to information about reproductive success, data from the study should also be used to provide information on development (i.e., growth and function of the offspring) and teratogenesis (i.e., birth defects, both structural and functional).

34. Where can I find sample protocols for reproductive and teratology studies?

We recommend that you refer to the OECD Guidelines for the Testing of Chemicals, Guidelines 415 ("One-Generation Reproduction Toxicity Study"),[59] 416 ("Two-Generation Reproduction

[57] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 408: Repeated Dose 90-day Oral Toxicity Study in Rodents. Paris: OECD Publishing; May 1981; revised September 1998. Available at: http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en.

[58] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 409: Repeated Dose 90-day Oral Toxicity Study in Non-Rodents. Paris: OECD Publishing; May 1981; revised September 1998. Available at: http://www.oecd-ilibrary.org/environment/test-no-409-repeated-dose-90-day-oral-toxicity-study-in-non-rodents_9789264070721-en.

[59] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 415: One-Generation Reproduction Toxicity Study. Paris: OECD Publishing; May 1983. Available at: http://www.oecd.org/chemicalsafety/risk-assessment/1948458.pdf

Toxicity Study"),[60] 421 ("Reproduction/Developmental Toxicity Screening Test"),[61] and 422 ("Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test")[62] to find protocols for conducting reproductive toxicity and teratology studies. You may also wish to consider how data from these studies are assembled and used for other regulatory programs (e.g., for pesticides, see EPA's "Harmonized Test Guidelines,"[63] and for medicinal products, see ICH's "Safety Guidelines"[64]). In particular, "Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility"[65] contains useful guidelines for detecting reproductive toxicity.

35. What is the purpose of repeat-dose toxicity testing?

In general, the purpose of repeat-dose toxicity testing is to define toxic effects on body systems and target organs based on repeated and/or cumulative exposure to the test substance or to constituents and/or metabolites of the test substance. Repeat-dose testing defines the nature of the tissue or organ damage, particularly in relation to dose and duration of exposure. Repeat-dose testing is also used to identify dosages associated with toxic and biological responses and to define a NOAEL.

The route of administration in repeat-dose testing for a dietary supplement containing an NDI should always be oral, and the study should include a range of doses at and above the proposed dose of the NDI in the dietary supplement. An "oral study," as described in this guidance, can include administration in feed or drinking water (with the feed or water consumption measured to confirm actual intake) or via gavage, which involves introduction of the test article through a tube passed through the mouth into the stomach. Ideally, the test article used in these studies should have the same composition and form as the dietary supplement described in the notification since the other ingredients can affect the safety of the NDI as used in the product.

[60] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 416: Two-Generation Reproduction Toxicity Study. Paris: OECD Publishing; May 1983; revised January 2001. Available at: http://www.oecd.org/chemicalsafety/risk-assessment/1948466.pdf

[61] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 421: Reproduction/Developmental Toxicity Screening Test. Paris: OECD Publishing; July 2015. Available at: http://www.oecd-ilibrary.org/environment/test-no-421-reproduction-developmental-toxicity-screening-test_9789264242692-en

[62] Organisation for Economic Co-operation and Development. OECD Guidelines for the Testing of Chemicals, Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Paris: OECD Publishing; March 1996. Available at: http://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264070981-en

[63] U.S. Environmental Protection Agency (EPA), Office of Chemical Safety and Pollution Prevention (OCSPP). OCSPP Harmonized Test Guidelines; September 2015. Available at: https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances.

[64] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Safety Guidelines. Available at: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html Accessed August 28, 2015.

[65] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2); June 1993; addendum dated November 2000 incorporated November 2005. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5/Step4/S5_R2__Guideline.pdf.

36. Am I required to conduct human clinical studies to assess the safety of my NDI or the dietary supplement containing my NDI?

