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Food

Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues

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*Contains Nonbinding Recommendations
Draft-Not for Implementation*

July 2011

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For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-2375.

**U.S. Department of Health and Human Service
Food and Drug Administration
Center for Food Safety and Applied Nutrition
July 2011**

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Guidance for Industry^[1]

Dietary Supplements: New Dietary Ingredient Notifications and Related Issues

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

This guidance is intended to assist industry in deciding when a premarket safety notification for a dietary supplement containing a new dietary ingredient (NDI) is necessary and in preparing premarket safety notifications (also referred to as "NDI notifications"). The guidance addresses in question and answer format what qualifies as a NDI, when a NDI notification is necessary, the procedures for submitting a NDI notification, the types of data and information that FDA recommends manufacturers and distributors consider when they evaluate the safety of a dietary supplement containing a NDI, and what should be included in a NDI notification. In addition, the guidance contains questions and answers about parts of the dietary supplement definition that can affect whether a particular substance may be marketed as a dietary ingredient in a dietary supplement. The agency encourages manufacturers and distributors to consult this guidance during their safety review of a dietary supplement that contains a NDI and in preparing NDI notifications.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's 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 Agency guidances means that something is suggested or recommended, but not required.

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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 Federal Food, Drug, and Cosmetic Act (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 a NDI, or of the dietary supplement that contains the NDI, to submit a premarket notification to FDA at least 75 days before introducing the supplement 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 is 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. If the required premarket notification is not submitted to FDA, section 413(a) of the FD&C Act 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. 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 assist industry in complying with DSHEA, FDA issued a regulation in [21 CFR 190.6](#)³ (section 190.6 or the NDI regulation) to implement the FD&C Act's premarket notification requirements for dietary supplements that contain a 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)):

- 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 also establishes the administrative procedures for these notifications. Section 190.6(c) defines the filing date of a notification as the date the agency receives 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, or delivering for introduction, the dietary supplement into interstate commerce for 75 days after the filing date (21 CFR 190.6(c)). Section 190.6(d) provides for the assignment of a new notification filing date that resets the 75-day period when the manufacturer or distributor submits additional substantive information in support of the original NDI notification. Consistent with section 413(a) of the Act, section 190.6(e) provides that FDA will not disclose the existence of, or the information contained in, a 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 Act. Finally, section 190.6(f) states that FDA's failure to respond to a NDI notification does not constitute a 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 Act (21 U.S.C. 342).

On January 4, 2011, the President signed into law the FDA Food Safety Modernization Act (FSMA) (Public Law 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 a NDI, when the manufacturer or distributor of a dietary ingredient or dietary supplement should submit a NDI notification to FDA under section 413(a)(2) of the FD&C Act, the evidence needed to document the safety of a NDI, and appropriate methods for establishing the identity of a NDI. This draft guidance is being published to comply with section 113(b).

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III. Scope of the Guidance

FDA's goal in promulgating the NDI regulation was to ensure that NDI notifications contained the information that would enable FDA to evaluate whether a dietary supplement containing a NDI is reasonably expected to be safe. After having gained some experience with the NDI notifications that have been submitted to the agency and from the many questions that industry has asked since the agency's regulation implementing the NDI notification requirement was issued, FDA has concluded that this guidance is needed to assist industry in achieving this goal.

DSHEA does not specify the type or amount of evidence that must be included in a NDI notification. The purpose of this guidance is to give manufacturers and distributors of these products information and recommendations to help them decide when a NDI notification is necessary and to improve the quality and quantity of NDI notifications. There are an estimated 55,600 dietary supplement products on the market, and FDA has received approximately 700 NDI notifications since we began reviewing NDI notifications approximately 16 years ago.^[2] Additionally, the Institute of Medicine has estimated that 1,000 new dietary supplements are introduced to the market each year.^[3] These figures, coupled with recent concern by both the agency and industry regarding the presence of undeclared active ingredients in products marketed as dietary supplements, highlight the necessity for marketers of dietary supplements to submit NDI notifications as an important preventive control to ensure that the consumer is not exposed to potential unnecessary public health risks in the form of new ingredients with unknown safety profiles.^[4]

This guidance answers frequently asked questions about NDI notifications and related issues. It also makes recommendations to industry for preparing better NDI notifications that the agency will be able to review more efficiently, which should result in quicker response times. The agency recommends that the data and information that are submitted should include (1) a full description of the identity and composition of the NDI and the dietary supplement in which it will be marketed, (2) a discussion of the basis for the notifier's conclusion that the substance is a NDI, (3) 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 (4) an explanation of how the history of use or other evidence of safety in the notification justifies the notifier's conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe.

This draft guidance focuses on interpreting the FD&C Act's requirements relating to NDIs and dietary supplements that contain

a 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 recently enacted FSMA^[5] that may apply to dietary ingredients and/or dietary supplements.

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IV. Determining Whether a New Dietary Ingredient (NDI) Notification is Necessary

A. **When Is a Dietary Ingredient New?**

1. **Is a dietary ingredient that was not marketed in the U.S. before October 15, 1994, a new dietary ingredient (NDI)?**

Yes. A NDI is defined by statute as "a dietary ingredient that was not marketed in the United States before October 15, 1994."^[6]

2. **Do I need to submit a 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 a NDI notification. See questions IV.A.6 and IV.A.9 for more on how FDA interprets the terms "marketed" and "dietary ingredient" in the definition of a NDI (21 U.S.C. 350b(c)).

3. **Is an ingredient that was used to make a conventional food marketed before October 15, 1994, a NDI if the ingredient was not a dietary ingredient marketed in the U.S. before October 15, 1994?**

Yes. The use of an ingredient in a conventional food before October 15, 1994 does not determine whether the ingredient is a NDI. What matters is whether the ingredient was marketed as a dietary ingredient -- meaning in or as a dietary supplement, or for use in dietary supplements -- in the U.S. before October 15, 1994. Therefore, an ingredient that was used to make a conventional food before October 15, 1994 is a NDI unless the ingredient was also marketed as a dietary ingredient in the U.S. before October 15, 1994. (See questions IV.A.6 and IV.A.9 for FDA's views on the meaning of "marketing" and "dietary ingredient" in the NDI definition.)

a. **Is a NDI Notification required for a dietary supplement containing a 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. Even though an ingredient that was used to make a conventional food before October 15, 1994 is a NDI (unless it was also marketed as a dietary ingredient before that date), a NDI notification is not required for a dietary supplement containing the NDI as long as 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 (21 U.S.C. 350b(a)(1)).

b. **Does the adulteration standard in 21 U.S.C. 342(f)(1)(B)^[7] apply to a dietary supplement containing a NDI for which a NDI notification is not 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?**

Yes. The adulteration standard in 21 U.S.C. 342(f)(1)(B) applies to all dietary supplements that contain a NDI, even 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 (see question IV.B.2). See section IV.B for more information about the exception to the NDI notification requirement for certain NDIs that have been present in the food supply as conventional foods.

4. **Is a substance that was a component of a conventional food marketed before October 15, 1994, a 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 the 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 a 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 a NDI. (If the substance was also marketed as a dietary ingredient before that date, then it is not a NDI. (See questions IV.A.6 and IV.A.9 for FDA's views on the meaning of "marketing" and "dietary ingredient" in the NDI definition.))

5. **Is a substance that was a component of a dietary supplement marketed before October 15, 1994, a NDI?**

No, if the substance was a dietary ingredient in the dietary supplement that was marketed before October 15, 1994, then it would not be a NDI. However, there are also two other possibilities about a substance's status if the substance was not a dietary ingredient in the dietary supplement marketed before October 15, 1994. If the substance was present in the pre-DSHEA dietary supplement as a food additive rather than as a dietary ingredient, and does not fit within one of the enumerated categories of dietary ingredients in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)), then it would not be a dietary ingredient that could be used in a dietary supplement. Finally, if the substance was present in the pre-DSHEA dietary supplement as a food additive rather than as a dietary ingredient, but does fit within one of the enumerated categories of dietary ingredients in section

201(ff)(1) of the FD&C Act, then it would be a NDI.

6. **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 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 physically offering the article for sale 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.

7. **Is a dietary ingredient marketed outside the U.S. prior to October 15, 1994, considered to be a 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 a NDI. The only kind of marketing that is relevant to whether a dietary ingredient is a NDI is marketing in the U.S. before October 15, 1994.