The FD&C Act contains no explicit requirement for a manufacturer or distributor to conduct human clinical studies before submitting an NDI notification. However, there may be circumstances in which you find it necessary to perform such studies because the existing history of use data, safety data, and data on population exposure do not provide a sufficient basis for you to conclude that the dietary supplement containing the NDI will reasonably be expected to be safe under its proposed conditions of use.[66]

37. What kinds of human clinical studies are useful to assess the safety of an NDI or dietary supplement containing an NDI?

The most useful studies are usually short-term tolerability studies and absorption, distribution, metabolism, and excretion (ADME) studies. The test article used in these studies should have the same identity and composition (including ingredients used in combination with the NDI) and forms as described in the dietary supplement composition section of your notification. When human ADME studies are done in conjunction with ADME studies conducted in the animal species used for toxicological testing, the relevance of the animal data to humans can be demonstrated and the safety factors used to calculate the margin of safety can be reduced (see question VI.C.5).

Tolerability studies identify acute toxicity, such as that associated with toxins or with indigestible nutrients at very high serving levels of ingredients like fats and oils. Human repeat-dose studies are more rarely used to directly demonstrate the safety of the test article in humans. They can be used to allay specific safety concerns raised by animal studies or history of use information, or to establish a margin of safety for an NDI when the proposed conditions of use would result in doses that cannot be humanely administered to animals.

38. What is the purpose of "repeat-dose" human studies, and how are such studies classified?

Human studies can be used alone or in conjunction with animal studies. If animal toxicity studies or history of use data do not document an adequate margin of safety between the NOAEL for your NDI and the expected intake of the NDI from its proposed dietary supplement use, we recommend a human clinical trial consisting of a repeat-dose study. Clinical trials should include male and female subjects, as well as an adequate sample size and duration. Sample size is a very important consideration, as the study should be sufficiently powered to show differences in your data. If a clinical trial is not powered by a large enough sample size, results showing no adverse effects cannot be relied on as evidence of safety because the absence of

[66] Human clinical studies must comply with FDA's regulations for the protection of human subjects (21 CFR Parts 50 and 56). A clinical study intended to evaluate the safety of a dietary ingredient or dietary supplement generally does not require an investigational new drug application (IND), but if the study also evaluates the use of the product to treat or mitigate a disease (i.e., a use of the product as a drug), it would require an IND. See FDA, Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND; September 2013. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf.

adverse effects from intake of the NDI could be due to chance. Duration of the clinical trial is also an important factor in your study design and depends on the proposed conditions of use.

Clinical trials may be grouped by their purpose and objective. Phase I trials are the first stage of testing in humans. They are designed to assess absorption, distribution, metabolism, and excretion (ADME), safety, tolerability, pharmacokinetics, and pharmacodynamics. Phase I studies are generally single-dose studies, followed by dose-range or dose escalation studies, and finally short-term repeat-dose studies to evaluate pharmacokinetic parameters and tolerance (see Table 3: Safety Testing Recommendations Matrix). Single-dose and repeat-dose studies are elements of Phase I studies to assess human pharmacology. Phase II studies (designed to assess dosing requirements and efficacy) and Phase III studies (randomized, controlled multicenter studies involving large sample sizes to evaluate effectiveness of a treatment) focus on efficacy and are generally not useful to establish the safety of a dietary supplement. A clinical trial of less than 90 days is considered subchronic and cannot, by itself, support safety of chronic use. The endpoints of any clinical study should be clearly defined.

39. Where can I find more information and examples of clinical protocols that can be used in conducting human studies for NDIs and dietary supplements?

FDA recommends consulting "Principles and Methods for the Risk Assessment of Chemicals in Food"[67] for a good general discussion of this topic. This reference, which recognizes the value of the experience gained from pharmaceutical safety studies in designing food safety studies, also includes a discussion of the similarities and differences between clinical studies conducted for foods and those for pharmaceuticals. "Guidance for Industry—M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"[68] contains a useful discussion of selecting an appropriate dose for subchronic oral studies in animals and clinical trials in human volunteers (pp. 1-5).

40. What information should I submit to demonstrate the safety of an NDI produced by fermentation using microorganisms like bacteria or yeast?

You should identify the microorganism using scientifically valid nomenclature for the genus, species, and the name of the strain. You should also discuss the history of use of the organism or related organisms as food or to produce food. In addition, you should identify any human pathogens that are phylogenetically related to the fermentation microorganism at the species or genus level. You should also identify any toxins, classes of toxins, or other deleterious substances known to be present in the same species as the microorganism or in a genus or species that is phylogenetically related to the microorganism. Finally, you should document the absence (or the amount, if present) of such toxins or other deleterious substances in the

[67] Principles and Methods for the Risk Assessment of Chemicals in Food. Environmental Health Criteria 240. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. 2009. Available at: http://whqlibdoc.who.int/ehc/WHO_EHC_240_4_eng_Chapter1.pdf

[68] FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for Industry: M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, Revision 1; January 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073246.pdf

microorganism. The absence of unsafe levels of such deleterious substances should be demonstrated by an appropriate combination of specifications for the NDI, safety testing in humans, and/or safety testing in an appropriate animal model.

41. What information should I submit to demonstrate the safety of a microbial NDI (live or killed)?

You should identify any human pathogens that are phylogenetically related to the microbial NDI at the species or genus level. You should identify any toxins, classes of toxins, or other deleterious substances known to be present in the same species or in a phylogenetically related family or genus. You should also document the absence (or the amount, if present) of such toxins or other deleterious substances in the NDI. You should document resistance to any clinically relevant antibiotics, and if applicable, the genetic nature of the resistance. If the microbial NDI is resistant to any clinically relevant antibiotics, it is also recommended that you perform an assessment of the ability of the antibiotic resistance genes to mobilize and transfer to human pathogens under the conditions of use of the dietary supplement.

If your notification cites the history of use of a live microorganism as evidence of safety, FDA recommends a careful assessment of the relative level of historical exposure compared to the proposed conditions of use of the NDI, including a discussion of how the form of the dietary supplement and any non-dietary ingredients (e.g., binders and fillers) used in it affect delivery of the NDI to various points in the human gastrointestinal tract.

If history of use data are inadequate to support the safety of the microbial NDI, you should include safety studies in humans or appropriate animal models in your notification. FDA considers pigs to be the most appropriate animal model for the human digestive tract. Human or animal safety studies should include measurements of the persistence of the organism in the body after administration, the ability of the organism to translocate outside of the gastrointestinal tract, and tolerance of the ingredient using the proposed serving form. Because this is a rapidly evolving scientific discipline, FDA recommends that notifiers be familiar with the state of the recent scientific literature at the time the notification is submitted.

42. What should I do to demonstrate the safety of an NDI that contains nanomaterials or otherwise involves the application of nanotechnology?

Because there is little scientific literature discussing the safety of nanomaterials in dietary supplements, FDA recommends that notifiers contact FDA[69] prior to submitting an NDI notification for an NDI that contains nanomaterials or otherwise involves the application of nanotechnology.[70]

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

[70] 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. See also FDA, Guidance for

C. Summary of the Basis for Your Conclusion of Safety

1. Should my notification include separate safety profiles for the NDI and the dietary supplement in which the NDI will be used?

Yes. FDA recommends that the discussion of history of use and other evidence of safety in your notification should include two separate safety profiles: first, a comprehensive safety profile evaluating the safety of the NDI, and second, a dietary supplement safety narrative explaining why the information in the notification provides a basis to conclude that the dietary supplement that contains the NDI will reasonably be expected to be safe when used under the conditions recommended or suggested in the dietary supplement's labeling. Each piece of data or information in the notification should be cited in the comprehensive safety profile, the safety narrative, or both, so that it is clear how each piece of data or information is used to form the basis for the safety of the dietary supplement containing the NDI.

When a notification describes a dietary supplement containing more than one NDI, FDA recommends including a comprehensive safety profile for each NDI, with the safety of the combination of NDIs addressed in the safety narrative. However, when there is history of use or other evidence of safety for the combination of NDIs used in the dietary supplement, it may be appropriate to have a comprehensive safety profile for that combination in addition to a separate profile for each NDI (or instead of separate profiles for the individual NDIs when most or all of the safety information is for the combination).