8. **What documentation would I need to show that my dietary ingredient was marketed prior to October 15, 1994?**

Documentation to show that a dietary ingredient is not a NDI should consist of written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994. Examples include sales records, manufacturing records, commercial invoices, magazine advertisements, mail order catalogues, or sales brochures. Documentation should include adequate information to establish that marketing took place in the U.S., the identity (e.g., chemical or botanical name) and form (e.g., ground herb, water extract, oil) of the marketed ingredient, and whether the ingredient was marketed as a dietary ingredient or for some other purpose.

Affidavits attesting to recollection of historical events which are unsupported by contemporaneously created written records are not adequate to show that an ingredient was marketed prior to October 15, 1994. Even if a person who submits an affidavit attesting to his or her recollection of when a dietary ingredient was first marketed is honestly stating his or her present beliefs, we do not regard such assertions alone, without any sort of objective, verifiable documentation from the time of marketing, as an adequate basis to establish prior marketing of a substance as a dietary supplement.

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

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

10. **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")?**

No. Each supplement manufacturer or distributor is responsible for establishing that the dietary ingredients in its dietary supplements comply with the NDI notification requirements. While some trade associations and other industry groups have published lists of "old dietary ingredients,"^[8] these lists have not been verified by FDA and are not backed by evidence that the ingredients listed were actually marketed 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." The

introduction to one trade association list^[9] 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." Moreover, 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." Therefore, 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 a NDI. See question IV.A.8 for information on the kinds of proof that FDA does accept.

11. **If I change the manufacturing process for a dietary ingredient that was marketed in the U.S. prior to October 15, 1994, and the changes alter the chemical composition or structure of the ingredient, does that make the ingredient a NDI?**

Most likely. If the changes in your manufacturing process alter the chemical composition or structure of the ingredient, the resulting compound is probably a NDI and a notification to FDA would be required. For example, using a solvent to prepare an extract from a pre-DSHEA dietary ingredient creates a NDI because the final extract contains only a fractionated subset of the constituent substances in the original dietary ingredient. In addition, changes that alter the composition of materials used to make the ingredient, such as 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 a NDI.

Firms planning a manufacturing change are encouraged to consult with FDA on any questions as to whether such a change would create a NDI.

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

Yes, unless the manufacturing change does not change the chemical properties of the dietary ingredient or the specifications needed to describe the ingredient. For example, a change in the manufacturing process for a NDI

intended to produce particles in the 1 nm to 100 nm (approximate) nanoscale range may alter the chemical properties of the NDI. If so, the resulting ingredient with different chemical properties would likely not be covered under an existing notification for a related substance manufactured without using nanotechnology and, therefore, would likely require a NDI notification. Manufacturers planning a manufacturing change are encouraged to consult with FDA on any questions as to whether such a change would be viewed as having created a different NDI.

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

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

A notification is not needed when a dietary supplement product contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food is not chemically altered. See questions IV.B.3 and IV.B.4 for FDA's current thinking on when a food has been "chemically altered."

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

No, as long as the direct food additive or GRAS substance has been used in the food supply and is to be used as a NDI without chemical alteration. If the NDI was legally marketed in the U.S. as an ingredient for use in conventional food, it would qualify under section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) as an ingredient exempt from the notification requirement 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. However, as discussed in the following question and answer, the NDI adulteration standard still applies, and voluntary NDI notification may be advisable.

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

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 to FDA is not required. Therefore, if the ingredient was not marketed as a dietary ingredient in the U.S. before October 15, 1994 (see questions IV.A.6 and IV.A.9), it is a NDI and the adulteration standard for NDIs applies. That is, a 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 (ADI) (see questions VI.C.5 and VI.C.7), FDA is likely to conclude that there is adequate information to provide reasonable assurance of safety. 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 absence of adequate information to provide reasonable assurance that the higher intake level of the NDI from its use in supplement form is safe, the dietary supplement product would be adulterated.

Although a NDI notification is not required in a situation like this, FDA recommends that manufacturers or distributors of this type of dietary supplement product consult with the agency about their 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. 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.

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

Minor loss of volatile components, dehydration, lyophilization, milling, and formation of a tincture or a solution in water, a slurry, a powder, or a solid in suspension do not chemically alter an ingredient.^[10] Examples:

- Leaves or roots of a plant consumed as conventional food (e.g., broccoli or carrots) are dried and ground for sale in powder form.
- A tincture is made by soaking pears in aqueous ethanol. The mixture is then milled and dried into a powder that is placed in a capsule.

4. **What are examples of processes that chemically alter an article of food present in the food supply to create a dietary ingredient?**

The following are examples of processes that FDA would likely consider to involve chemical alteration.

- A process which makes or breaks chemical bonds such as hydrolysis or esterification, 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.
- Removal of some components of a tincture or solution in water (e.g., by chromatography, distillation or membrane filtration), which changes the chemical composition of the mixture.
- Use of solvents other than water or aqueous ethanol (tincture) to make an extract. Water and aqueous

ethanol are specifically excluded from processes that chemically alter a food in the official legislative history of DSHEA. ^[11] Other solvents 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 loss of volatile components with no other changes to the chemical composition of the ingredient.
- Changing the manufacturing method for an ingredient such that the chemical composition is significantly different (e.g., changes that alter the composition of materials used to make the ingredient, use of a different solvent, 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 composition of the ingredient, such as by 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 (e.g., 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 previously used (e.g., making an extract from unripe instead of ripe apples or using the mycelium instead of the fruiting body of a fungus.)

C. Other Questions About When a NDI Notification is Necessary

1. When should I submit separate NDI notifications for supplements that I manufacture or distribute containing the same NDI?

It depends. If you have already submitted a NDI notification for a dietary supplement containing a NDI, you need not submit a notification for a different dietary supplement containing the same NDI as long as (1) the daily intake level recommended or suggested in the labeling of the new supplement will be equal to or less than that specified in your prior NDI notification, (2) the new supplement does not have other dietary ingredients that were not included in your original NDI notification, (3) the target populations (e.g., children or pregnant or lactating women) are the same or a subset of the target populations specified in your original notification, (4) all other conditions of use are the same as or more restrictive (e.g., fewer intended uses, shorter duration of use) than the conditions of use described in your prior NDI notification, and (5) FDA did not express safety or other concerns in response to your prior NDI notification.

2. If another manufacturer or distributor has already submitted a notification for a particular NDI, and I intend to market a dietary supplement containing the same NDI, should I also submit a NDI notification?

Yes. Section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)) makes clear that any dietary supplement that contains a NDI is deemed adulterated unless the manufacturer or distributor of the dietary ingredient or the dietary supplement submits a NDI notification at least 75 days before introducing it into interstate commerce. The statute places the obligation for submitting the notification on each manufacturer or distributor. The original notifier conducted its safety evaluation based on the characteristics and intended use of the specific product under review, including the composition and labeling of the dietary supplement that the notifier was proposing to market. Any other manufacturer or distributor who wishes to market its own dietary supplement containing the same NDI should submit a NDI notification to FDA explaining its own basis for concluding that this new product containing the NDI will "reasonably expected to be safe" under the conditions recommended or suggested in the new product's labeling. Manufacturing processes and specifications needed to establish the identity of a 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.

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

Yes, if it is a 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 a NDI. For example, pathogenic species of bacteria, such as *Salmonella* species or *E. 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.

4. Can you provide a visual aids to help me decide whether I should submit a NDI notification?

Yes. The following table illustrates when a NDI notification is required and whether the supplement is governed by the NDI adulteration standard. In addition, [Appendix A](#) has a decision tree to walk you through the steps of deciding whether to submit a NDI notification.

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 [12] 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

D. Additional Issues to Consider Before Submitting a NDI Notification**1. Can 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 poisonous (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)).

2. Is a synthetic copy of a constituent or extract of an herb or other botanical a dietary ingredient?

No. A synthetic copy of a constituent of a botanical was never part of the botanical and thus cannot be a "constituent" of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(F)).^[13] Similarly, a synthetic version of a botanical extract is not an "extract" of a botanical under section 201(ff)(1)(F) because it was not actually extracted from the botanical.

3. Are food contact substances and other indirect food additives dietary ingredients?

Not usually. Although food contact substances and other indirect food additives 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. An indirect food additive 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 an indirect food additive falls under one of the other dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act, it could be a dietary ingredient.

4. 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; however, in rare instances, 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.

5. 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)). 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)).

6. When FDA reviews a NDI notification, does the agency consider whether the prohibition in section 301(II) applies to the use of the NDI in a dietary supplement?