2. What should I include in my comprehensive safety profile for the NDI?

The NDI comprehensive safety profile should provide objective summaries of all available human and animal toxicological information (including both published and unpublished safety studies) and any other information relevant to the safety assessment of the NDI.

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

If the NDI notification relies on safety studies, the NDI comprehensive safety profile should qualitatively and quantitatively compare the ingredients tested in each of the studies cited with the NDI. If you cite a study on the feeding of a whole herb to a test animal and the NDI is an

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Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology; June 2014. Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm.

extract of that herb, the NDI comprehensive safety profile should qualitatively and quantitatively compare the dose and total daily intake of the herb in the study to the proposed dose and total daily intake of the NDI. Whenever possible, the notification should identify the effect and no-effect doses in each human and animal study, and the relationships between observed adverse effects and other related observed effects should be described.

The NDI comprehensive safety profile should identify the NOAEL (see question VI.C.4) and describe the toxicity data or adverse events that were the basis for determining it. The comprehensive safety profile should also describe the acceptable daily intake (ADI) for the NDI and explain how it was calculated (see question VI.C.5). Finally, the comprehensive safety profile should state the basis for the margin of safety for the NDI and how the margin of safety was calculated.

The NDI comprehensive safety profile may need to rely heavily on trade secrets or confidential commercial information. Any information in the NDI comprehensive safety profile that you believe to be a trade secret or confidential commercial information should be identified as such (see question V.A.16).

3. What should I include in my dietary supplement safety narrative?

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

The dietary supplement safety narrative should be based on the identity information, safety information, and analyses in other sections of the NDI notification, including the NDI comprehensive safety profile. The dietary supplement safety narrative should include a summary of the more detailed discussion in the comprehensive safety profile of how you concluded that the NDI in the dietary supplement will reasonably be expected to be safe based on the margin of safety between the NDI intake level that shows no adverse effects (the NOAEL) and the proposed intake level and other conditions of use of the NDI in the dietary supplement.

If the supplement contains dietary ingredients other than the NDI, the dietary supplement safety narrative should identify the NOAEL and ADI for each ingredient (see questions VI.C.4 and VI.C.5), describe the toxicity data or adverse events that were the basis for determining the NOAEL, state the basis for the margin of safety for each ingredient, and discuss whether there is any possible synergy or interaction among any or all ingredients that could affect the safety of the dietary supplement. For each dietary ingredient other than the NDI, the dietary supplement safety narrative should concisely evaluate known safety concerns and describe how the notifier concluded that the combination of ingredients will reasonably be expected to be safe. If the formulation of the product, including other ingredients, affects the bioavailability of dietary ingredients, then the safety narrative should include a discussion of the effective per-serving intake level of the dietary ingredient(s) in the products compared to per-serving intake levels or dosages described in the history of use or other evidence of safety.

The safety narrative should also describe the function of each food additive, color additive, and GRAS substance (i.e., each non-dietary ingredient), including the technical effect and the quantity needed to achieve that technical effect. References to the applicable food additive regulation, color additive regulation, GRAS regulation, or GRAS notification are also recommended.

The dietary supplement safety narrative should estimate the total daily human intake of the dietary supplement containing the NDI and describe any potential toxicity or health concerns associated with human consumption of the dietary supplement, particularly if concerns that may result from the proposed use of the dietary supplement by a vulnerable population have been identified. The description of toxicity and health concerns should include the effects of binders, fillers, formulation aids, and other non-dietary ingredients present in the dietary supplement, particularly if they alter the safety profile of one or more ingredients, such as by increasing uptake into the body after ingestion. If any ingredient in the dietary supplement is present at a level close to the ADI, the presence of that ingredient from other sources in the diet should also be addressed.

Because of the central importance of the dietary supplement safety narrative to the overall conclusion of safety, the dietary supplement safety narrative should be written in such a way that it will be comprehensible after FDA has redacted any trade secrets and confidential commercial information and placed the notification in the public docket. As with the comprehensive safety profile, any information in the dietary supplement safety narrative that you believe to be a trade secret or confidential commercial information should be identified as such (see question V.A.16).

4. What is the difference between a NOEL and a NOAEL, and which should I use?

The No-Observed-Adverse-Effect Level (NOAEL) is a number signifying the highest dose or total daily intake level that did not elicit an adverse effect in a properly designed and executed toxicological study.[71] The No-Observable-Effect Level (NOEL) is the highest dose at which no

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

effects of any kind were observed, including beneficial and neutral effects as well as adverse effects. Therefore, the NOAEL, which is the threshold for adverse effects, is the appropriate level to use in calculating the margin of safety for an NDI.

FDA expects that many dietary ingredients, because they are intended to have beneficial nutritional effects or other effects on the structure or function of the body, will cause changes in parameters that are measured in animal and clinical safety studies. FDA also expects that, as dose and total intake increase, effects that are neutral or beneficial at lower exposures may become adverse effects or be supplanted by adverse effects. Thus, it is important that the notification contain a discussion of the nature of the effects that are observed in safety studies. This discussion should distinguish between adverse effects and other effects (neutral or beneficial effects).

The purpose of the NOAEL, which is typically higher than the NOEL, is to identify a safe level of a substance (that is, the level at which no adverse effects are observed); therefore, the NOAEL should be used to calculate the margin of safety in the NDI notification. A comparative discussion of the effects observed at different doses of an NDI should appear in the comprehensive safety profile for the NDI. FDA also recommends that this discussion be summarized in the dietary supplement safety narrative because it is central to the overall safety evaluation**.**

5. What safety factors should be used if only animal toxicity studies are available?

It is important for the notifier to determine the ADI, in addition to the NOAEL, to conduct an adequate risk assessment of the NDI. The NOAEL, expressed on a body weight basis (e.g., mg/kg/day), is divided by a safety factor (also referred to as an uncertainty factor) to derive the ADI. Safety factors account for the uncertainty in extrapolating from experimental data to predict the safety of a substance in humans.

If the NOAEL is derived from a chronic toxicity study (one-year duration or longer) in animals, the combined safety factor is usually 100. This number is calculated using a factor of 10 to account for interspecies variation between animals and humans and another factor of 10 to account for the variation in sensitivity within the human population.

Extrapolation from subchronic toxicity studies to chronic use of an NDI or dietary supplement necessitates an additional safety factor. In this situation, FDA recommends using at least two subchronic toxicity studies, at least one of which was conducted in a non-rodent species and the other in a rodent species, and introducing another safety factor of 10 for a combined safety factor of 1,000. In the absence of supporting history of use data, using only a single rodent subchronic toxicity study as a basis to conclude that chronic use of an NDI in humans will be safe is strongly discouraged, but may be acceptable if a safety factor of 2,000 is used and there is no toxicity to the rodents at the maximum tolerated dose (MTD). The additional safety factor of 2 is used in this situation because a complete animal toxicology assessment includes two subchronic (90-day) animal studies.

The safety factors in these examples are approximate values, which can vary with the specific data that are available. For example, a higher value may be appropriate if toxicity is particularly

severe or the variation in human sensitivity is expected to be great. On the other hand, a lower value may be appropriate if subchronic studies in both rodent and non-rodent species showed no adverse effects. If human data from chronic toxicity or ADME (absorption, distribution, metabolism, and excretion) studies (typically one year in duration) are available, a safety factor lower than 100 may be appropriate. While FDA does not consider the ADI to be a sharp dividing line between safe and unsafe levels, the ADI does provide a useful benchmark for protecting the consumer.

In summary, safety factors are uncertainty factors used multiplicatively to arrive at the combined safety factor that is applied to a particular dataset provided in a notification. This combined safety factor is used to calculate the ADI.