No. Section 301(II) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(II)) 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(II)(1)-(4) applies. When reviewing NDI notifications, FDA's current practice is not to consider whether section 301(II) or any of its exemptions apply to the NDI. Accordingly, a "no objection" response to a NDI notification should not be construed to be a statement that a dietary supplement containing a NDI, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

7. Can 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 a 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 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.

8. Can 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 has been authorized for investigation as a new drug or as a biologic before being marketed as a food or as a dietary

supplement cannot be marketed as a dietary supplement if substantial clinical investigations of the article have begun and the existence of such investigations has been made public. 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.

9. 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)).^[14] 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^[15] that is being studied for its possible therapeutic action. Any compound that delivers Substance A is excluded from being used in a dietary supplement.^[16]

10. Can a dietary ingredient that was authorized for investigation as a new drug in the past become a ND if the IND was withdrawn or the ingredient is no longer being studied?

It depends on the facts of the particular situation (see answer to IV.D.8 above), but withdrawal of the IND and cessation of clinical trials of the ingredient 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 finding that the article would be lawful under the 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).

11. Can 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 offered for sale or sold as an ingredient for use in manufacturing 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.^[17] 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.^[18] Merely showing that the substance was present in a food as a component would not be enough to show that the substance was "marketed," however.

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V. NDI Notification Procedures and Timeframes

A. Procedure for Submitting a NDI notification

1. Who is required to submit a NDI notification?

Either the manufacturer or distributor of a dietary supplement that contains a NDI, or the manufacturer or distributor of the NDI, must notify FDA at least 75 days before the dietary supplement containing the NDI is marketed 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 or 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.

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

The required elements of a 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. FDA recommends 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.

If you would prefer to use a form to submit your notification, **Appendix B** of this guidance contains a non-fillable sample of the fillable PDF form that you can use. Appendix B also contains a link to the fillable version of the PDF form. The form provides a checklist of the information FDA finds most useful in evaluating notifications and organizes the information in a format consistent with the agency's current electronic review system. Although the format of the form and template differ slightly, either will help you produce a well-organized notification that meets FDA's content recommendations

Recommended Template for Organizing a NDI Notification

I. Cover Letter

Consumer Safety Officer
Office of Nutrition, Labeling and Dietary Supplements (HFS-810)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Department of Health and Human Services
5100 Paint Branch Parkway
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 new dietary ingredient*), which contains the following new dietary ingredient: _____ . [*For herbs and other botanicals, the name should include the Latin binomial name, including the author citation.*]

Additional information necessary to uniquely characterize the new dietary ingredient:

-
- *If the new dietary ingredient is a botanical or is derived from a botanical, the plant part of the botanical that is the source of the new dietary ingredient should be indicated.*
 - *Examples of information sufficient to uniquely characterize a new dietary ingredient 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 communicate 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 of the dietary supplement that contains the new dietary ingredient) [This signature is required by 21 CFR 190.6 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 with 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 question 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.B.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 provided 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 include (1) a statement that indicates what category of dietary ingredient, as defined in section 201(ff)(1)(A)-(F) of the FD&C Act, describes the NDI, and that explains the basis for this conclusion; (2) a description of the manufacturing process used to make the NDI, including process controls; (3) a description of the physical properties and chemical composition of the NDI; (4) a specification sheet that describes the critical 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., excipients 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; (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), number of servings per day, serving instructions, duration of use, target population, and excluded populations (if any). For purposes of review, the highest described serving size and number of servings with a duration of daily lifetime use by all age groups and other populations 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 in which the NDI will be used. 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 pre-market NDI notification.^[19] Published review articles and publications and websites that promote other products should not be included 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?

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.

7. Does FDA have a form for NDI notifications, and, if so, do I have to use it?

Yes, Appendix B of this guidance contains a NDI notification form in PDF format, but use of the form is not required. FDA recommends the use of the form because it provides a checklist of the information FDA finds most useful in evaluating notifications and organizes the information in a format consistent with the agency's current electronic review system.

At the present time, FDA is not able to accept NDI notifications electronically, but we are making plans to convert to an electronic submission system for NDI notifications. If you use the NDI notification form in Appendix B, you can fill it out on your computer, but you must then print it out and mail it or deliver it to FDA along with your references and other attachments (21 CFR 190.6(a)).

The format of the NDI notification form is slightly different from the format described in the template in question V.A.2, above. For example, the form functions as a table of contents for the notification and contains fillable fields for conditions of use and contact information. Either format will help you produce a well-organized notification that meets FDA's content recommendations.

8. When should a NDI notification be submitted?

You must submit your NDI notification at least 75 days before you introduce or deliver for introduction into interstate commerce a dietary supplement that contains a NDI for which a notification is required (i.e., a 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); 21 CFR 190.6(a)).

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

You should submit an original and one copy of the NDI notification. Although the regulation requires two copies to be submitted (see 21 CFR 190.6(a)), FDA no longer needs the second copy and does not intend to enforce that part of the requirement. The original must be a paper document, as the regulation does not provide for electronic submissions. For the required 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 a NDI notification be submitted?

Submit your NDI notification to: Consumer Safety Officer, Office of Nutrition, Labeling and Dietary Supplements (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy. College Park, MD 20740.

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

The notification should include a table of contents with a reference section at the end of the notification (see suggested table of contents format in question V.A.2). The reference section should list all studies and publications cited in the notification, including reference numbers or descriptors 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 reprint 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 (21 CFR 190.6(b)(4)). 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 a 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 substantial amendment, FDA will reset the filing date and start a new 75-day review period.

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

As provided for 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).

FDA recommends 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 identifying this information in a separate document that accompanies the notification -- and that you provide an explanation for the basis for this belief. Likewise, if you believe there is no trade secret or CCI contained in the notification, FDA requests that you state this in your notification.

Trade secret information is 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. There must be a direct relationship between the trade secret and the productive process; for example, information relating to the manufacturing process (21 CFR 20.61(a)). Examples of trade secret information might include manufacturing methods and the 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.

Confidential commercial information 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 a NDI notification, the information is "confidential" if its disclosure is likely to cause substantial harm to the competitive position of the submitter.^[20] Examples of confidential commercial information 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), name 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 the history of use or other safety information related to the dietary ingredient, including both published and unpublished studies.
- (2) All correspondence and written summaries of oral discussions relating to the notification, except specific information that is exempt for 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 name, title, address, telephone number and, if available, email address 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 a NDI Notification is Submitted?**1. When is a 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 a dietary supplement product containing the NDI that is the subject of the notification may not be marketed (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 New Dietary Ingredient Review Team 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 guidance on how to produce 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)), and 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.
- Receipt of a copy of the notification that is not a duplicate of 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, but are not limited to: (1) letter of acknowledgement without objection; (2) letter listing deficiencies that make the notification incomplete under 21 CFR 190.6; (3) objection letter raising safety concern based on information in the notification or identifying gaps in the history of use or other evidence of safety; and (4) letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient under 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 the agency's review of your notification, and it may ask you to submit additional information if your notification is incomplete or raises safety questions. The letter also contains a report number which identifies the notification in the FDA docket. If you provide FDA with a facsimile number in your notification, FDA will send a facsimile of the response letter to that number on the day that the response letter is mailed.

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VI. What to Include in a 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 a notification?**

The purpose of including identity information in the 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 ingredients in the dietary supplement and the substances that are described in the history of use or other evidence of safety provided in your notification. Without this 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?**

You should describe the manufacturing process, the physical and chemical composition of the NDI, controls for batch-to-batch variability, as well as the identity and level of any impurities and contaminants that may be in the NDI. FDA recommends that you establish identity specifications for the NDI and for those components of the NDI or dietary supplement that are relevant to establishing the basis for the safety of the dietary supplement. You should describe these specifications in your notification as recommended in question VI.A.4, 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, 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., a 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 a NDI notification, the specification 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 explicit, 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 preparation of 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 assure 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?

As a manufacturer or distributor of a dietary supplement, you must establish specifications for the components of your product, including:

- 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 (21 CFR 111.70).

You should describe in your notification those specifications that are relevant to the identity of the NDI and to the safe consumption of your dietary supplement product. You should also list and explain the role of those specifications that establish the identity of the NDI and are relevant to the safe use of your dietary supplement, 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, or interim or final product specifications for the NDI or the dietary supplement. 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 for 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 HPLC analyses 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 1. An Example of a Specification Sheet or Table for a Dietary Ingredient

Analytical Method (Referenced Method or In-House Method Name)

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 <i>Staphylococcus aureus Pseudomonas aeruginosa</i>	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 must 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 or 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 ingredient 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 ingredient 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. Undesirable byproducts include unreacted chemical reagents, reaction byproducts, and solvents like methanol or hexane.