ADI = NOAEL/combined safety factor = NOAEL/ (Uf_{intra} x Uf_{extrap} x Uf_{inter})

- Uf_{intra}: An uncertainty factor to account for *intraspecies* variation is introduced to protect sensitive members of the population when clinical trials include only healthy subjects, since dietary supplements may be consumed by anyone—the young, the aged, the healthy, and the infirm. A value of 10 is usually used. The size of the intraspecies uncertainty factor should be smaller when there is a long history of food use by a large, diverse population. The size of the intraspecies uncertainty factor should be larger when toxicity is severe or when a notification relies on studies with limited duration or small populations.

- Uf_{inter}: Extrapolation from animal to human requires an uncertainty factor for *interspecies* variation. A factor of 10 is usually used to capture the uncertainty associated with using chronic animal studies to predict the safety of chronic human exposure. A factor of 10 can also be used to account for the uncertainty of using subchronic animal studies to predict the safety of subchronic (including intermittent) human exposure.

- Uf_{extrap}: Extrapolating from a set of two subchronic toxicity studies in different animal species to chronic exposure in humans is not recommended, but the associated uncertainty may be approximated by an additional safety factor of 10 to account for the use of subchronic data to predict chronic use. If subchronic toxicity data are available in only a single animal species, an additional safety factor should be used. Usually, this additional safety factor should be approximately 2.

6. Does FDA recommend including margin of safety discussions in NDI notifications?

Yes. To conclude that a dietary supplement containing an NDI is reasonably expected to be safe based on animal or human safety studies, it is necessary to determine the margin of safety between the level of the NDI shown to cause no observed adverse effects (the NOAEL) in each animal and/or human study and the intake level that would result from the proposed conditions of use of the NDI in the dietary supplement.

The margin of safety is calculated by dividing the NOAEL (not the NOEL) in animal or human studies by the estimated daily intake (EDI) of the NDI. If you are calculating a margin of safety

for a combination of ingredients or for the finished dietary supplement, the same principles apply.

Appropriate safety factors and margin of safety should be discussed for each particular study or safety endpoint and should also be summarized in the dietary supplement safety narrative because of its importance to the overall safety evaluation.

7. What is the difference between a safety factor and a margin of safety?

Safety factors are 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 and differences in sensitivity among humans. The use of safety factors is based on the observation that toxic substances usually have thresholds below which toxic effects cannot be detected. 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. Safety factors can be combined multiplicatively to predict toxicity in the human population.

- ADI = NOAEL/combined safety factors

- Margin of safety = NOAEL/EDI

In contrast, the margin of safety is a calculation derived from the NOAEL in a single study and the highest total daily intake level determined from the conditions of use in the NDI notification, the EDI. A margin of safety is a measure of how close the EDI is to the level that has been shown to have no adverse effect in animal or human studies (the NOAEL). When reviewing notifications, FDA intends to calculate the EDI based on the highest daily intake level that is possible under the conditions of use proposed in the notification as well as cumulative exposure from all dietary sources.

The margin of safety for a dietary ingredient is calculated by dividing the NOAEL in animal or human studies by the EDI of the dietary ingredient. So a margin of safety of 100-fold means the doses shown to be without adverse effects in animals or humans are 100 times greater than the levels that would be consumed from the use of the dietary supplement. Discussions of how ADIs and EDIs are calculated and used in safety evaluations for a variety of products can be found in the following references:

- Frankos, V.H., and J.V. Rodricks. Food additives and nutrition supplements. Regulatory Toxicology, 2nd Ed., S.C. Gad, ed. London: Taylor and Francis, 2001.

- World Health Organization. Principles for the Safety Assessment of Food Additives and Contaminants in Food. Environmental Health Criteria 70. Geneva, Switzerland: 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc70.htm.

- Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients. Washington, DC: National Academy Press, 1998.

Example: The only safety evidence available is a single subchronic rat study during which no adverse effects were noted at the highest dose, which was the maximum tolerated dose of 3,000 mg/kg body weight. The top dose was limited by the fact that larger volumes could not be humanely administered to the animals.

If the proposed conditions of use for the ingredient are 1 mg/person per day in adults daily, the EDI is (1 mg/person)/70 kg average adult = 0.014 mg/kg. The margin of safety is 3,000/0.014 $=2.1x10^5$. The safety factors chosen are Uf_{intra} x Uf_{extrap} x Uf_{inter} =10x20x10 = 2,000. The ADI is 3,000/2,000 = 1.5 mg/kg. The EDI/ADI ratio is 0.014/1.5 = 0.01. This value is much less than 1, which suggests that, if these safety factors are appropriate, the test article may reasonably be expected to be safe at the proposed daily intake level. An intake level of 1 g per day (1,000 times greater) would result in an EDI/ADI ratio of close to 10. More studies would be needed to justify the higher serving level.

8. When is the ratio of the EDI to the ADI adequate to support the conclusion that a dietary supplement containing an NDI will reasonably be expected to be safe?

The ratio of the EDI to the ADI should be less than or equal to 1 to support a conclusion that the proposed use of the NDI in the dietary supplement will reasonably be expected to be safe under the conditions recommended or suggested in the supplement's labeling. The size of the EDI/ADI ratio will vary in accordance with the nature and extent of data available and the circumstances of use of the NDI. For example, a ratio of 1, where the proposed dose (EDI) is equal to the safe dose (ADI), could be adequate if the levels of historical chronic safe use of the ingredient are the same as the levels proposed in the dietary supplement.

Stated another way, the EDI of the NDI or dietary supplement must be less than or equal to the ADI of the NDI or dietary supplement.

The EDI for the NDI or for the dietary supplement is the highest total daily intake level under the proposed conditions of use described in the notification. The ADI is calculated as the ratio of the NOAEL to the combined safety factor, which is calculated by multiplying the individual safety factors for each study. If the ratio of the EDI to the ADI is greater than unity (EDI/ADI > 1), then the study does not support a reasonable expectation of safety for the NDI under the proposed conditions of use.

9. What is an example of a common error about margin of safety in NDI notifications that have been submitted to FDA for review?

Many manufacturers or distributors assume that if the NDI has a history of safe use in humans, no further safety discussion is warranted. That is incorrect. A margin of safety for NDI intake should be calculated, and the method of calculation explained and justified in the notification, even if a history of safe use is the basis of the safety evaluation. When the notification relies on a history of safe use, the margin of safety should be calculated based upon the historical levels of the NDI that were safely consumed and the NDI intake levels that would result from the conditions of use proposed in the notification. A margin of safety less than or equal to 1 corresponds to the argument that a history of safe use alone is sufficient to demonstrate the safety

of the proposed use based on conditions of use that are the same or lower than the conditions of historical use (see question VI.B.14).

10. Are the recommendations in section VI requirements for safety information to include in an NDI notification?

No. The answers to the questions in section VI.A, VI.B, and VI.C are guidance on how to approach the task of describing the basis for the safety of the dietary supplement containing an NDI. These answers are recommendations and not requirements. In many cases FDA has tried to provide detailed recommendations to illustrate specific examples of situations which might arise. These details are specific to the situation described. The amount of information needed to identify an ingredient and provide a basis for a reasonable expectation of safety will vary enormously from notification to notification based on factors such as the complexity of the ingredient, history of use, and the presence or absence of specific safety concerns.

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**.**

Master File: In the dietary supplement context, a master file is a file containing manufacturing or other identity information submitted to FDA for use in an NDI notification by the submitter of the master file or by a person designated by the submitter. The submitter may rely on information from the master file in an NDI notification by incorporating it by reference, or may grant written authorization to other parties to incorporate information from the master file by reference in notifications covering the use of the NDI in their own products. A written authorization granting a right of reference to a master file in NDI notifications does not include the right to see or copy the master file unless the submitter of the master file otherwise specifies.

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.