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

Covalent modification alters the identity of the ingredient. 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 a 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)). If not, the new ingredient cannot be a NDI because it is not a dietary ingredient.

9. What information should I submit if there is a history of use or other evidence of safety for a substance or product that is similar to, but not exactly the same as, 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.

10. 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, including binders, fillers, and color additives. You should also describe how the combination of all the ingredients 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 excipients that affect bioavailability of any of the dietary ingredients in the dietary supplement.

11. What 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 Botanical Nomenclature (ICBN). FDA recommends use of the most recent edition of ICBN. [\[21\]](#)

12. What information should I submit to describe a botanical NDI or a NDI derived from a botanical?

You should provide the following:

- Properly prepared and curated vouchers of the botanical source material;
- Conditions of propagation, if they involve deliberate manipulation of propagation in a manner that is significantly different than common plant propagation and breeding practices;
- Geographic origin of cultivated or wild harvested plant material;
- Conditions of cultivation (e.g., wild harvest, field, or greenhouse);

- Period during which the botanical is cultivated and harvested (season or month and year); and
- Part of the plant from which the ingredient is derived.

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 it 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 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 process step (e.g., a flow chart), 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 efficacy, 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.
- How the extract or concentrate is standardized from batch to batch and how adulterants such as non-food solvents, pesticides, heavy metals, and filth are excluded.
- 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 a strong 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 ingredient 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 and/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, unless the presence of the allergen is 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 information should I submit to demonstrate the identity of 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 dietary ingredient.

The use of scientific names 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),^[22] validated lists of names in the International Journal of Systematic and Evolutionary Microbiology, and published lists of prokaryotic names with standing in nomenclature (e.g., the German Collection of Microorganisms and Cell Cultures^[23] or the List of Prokaryotic Names with Standing in Nomenclature^[24]). 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 same bacterial species. Examples of species that should not be used as dietary ingredients 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. The agency recommends that the fermentation and other parts of the manufacturing process be described in detail in your notification, as recommended in question VI.A.16, above.

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 (CFU)) 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 versus 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 if my notification includes an expiration date or "use by" date for the labeling of the NDI or the dietary supplement to which the NDI will be added?

The expiration or "use by" date should be based on appropriate supporting 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 supporting 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), frequency of use (e.g., number of servings per day), duration of use, instructions for use, target population, and any restrictions on use, such as excluded populations.

For purposes of review, daily lifetime use by all age groups at the highest recommended serving size will be assumed. 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 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 a 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.

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 and/or animal testing; 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 and/or animal studies 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 a 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.

Elements that FDA recommends to substantiate that a 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 identity 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 (amount per serving) 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 be useful, 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 a NDI's proposed use that might necessitate further supportive data include: higher dosage, different route of administration (e.g., an article that has been consumed in sublingual form and is now intended for ingestion as a 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 a NDI's history of use should I submit?**

Documentation of a 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 address the safety of a NDI that is a constituent of soybeans.

6. **How do I determine whether historical use was "daily" or "intermittent," and what do the terms**

"chronic" and "sub-chronic" mean?

Daily use of the historically consumed material refers to ingestion at least once a day, every day, for at least three months in a row or for more than 90 days in a year. Intermittent use is any use that is less frequent than daily use. FDA assumes that conditions of use that specify daily use are referring to daily lifetime use, unless a shorter duration of use is specified in the notification. Chronic use means long-term use, which FDA assumes to be consumption of the substance every day by men, women and children throughout life, unless the notification specifies otherwise. This is in contrast to sub-chronic use, which is by definition intermittent. Intermittent use can be either daily and finite in duration or non-daily and lifetime in duration. For example, a rodent study in which a dietary supplement is fed daily for 90 days is a sub-chronic study (see also question VI.B.30).

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.9) 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 amount consumed by the mean or by the 90% of the population with the highest intake) 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"](#)⁴[\[25\]](#) and [section III.G, "Intake Estimate," in "Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions."](#)⁵[\[26\]](#) 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 a NDI for use in a dietary supplement.

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

An important component of reliability is the length of an ingredient's history of use. A description of the population and the ways in which they use the food is also important. The frequency of food consumption and the number of consumers who used the food are at least as important as the number of years over which the product was available. Because there is little scientific literature addressing this topic, FDA cannot make specific recommendations at this time, although the agency considers 25 years of widespread use to be the minimum to establish a history of safe use.[\[27\]](#)

10. Should I cite the history of use of a 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 a 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 medicine to the safety of a 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 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. Are additional animal and human studies needed to support 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 a 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 administration, other changes that increase exposure to potential toxic effects,

and any other differences which 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 level safely consumed in the past. When historical use of a 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 other factors would be helpful in determining when animal or human safety studies are needed in addition to history of use data?

Generally, the best way to determine whether history of use data provide a basis for a reasonable expectation that a dietary supplement containing a 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 serving 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 a 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. Can 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 supplement containing the NDI?

FDA generally recommends that the substance 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 a 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 additional safety data would not be needed 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. (See [Table 2: Safety Testing Recommendations Matrix](#).)

15. What types of data would help in assessing 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 chromosome 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 sub-chronic oral study (see questions VI.B.6, VI.B.29-31) 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); and
- (5) a teratology study (rodent or non-rodent);

except that the latter two studies are 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. (See [Table 2: Safety Testing](#))

[Recommendations Matrix.](#))**16. What types of data would help in assessing 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 sub-chronic 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; and
 - (7) a teratology study (rodent or non-rodent);
- except that the latter two studies are 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. (See [Table 2: Safety Testing Recommendations Matrix.](#))

17. What types of data would help in assessing 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 15;
 - (2) 14-day range-finding oral studies to establish a maximum tolerated dose (MTD) in at least two appropriate species, at least one of which is non-rodent;
 - (3) two 90-day sub-chronic 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); and
 - (7) a teratology study (rodent or non-rodent);
- except that the latter two studies are generally 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. (See [Table 2: Safety Testing Recommendations Matrix.](#))

18. What types of data would help in assessing 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 16;
 - (2) a 14-day range-finding oral study to establish a maximum tolerated dose (MTD) in an appropriate animal model;
 - (3) a 90-day sub-chronic 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 and/or humans;
 - (5) a one-generation rodent reproductive study; and
 - (6) a teratology study (rodent or non-rodent);
- except that the latter two studies are 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. (See [Table 2: Safety Testing Recommendations Matrix.](#))

19. What types of data would help in assessing 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 16;
- (2) a 14-day range-finding oral study to establish a maximum tolerated dose (MTD) in an appropriate animal model;
- (3) a 90-day sub-chronic 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 and/or humans; and
- (5) a teratology study (rodent or non-rodent);

except that the teratology study 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. (See [Table 2: Safety Testing Recommendations Matrix](#).)

20. What types of data would help in assessing 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 genotox battery as described in question 15;
- (2) 14-day range-finding oral studies to establish a maximum tolerated dose (MTD) in at least two appropriate species, at least one of which is non-rodent;
- (3) two 90-day sub-chronic 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 2: Safety Testing Recommendations Matrix);
- (4) a repeat-dose tolerability study in humans and/or an ADME study in animals and/or humans (30-90 day duration);
- (5) if proposed use is either intermittent or daily chronic, a one-year chronic toxicity study or a two-year carcinogenesis study in at least two animal species;
- (6) a multi-generation rodent reproductive study (minimum of two generations); and
- (7) a teratology study (rodent or non-rodent);

except that the latter two studies are 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.

Note: 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 2: Safety Testing Recommendations Matrix](#).)

TABLE 2: Safety Testing Recommendations Matrix

Documented Historical Use	Proposed Use of the NDI	Two-Study Genetic Toxicity Battery §	Three-Study Genetic Toxicity Battery§	14-Day Range-Finding Oral Study in Animals	90-Day Sub-chronic Oral Study in Animals‡	One-Generation Rodent Reproductive Study	Multi-Generation Rodent Reproductive Study	Teratology Study
Daily Chronic	Less Than Historical Use (see Question VI.B.14)							Documented history of use should be sufficient as evidence.
	Greater Than Historical Use (see Question VI.B.19)	✓		✓	✓			✓
	Less Than Historical Use (see Question VI.B.14)							Documented history of use should be sufficient as evidence.
	Greater Than Historical Use (see Question VI.B.16)	✓		✓	✓	✓		✓
Intermittent	Less Than Historical Use (see Question VI.B.14)							Documented history of use should be sufficient as evidence.
	Greater Than Historical Use (see Question VI.B.18)	✓		✓	✓	✓		✓
	Less Than Historical Use (see Question VI.B.15)		✓	✓	✓		✓	✓
No History	Greater Than Historical Use (see Question VI.B.17)		✓	✓	✓‡		✓	✓
	Daily Chronic (see Question VI.B.20)		✓	✓	✓‡		✓	✓
	Intermittent (see Question VI.B.20)		✓	✓	✓‡		✓	✓

Documented Historical Use	Proposed Use of the NDI	Two-Study Genetic Toxicity Battery §	Three-Study Genetic Toxicity Battery§	14-Day Range- Finding Oral Study in Animals	90-Day Sub-chronic Oral Study in Animals†	One-Generation Rodent Reproductive Study	Multi- Generation Rodent Reproductive Study	Teratolo Study Anima
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§ Genetic toxicity batteries are described in Questions 15 and 16.

† 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.

‡ In general, if there is no history of use, two species should be used for 90-day sub-chronic 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 sub-chronic 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 circumstance (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 and/or humans should be conducted on a case-by-case basis, as appropriate if the toxicology data or the identity of the NDI raise a special safety concern.

21. Where can I find FDA's current thinking about testing for food and color additives, and can I rely on this information when preparing my NDI notification?

FDA's current thinking about testing for food and color additives is discussed in "[Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients \(Redbook 2000\)](#)."^{6[28]} This document provides general guidance on conducting standard toxicity tests. It also includes guidelines on conducting certain genetic toxicity tests, short-term toxicity tests, sub-chronic toxicity tests, one-year toxicity studies, and reproductive and developmental toxicity studies.

You should use your own best judgment in compiling 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. The NDI safety standard is different than the standard for food additives, drugs, pesticides, 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 and dietary supplements.

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

No. Because there are no safety test protocols developed specifically for dietary ingredients, 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.

23. What are some sources of safety testing protocols that can be used in testing NDIs?

Useful guidelines for safety testing include:

- FDA's "Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000)"^[29];
- [OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects, published by the Organisation for Economic Co-operation and Development](#)^{7[30]};
- "[Harmonized Test Guidelines](#)," published by the Office of Chemical Safety and Pollution Prevention of the U.S. Environmental Protection Agency (EPA)^{8[31]}; and
- "[Safety Guidelines](#)," published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use^{9.[32]}

24. What is the appropriate highest dose of a 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 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 concerning discussion of NOAEL). 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 a 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 (IRB). However, in clinical trials, the top dose should be as high as feasible. At a minimum, the top dose or total daily intake level in a clinical trial of a NDI should be as high as the top dose or total daily intake level of the NDI under the condition of use proposed in the notification. Preferably, the top total daily intake level in the trial should be higher than the proposed top total daily intake level of the NDI.

25. 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.

26. 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.^[33]

27. 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. This history of use or other evidence of safety should be addressed in your NDI notification. A risk assessment should be used to determine whether the genetic toxicity of the NDI prevents the dietary supplement from being reasonably expected to be safe under the intended conditions of use.

28. Where can I find good examples of genotoxicity protocols that can be used in conducting animal and human studies on new dietary ingredients?

The sources cited in the answers to questions VI.B.21 and VI.B.23 contain test guidelines and testing batteries for evaluating genetic toxicity. The Redbook 2000^[34] is particularly relevant to safety testing of food ingredients.

29. What is the purpose of a sub-chronic oral toxicity study?

When properly conducted (e.g., with doses selected based on shorter term repeat-dose studies), sub-chronic 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 sub-chronic 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.

30. What is the appropriate duration for a sub-chronic oral toxicity study?

Sub-chronic oral toxicity studies are generally conducted for at least 90 days (3 months). Protocols described as lasting 12 or 13 weeks are considered equivalent. The 90-day study provides information on the possible health hazards likely to arise from repeated exposure to a substance over a three-month period of time.

31. Where can I find more information and examples of a sub-chronic oral study?

For further information and sample protocols, we recommend that you refer to the Redbook 2000¹⁰ on FDA's website,^[35] which includes guidelines for sub-chronic oral toxicity studies with rodents and sub-chronic oral toxicity studies with non-rodents. [OECD Guidelines for the Testing of Chemicals, Guideline 408 \("Repeated Dose 90-day Oral Toxicity Study in Rodents:\)](#)^{11[36]} also provides protocols for rodent studies. The appropriate animal species and study design may vary depending on the safety questions associated with the NDI being studied.

32. 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, lactation, and pre-natal 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).

33. 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 VI.C.2, below).

34. **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).

35. **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),^[37] 416 (Two-Generation Reproduction Toxicity),^[38] 421 (Reproduction/Developmental Toxicity Screening Test),^[39] and 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test)^{12[40]} to find protocols for conducting reproductive toxicity and teratology studies. You may also refer to the guidelines for reproductive studies in section IV.C.9 of the Redbook 2000, "Guidelines for Reproduction Studies,"^[41] for guidance on conducting reproduction and developmental toxicity studies, including reproduction testing with a teratology phase. Information about how data from these studies are assembled and used for other regulatory programs [e.g., pesticides (see EPA's "Harmonized Test Guidelines")^[42] and medicinal products (see ICH's "Safety Guidelines")^[43] may also be helpful. In particular, "Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility"^{13[44]} contains useful guidelines for detecting reproductive toxicity.

36. **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 metabolite 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 a 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. The test article used in these studies should have the same composition (including excipients) and form as the dietary supplement described in the notification.

37. **Am I required to conduct human clinical studies to support 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 a 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.

38. **What kinds of human clinical studies are useful to support the safety of a NDI?**

The most useful studies are usually short-term tolerability studies and ADME studies. 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 VI.C.5).

Tolerability studies identify acute toxicity, such as that associated with toxins or 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 a NDI when the proposed conditions of use would result in doses that cannot be humanely administered to animals.

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

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 both males and females, 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 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 because it should be long enough to mimic chronic consumption. The clinical trial should last at least 90 days, and its endpoints should be clearly defined.

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 2: **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.

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

For more information and sample clinical protocols, refer to Chapters V^[45] and VI^[46] of the Draft Redbook II, which provide general guidance on conducting human clinical studies on foods and food ingredients. FDA also recommends consulting "Guidance for Industry--M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"^[47] for its discussion of selecting an appropriate dose for sub-chronic oral studies in animals and clinical trials in human volunteers (pp. 1-5).

41. What information should I submit to demonstrate the safety of a 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 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.

42. 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 excipients 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

43. What should I do to demonstrate the safety of a 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 prior to submitting a NDI notification for a NDI that contains nanomaterials or otherwise involves the application of nanotechnology.

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 its 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 product containing the NDI.

When a notification describes a product 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 ingredients 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 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 (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 amount, 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 extract of that herb, the NDI Comprehensive Safety Profile should qualitatively and quantitatively compare the dose of the herb to the dose 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 effects and observed adverse 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 CCI. Any information in the NDI Comprehensive Safety Profile that you believe to be a trade secret or CCI 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 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 Acceptable Daily Intake (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 can reasonably be expected to be safe. 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, color additive, or GRAS determination are also recommended.

The dietary supplement Safety Narrative should estimate the 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 excipients, 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.

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.^[48] The No-Observable-Effect Level (NOEL) is the highest dose at which no effects are 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 a 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), and 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 a 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 acceptable daily intake (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 sub-chronic toxicity studies to chronic use of a NDI or dietary supplement necessitates an additional safety factor. In this situation, FDA recommends using at least two sub-chronic 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 1000. In the absence of supporting history of use data, using only a single rodent sub-chronic toxicity study as a basis to conclude that chronic use of a NDI in humans will be safe is strongly discouraged, but may be acceptable if a safety factor of 2000 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 sub-chronic (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 sub-chronic studies in both rodent and non-rodent species showed no adverse effects. If human data from chronic toxicity or ADME 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. Safety factors are used to calculate the ADI (see VI.C.3).

$$ADI = NOAEL / \text{combined safety factor} = NOAEL / (U_{intra} \times U_{extrap} \times U_{inter})$$

- *U_{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 food is consumed by everyone: 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.
- *U_{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 sub-chronic animal studies to predict the safety of sub-chronic (including intermittent) human exposure.
- *U_{extrap}*: Extrapolating from a set of two sub-chronic 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 sub-chronic data to predict chronic use. If sub-chronic 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 a NDI will reasonably be expected to be safe, 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 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. While the discussion of the difference between a NOEL and a NOAEL may be relevant to a particular study or comprehensive safety profile, because of its importance to the overall safety evaluation the discussion should be placed in the dietary supplement Safety Narrative.