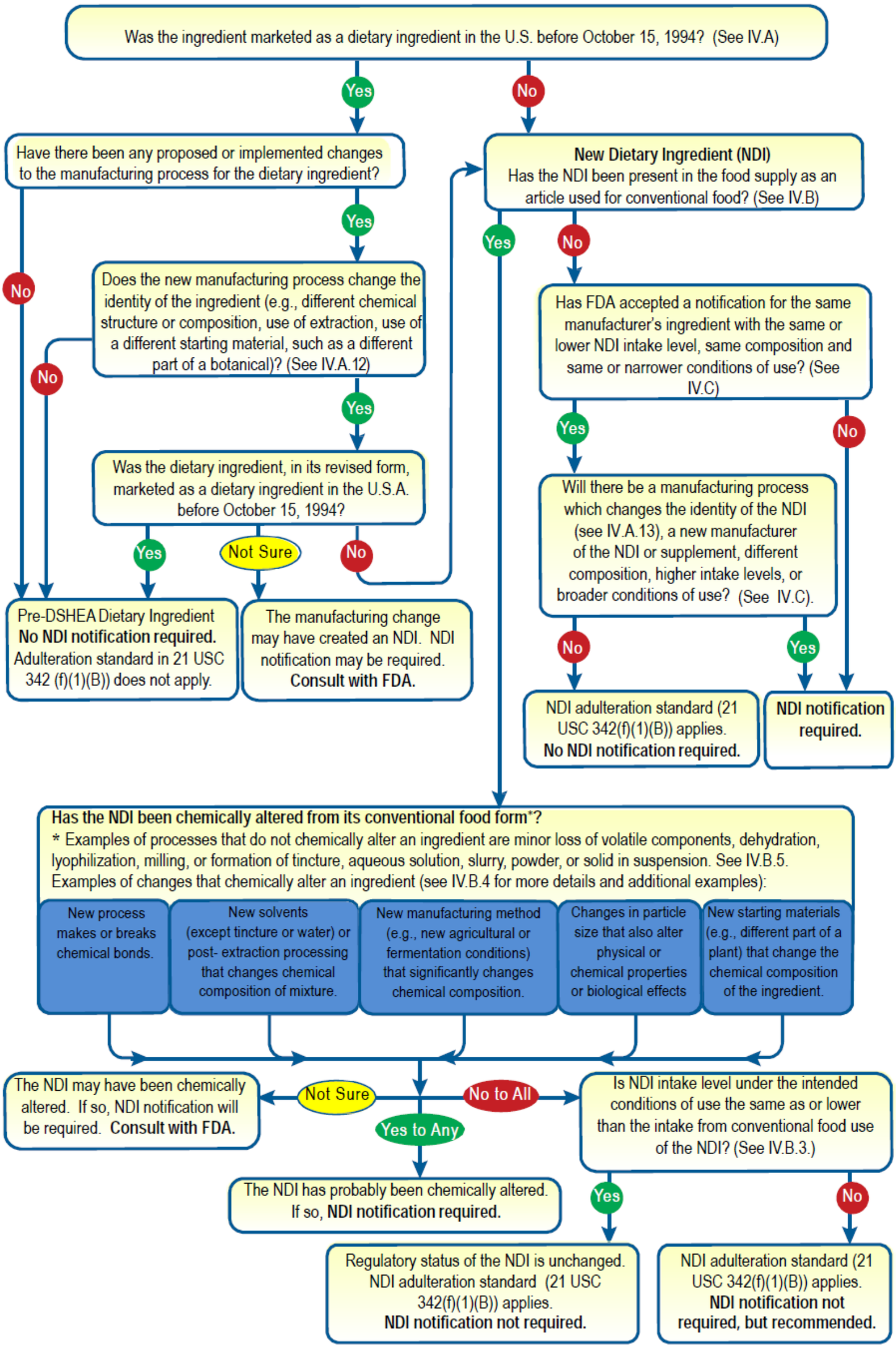
Target Population: The target population for a dietary supplement means the population group or groups (defined by gender, age, and/or health status) that a manufacturer or distributor identifies (e.g., in product labeling, promotional materials, or in an NDI notification) as those for whom the product 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.**