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 (Acceptable Daily Intake) = 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 estimated daily intake (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. International Programme on Chemical Safety. Geneva, Switzerland. 1987. Environmental Health Criteria 70: Principles for the safety assessment of food additives and contaminants in food.
- NAS National Academy of Sciences. Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients. 1998. Food and Nutrition Board, Institute of Medicine. Washington DC, National Academies Press.

Example: The only safety evidence available is a single sub-chronic 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 $3,000/0.014 = 2.1 \times 10^5$. The safety factors chosen are $U_{intra} \times U_{extrap} \times U_{inter} = 10 \times 10 \times 20 = 2000$. 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 one, 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 1g per day (1000 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 a NDI will reasonably be expected to be safe?

The ratio of the Estimated Daily Intake (EDI) to the Acceptable Daily Intake (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 one, 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 Estimated Daily Intake (EDI) of the NDI must be less than or equal to the Acceptable Daily Intake (ADI) of the NDI or dietary supplement.

The EDI for the NDI or for the dietary supplement is the top 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, a 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 of one (or less than one) 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, respectively, than the conditions of historical use (see question

VI.B.14).

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VII. DEFINITIONS

The following definitions represent FDA's current thinking on the meaning of the terms below in the context of the new dietary ingredient provisions of the Act and regulations. The definitions are intended for use only in that context and may not be appropriate in other contexts.^[49]

Acceptable Daily Intake (ADI):

The daily intake of a NDI or dietary supplement containing the NDI that, during the human lifetime, appears to be without appreciable risk (affects 1 in 1 million people or less) on the basis of all known facts at the time. It is calculated as the ratio of the NOAEL to the total safety factor (determined from the studies submitted in the notification).^[50]

Amino acid:

An alpha-amino carboxylic acid used as a constituent of proteins or peptides.^[51]

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 question IV.B.4.

Chronic:

In the context of historical use by humans (i.e., outside of controlled studies), refers to daily lifetime use. In the context of animal and human studies, refers to studies with a duration of one year or longer.

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 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).^[52]

Dietary substance:

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

Enantiomers:

Mirror-image isomers that have different chemical, physical, and biological properties.

Estimated Daily Intake (EDI):

For a dietary supplement, the highest total daily intake level (in mg/day) or dose (in mg/kg/day), as determined from the proposed conditions of use in the notification. It is the maximum amount that would be consumed based on the conditions of use proposed and recommended in the notification and should take 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.

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.

Marketed:

See question IV.A.6.

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.

Maximum tolerated dose (MTD):

The dose that causes no more than a 10% 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. [53]

Metabolite:

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. 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. [54]

Mineral:

A substance of defined chemical composition which provides a form or source of inorganic elements to the diet. An element is any class of substances, such as calcium, iodine, or zinc, which cannot be separated into simpler substances by chemical means.

Nanomaterial, Nanotechnology:

FDA has not adopted a formal definition of "nanotechnology," "nanomaterial," "nanoscale," or related terms. In the absence of a formal definition, when considering whether an FDA-regulated product, including dietary ingredients, contains nanomaterial: or otherwise involves the application of nanotechnology, FDA intends to ask: 1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or 2. Whether an engineered material or end product exhibits 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 one micrometer. [55]

New dietary ingredient:

A dietary ingredient that was not marketed in the U.S. before October 15, 1994. [56]

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. [57]

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 sub-chronic to chronic data (uncertainty factor of extrapolated data from sub-chronic 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 VI.C.5 and VI.C.7.

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.

Sub-chronic:

Refers to intermittent use that is either daily and finite in duration, or less than daily throughout the lifetime (i.e., use that is less than chronic). For example, a 90-day sub-chronic study in rodents whereby a dietary supplement is fed daily for a finite period of 90 days is a sub-chronic study. See question VI.B.6.

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 a 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 one part botanical to 5 parts alcohol.

Uncertainty Factor:

See **Safety Factor**.

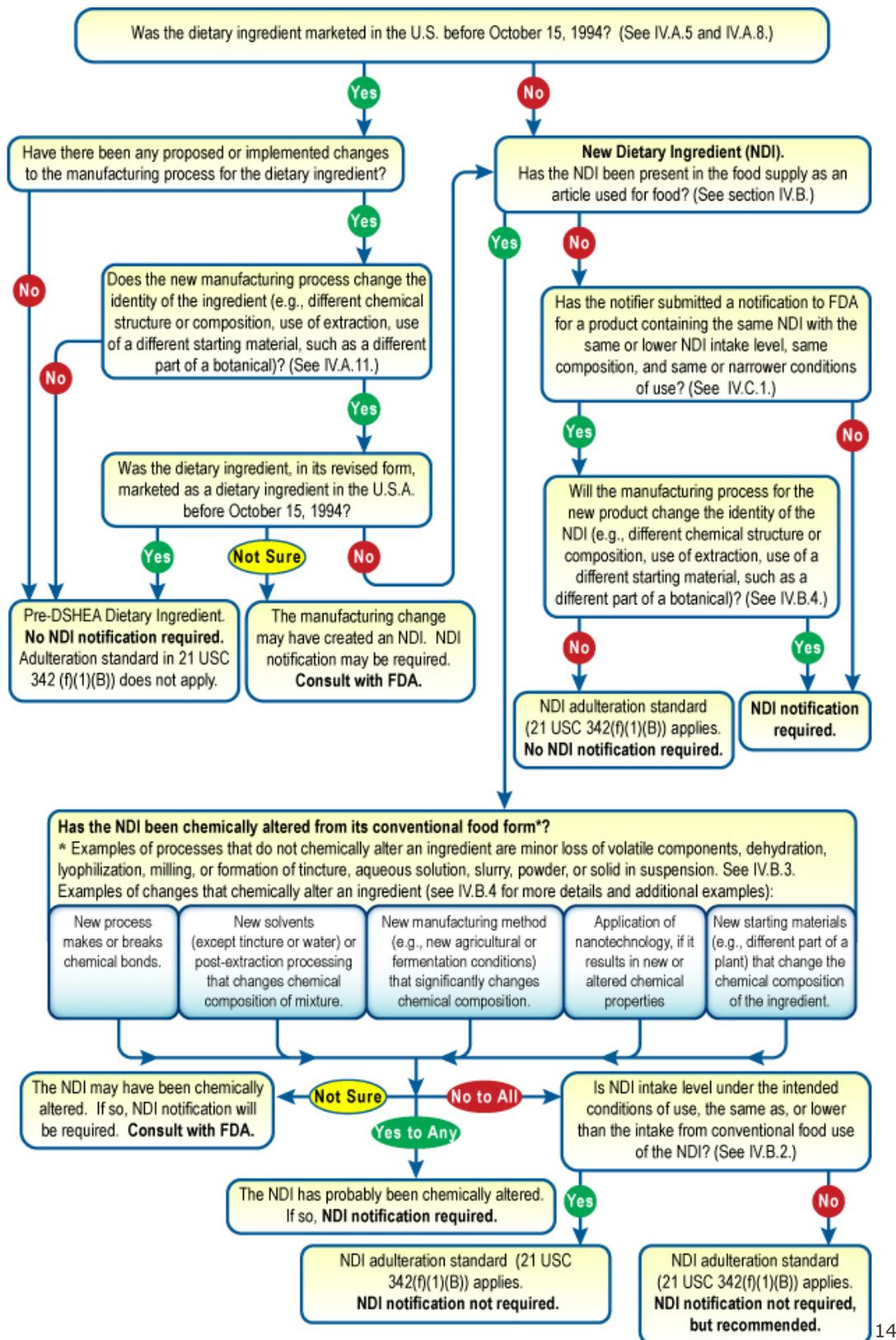
Vitamin:

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.

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VIII. APPENDICES

Appendix A: Decision Tree for NDI Notification^[58]



[Text description](#)¹⁵
[Printable PDF](#)¹⁶

Appendix B: 75-Day Pre-Market New Dietary Ingredient Notification Form

Below is a non-fillable image of the fillable PDF form. The [fillable pdf](#)¹⁷ form is available.

Save As...		Print	Export Data	Import Data	Next Page	Goto Page?	E-mail Form	Reset Form
Department of Health and Human Services Food and Drug Administration 75 DAY PRE MARKET NEW DIETARY INGREDIENT (NDI) NOTIFICATION Version : 2.1					Form Approved: OMB No. XXXX-XXXX Expiration Date: mm/dd/yyyy Draft for Test Only (See last page for OMB Statement)			
FDA USE ONLY								
NDI Number					AIMS Number			
Date of Receipt								
PART I - INTRODUCTORY INFORMATION ABOUT THE NOTIFICATION								
1. Type of Notification (Complete a. or b. below)								
<input type="checkbox"/> New Dietary Ingredient								
Transmit completed form and attachments in paper format or on physical media to: Office of Nutrition Labeling and Dietary Supplements (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835								
b. If Additional Information/Incoming Correspondence, check one of the following.								
<input type="checkbox"/> Amendment <input type="checkbox"/> Correspondence (ID, CCI) <input type="checkbox"/> Correspondence, Others								
Enter the appropriate number(s) applicable to this update or amendment.								
NDI Number <input type="text"/>								
2. <input type="checkbox"/> All electronic fields included in this notification have been checked and found to be virus free. (Check box to verify)								
3a. For New Notifications only: Enter the date of most recent prenotification consultation (if any) with FDA on the subject substance (yyyy/mm/dd):								
3b. For Amendments only: Is your amendment submitted in response to a communication from FDA? (Check one)								
<input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, enter the date of communication (yyyy/mm/dd):								
PART II - CONTACT INFORMATION								
pursuant to 21 U.S.C. 350b(a)(2) (section 413 of the Federal Food, Drug and Cosmetic Act)								
1a. Responsible Person:		Name of Contact Person			Position			
<input type="checkbox"/> Manufacturer		Company (if applicable)						
<input type="checkbox"/> Distributor		Mailing Address (number and street)						
<input type="checkbox"/> Agent/Attorney/Consultant		City		State or Province		Zip Code/Postal Code		Country
Telephone Number			Fax number			E-Mail Address		
1b. Other Contact(s)		Name of Contact Person			Position			
<input type="checkbox"/> Manufacturer		Company (if applicable)						
<input type="checkbox"/> Distributor		Mailing Address (number and street)						
<input type="checkbox"/> Agent/Attorney/Consultant		City		State or Province		Zip Code/Postal Code		Country
Telephone Number			Fax number			E-Mail Address		
Add Continuation Page								

<input type="button" value="Save As"/> <input type="button" value="Print"/> <input type="button" value="Export Data"/> <input type="button" value="Import Data"/> <input type="button" value="Next Page"/> <input type="button" value="Previous Page"/> <input type="button" value="Goto Page?"/> <input type="button" value="E-mail Form"/> <input type="button" value="Reset Form"/>	
PART III - GENERAL ADMINISTRATIVE INFORMATION	
<p>1. Title of Notification/Name of New Dietary Ingredient(s)</p> <hr/> <p>2. Notification Format <i>(Check appropriate box(es))</i></p> <p><input type="checkbox"/> Paper <input type="checkbox"/> Electronic files on physical media with paper signature page</p> <p>If applicable, give number and type of physical media</p>	<p>3. For paper notifications only</p> <p>Number of Volumes: _____</p> <p>Total number of Pages: _____</p> <p>Total number of Copies: _____</p>
<p>5. Previous notification(s). <i>(Check all that apply)</i></p> <p><input type="checkbox"/> a) Previous notification(s), same notifier NDI No. _____</p> <p><i>FDA use only</i></p> <p><input type="checkbox"/> b) Related Notifications from other notifiers NDI No. _____</p> <p><input type="checkbox"/> c) No previous notification with this NDI</p> <p><input type="checkbox"/> d) Other information (briefly describe) _____</p>	
<p>6. Have you designated information in your notification that you view as trade secret or as confidential commercial or financial information? <i>(Check one)</i></p> <p><input type="checkbox"/> Yes, see attached designation of confidential information <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes, information is designated at the place where it occurs in the notification</p>	
<p>7. Have you attached a redacted copy of some or all of the notification? <i>(Check one)</i></p> <p><input type="checkbox"/> Yes, redacted copy of complete notification</p> <p><input type="checkbox"/> Yes, redacted copy of part(s) of notification <input type="checkbox"/> No</p>	
<p>8. Are all citations to published information accompanied by reprints or full photostatic copies of the publication? <i>(Check one)</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p>	
<p>9. Are published materials all in English or a complete and accurate translation provided? <i>(Check one)</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p>	
<p>10. Have you described the dietary supplement that contains the new dietary ingredient? <i>(Check one)</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p>	
PART IV.A - NEW DIETARY INGREDIENT NAME(S)	
<p>New Dietary Ingredient Type <i>(Check all that apply) - 201(ff)(1)(A-F)</i></p> <p><input type="checkbox"/> A. Vitamin <input type="checkbox"/> B. Mineral <input type="checkbox"/> C. Herb/Botanical <input type="checkbox"/> D. Amino Acid <input type="checkbox"/> Not a Dietary Ingredient <input type="checkbox"/> To Be Determined</p> <p><input type="checkbox"/> E. A dietary substance to supplement the diet</p> <p><input type="checkbox"/> F. A concentrate, metabolite, constituent, extract or combination of any ingredient described above</p> <p>Level of this new dietary ingredient in each serving of the dietary supplement product:</p> <p>_____</p>	
<p>NDI Name: _____</p> <p>Synonyms/Trade Name: _____ Plant Part/Strain: _____</p> <p>Latin Binomial Name (LBN): _____ Author of LBN: _____</p> <p style="text-align: right;"><input type="button" value="Add Continuation Page"/></p>	
<p>Serving Form <i>(Check all that apply)</i>:</p> <p><input type="checkbox"/> Tablet <input type="checkbox"/> Capsule <input type="checkbox"/> Powder <input type="checkbox"/> Softgel</p> <p><input type="checkbox"/> Liquid <input type="checkbox"/> Gelcap <input type="checkbox"/> Other</p>	

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Description of dietary supplement product
(Include level of the NDI and all other ingredients in the dietary supplement).

Serving Instructions (include total daily intake level)

Conditions of use
(Serving size, # of servings/day, serving instructions, and duration of use).

Target and/or excluded populations/other restrictions

Other

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PART V - COMPOSITION OF THE DIETARY SUPPLEMENT PRODUCT
(Including all constituents)

Note: Abbreviations for Chemical Classifications: NDI (New Dietary Ingredient), DI (dietary ingredient that is not an NDI). List non-dietary ingredients as either GRAS (Generally Recognized as Safe for *this* intended use), FAP/CAP (approved food or color additives), C (other constituent including marker compounds), I (impurity/contaminant e.g. toxicants, residual solvents, pesticides, pathogens, heavy metals).

Chemical Classification/ Function	Chemical Name	CAS* Registry Number	Trade Name (if any)	Link To Chemical Structure/Spectrum/ Chromatogram.
				Go To Link
				Go To Link
				Go To Link
				Go To Link
				Go To Link
				Go To Link
				Go To Link

* CAS = Chemical Abstracts Service

[Add Continuation Page](#)

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PART VI - Other Supportive Information in the Notification Which Could be Useful to Determine Identity or Safety of an NDI (Check the list below to help ensure your notification is complete. Check all that apply.)								
<p>1. <input type="checkbox"/> Administrative</p> <p>1.1 <input type="checkbox"/> Designation of Nondisclosable information</p> <p>1.2 <input type="checkbox"/> Redacted document</p> <p>1.3 <input type="checkbox"/> If additional information or correspondence, check all that apply.</p> <p>1.3.1 <input type="checkbox"/> Amendment</p> <p>1.3.2 <input type="checkbox"/> Correspondence</p> <p>1.4 <input type="checkbox"/> Safety Narrative</p> <p>2. <input type="checkbox"/> Chemistry/Identity</p> <p>2.1 <input type="checkbox"/> Detailed description of ingredients and product</p> <p>2.2 <input type="checkbox"/> Manufacturing Methods</p> <p>2.3 <input type="checkbox"/> Specifications</p> <p>2.3.1 <input type="checkbox"/> Dietary ingredients</p> <p>2.3.2 <input type="checkbox"/> Other ingredients</p> <p>2.3.3 <input type="checkbox"/> Dietary Supplement</p> <p>2.3.4 <input type="checkbox"/> Analytical Methods</p> <p>2.3.5 <input type="checkbox"/> Certificates of Analysis</p> <p>2.4 <input type="checkbox"/> Studies (Check all that apply)</p> <p>2.4.1 <input type="checkbox"/> Composition</p> <p>2.4.2 <input type="checkbox"/> Fingerprint/Markers Describe how the constituents of complex mixtures are standardized from batch to batch and how adulterants are excluded</p> <p>2.4.3 <input type="checkbox"/> Stability/shelflife</p> <p>2.4.4 <input type="checkbox"/> Dissolution/absorption</p> <p>2.4.5 <input type="checkbox"/> Other studies</p> <p>2.5 <input type="checkbox"/> References (Identity)</p> <p>2.5.1 <input type="checkbox"/> Cited Literature (published)</p> <p>2.5.2 <input type="checkbox"/> Cited Literature (unpublished)</p> <p>3. <input type="checkbox"/> Safety</p> <p>3.1 <input type="checkbox"/> Comprehensive Safety Profile(s)</p> <p>3.2 <input type="checkbox"/> Toxicology Studies</p> <p>3.2.1 <input type="checkbox"/> Genetic Toxicity Studies</p> <p>3.2.2 <input type="checkbox"/> Short Term Toxicity Studies: Rodents</p> <p>3.2.3 <input type="checkbox"/> Short Term Toxicity Studies: Non-Rodents</p> <p>3.2.4 <input type="checkbox"/> Subchronic Toxicity Studies: Rodents</p> <p>3.2.5 <input type="checkbox"/> Subchronic Toxicity Studies: Non-Rodents</p> <p>3.2.6 <input type="checkbox"/> One-Year Toxicity Studies</p> <p>3.2.7 <input type="checkbox"/> Chronic Toxicity or Combined Chronic Toxicity/Carcinogenicity Studies: Rodents</p>					<p>3. Safety (Continued)</p> <p>3.2 Toxicology Studies (Continued)</p> <p>3.2.8 <input type="checkbox"/> Carcinogenicity Studies: Rodents</p> <p>3.2.9 <input type="checkbox"/> Reproductive Studies</p> <p>3.2.10 <input type="checkbox"/> Developmental/Teratology Studies</p> <p>3.2.11 <input type="checkbox"/> Immunotoxicity Studies</p> <p>3.2.12 <input type="checkbox"/> Metabolism (ADME) and Pharmacokinetic Studies</p> <p>3.2.13 <input type="checkbox"/> Neurotoxicity Studies</p> <p>3.2.14 <input type="checkbox"/> Ingredient Interaction Studies</p> <p>3.2.15 <input type="checkbox"/> Molecular Biology/Genetic Studies</p> <p>3.2.16 <input type="checkbox"/> Antibiotic Resistance/Genetic Stability Studies</p> <p>3.3 <input type="checkbox"/> Human Studies</p> <p>3.3.1 <input type="checkbox"/> Clinical trials primarily designed to study safety</p> <p>3.3.2 <input type="checkbox"/> Clinical efficacy trials</p> <p>3.3.3 <input type="checkbox"/> Adverse Event Reports (including Periodic Safety Update Reports, if any)</p> <p>3.4 <input type="checkbox"/> Other Studies</p> <p>3.5 <input type="checkbox"/> History of Use</p> <p>3.5.1 <input type="checkbox"/> Identity and description of substances that contained the NDI How are these substances qualitatively and quantitatively similar to the NDI</p> <p>3.5.2 <input type="checkbox"/> Estimate the historical consumer exposure to these substances (serving level, duration, frequency)</p> <p>3.5.3 <input type="checkbox"/> Monitoring of exposed populations: adverse event reporting/periodic safety update reporting</p> <p>3.5.4 <input type="checkbox"/> Monitoring of exposed populations: other</p> <p>3.6 <input type="checkbox"/> Other Evidence of Safety</p> <p>3.7 <input type="checkbox"/> References</p> <p>3.7.1 <input type="checkbox"/> Literature Publications</p> <p>3.7.2 <input type="checkbox"/> Other (including unpublished, etc)</p> <p>4. <input type="checkbox"/> Other (Information in original notification that does not fall under any of the above categories)</p> <p>5. <input type="checkbox"/> Complete reference list for notification</p>			
FORM FDA XXXX (MM/YY)					Page 5 of 6			

Notes:

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

[2] Dietary Supplement Labeling Requirements and Recommendations under the Dietary Supplement and Nonprescription Drug Consumer Protection Act¹⁸, 74 FR 8262 (Feb. 24, 2009).

[3] Institute of Medicine, Food and Nutrition Board; National Research Council, Board on Life Sciences. *Dietary Supplements: A Framework for Evaluating Safety*¹⁹. Washington, DC: The National Academies Press; 2004 Apr.

[4] Letter from Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, to Dietary Supplement Manufacturers²⁰ (Dec. 15, 2010).

[5] FDA Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat. 3886 (2011).

[6] 21 U.S.C. 350b(c).

- [7] Under 21 U.S.C. 342(f)(1)(B), a dietary supplement containing a 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.
- [8] See, e.g., [National Nutritional Foods Association, NNFA List of Dietary Supplement Ingredients In Use Before October 15, 1994](#)²¹ (April 26, 1996). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0012].
- [9] [Council for Responsible Nutrition, CRN List of Dietary Ingredients "Grandfathered" Under DSHEA](#)²² (September 1998). Docket No. FDA-2005-P-0259 [Document ID: FDA-2005-P-0259-0010].
- [10] Statement of Agreement, 140 Cong. Rec. S14801 (daily ed. Oct. 7, 1994).
- [11] Statement of Agreement, 140 Cong. Rec. S14801 (daily ed. Oct. 7, 1994).
- [12] Adulteration standard 21 U.S.C. 342(f)(1)(B) (section 402f(1)(B) of the FD&C Act): A food shall be deemed to be adulterated if it is a dietary supplement or contains a dietary ingredient that is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.
- [13] [Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk](#), 69 FR 6788, 6793²³ (Feb. 11, 2004).
- [14] *Pharmanex v. Shalala*, 221 F.3d 1151, 1154-1160 (10th Cir. 2000).
- [15] Under 21 CFR 316.3(b)(2)²⁴, "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)²⁵.
- [16] 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].
- [17] See *Pharmanex v. Shalala*, 2001 WL 741419, at *4 & n.5 (D. Utah March 30, 2001).
- [18] *Id.* at *3.
- [19] 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 that review NDI notifications.
- [20] *National Parks & Conservation Ass'n v. Morton*, 498 F.2d 765 (D.C. Cir. 1974).
- [21] McNeill, J.; Barrie, F.R.; Burdet, H.M. et al., editors. [International Code of Botanical Nomenclature \(Vienna Code\)](#)²⁶ (electronic ed.) Vienna: International Association for Plant Taxonomy; 2006.
- [22] 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.
- [23] [Bacterial Nomenclature Up-to-Date](#)²⁷ (German Collection of Microorganisms and Cell Cultures Database). Braunschweig, Germany: Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH; cited May 10, 2011. [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.]
- [24] Euzéby, J. P., editor. [List of Prokaryotic Names with Standing in Nomenclature \(LPSN\) Database](#)²⁸ (formerly List of Bacterial Names with Standing in Nomenclature (LBSN)). [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.] Toulouse (France): Editorial Board of the International Journal of Systematic and Evolutionary Microbiology (IJSEM) and the International Committee on Systematics of Prokaryotes (ICSP); cited May 10, 2011.
- [25] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. *Guidance for Industry: Estimating Dietary Intake of Substances in Food*; August 2006.
- [26] U.S. Food and Drug Administration, 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.
- [27] 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*²⁹ C 122 E (Nov. 5, 2010); p. 38 - 57.
- [28] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. *Guidance*

for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[29] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

[30] Organisation for Economic Co-operation and Development (OECD). OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects (electronic ed.). Netherlands: OECD iLibrary; cited May 12, 2011.

[31] U.S. Environmental Protection Agency (EPA), Office of Chemical Safety and Pollution Prevention (OCSP). OCSP Harmonized Test Guidelines; April 2010.

[32] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Safety Guidelines. Geneva: ICH; cited May 12, 2011.

[33] 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.

[34] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety. Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000); July 2000; revised July 2007.

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

in this section.

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[51] 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].

[52] 21 U.S.C. 321(ff)(1).

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[54] 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](#)³³; College Park, MD; dated June 3, 2003.

[55] FDA recently issued a draft guidance to industry titled "[Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology](#)"³⁴.

[56] 21 U.S.C. 350b(c).

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[58] The adulteration standard for NDIs can be found in 21 U.S.C. 342(f)(1)(B)(section 402(f)(1)(B) of the FD&C Act).

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4. /Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm074725.htm
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