DOCKET NO. FDA–2011–D–0376

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON

DRAFT GUIDANCE FOR INDUSTRY; DIETARY SUPPLEMENTS: NEW DIETARY INGREDIENT NOTIFICATIONS AND RELATED ISSUES

December 2, 2011

Table of Contents

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA is comprised of domestic and foreign companies doing business as growers, processors, manufacturers and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs, including conventional human foods and dietary supplements.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Dietary Supplement Health and Education Act (DSHEA) establishes certain definitions and requirements for new dietary ingredients (NDIs). The Food and Drug Administration (FDA or the agency) issued a Federal Register notice on July 5, 2011 that announced the availability of a draft guidance for industry entitled, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (the draft guidance). The July 5 notice stated that this draft guidance was issued in compliance with section 113(b) of the Food Safety Modernization Act (FSMA). FSMA was signed into law on January 4, 2011, and section 113(b) established a requirement for FDA to issue draft guidance on specific aspects of NDI regulations within 180 days.

AHPA's summary position

The draft guidance is hugely flawed. Instead of providing guidance regarding DSHEA's NDI notification provision, as directed by section 113(b) of FSMA, the draft guidance seeks to erect extra-legal barriers to market entry, impose food additive type evaluative criteria, require multiple NDI notifications for dietary supplements beyond those required by law, and transform the legal requirements for marketing of dietary supplements that contain NDIs from the notification process described under law to an FDA approval process. Instead of facilitating compliance with the NDI provision of the law, the draft guidance would, if implemented as written with the flaws identified in these comments, change the rules that have been in place for the last 17 years and significantly increase the burden on the supplement industry far beyond the intent of Congress with no concomitant benefit for consumers.

In submitting these comments AHPA therefore strongly recommends and hereby calls for FDA to withdraw the draft guidance in its entirety. The agency should issue new guidance on this subject and should (1) ensure that such subsequent guidance is consistent with the Act by incorporating the revisions suggested in these comments and making such additional modifications as are needed to conform with the Act and with the intent of Congress with regard to new dietary ingredients, and (2) issue such subsequent guidance in the form of a draft to provide appropriate opportunities for comment.

DSHEA established a regulatory framework for dietary supplements as a separate class of foods and put an end to FDA's capacity to classify ingredients now in this class as

unapproved food additives. Even before DSHEA, Congress had taken away FDA's power to regulate vitamins and minerals above certain levels as drugs. Under the comprehensive regulatory framework established by DSHEA and through subsequent revisions to the Act, a company seeking to engage in manufacturing or distributing dietary supplements must, in accordance with the Act and FDA's implementing regulations:

- Register with FDA, if the company operates manufacturing, packaging, or warehousing facilities.
- Formulate products for ingestion with dietary ingredients.
- Submit premarket notifications to FDA, where required, regarding new dietary ingredient in any products, though no such notification is required if only dietary ingredients already marketed in the U.S before October 15, 1994 are used, and in certain other circumstances.
- Manufacture, pack, label and hold products in accordance with current good manufacturing practice regulations.
- Label products with Supplement Facts, identify other ingredients, and provide the name and address of the manufacturer or distributor.
- Notify FDA within 30 days of first marketing of structure function claims and have substantiation on file for such claims.
- Submit any serious adverse event report to FDA and maintain records of all adverse event reports.

Into this settled regulatory environment, FDA proposes in the draft guidance that manufacturers must establish the pedigrees of all old dietary ingredients they use and submit NDI notifications where required for each supplement containing new dietary ingredients. The draft guidance would require these notifications to be supported by safety documentation meeting food additive petition requirements, the very requirements DSHEA struck out of the dietary supplement regulatory paradigm.

AHPA includes among its members companies that sell dietary supplements that consist only of dietary ingredients that were marketed prior to October 15, 1994 and other companies that sell at least some dietary supplements that contain a NDI. The former should have no regulatory burden whatsoever with regard to NDIs and the regulatory burdens for the latter should be neither more nor less than is required under the Act, as amended by DSHEA. In reviewing the draft guidance, however, it is obvious that implementation of this document as written would, in fact, place burdens on companies that sell only supplements that consist entirely of dietary ingredients that were marketed in the United States prior to October 15, 1994 (referred to in the draft guidance and hereinafter as "pre-DSHEA dietary ingredients"), and would apply regulatory burdens contrary to or unintended by the Act with respect to products that contain NDIs.

This was clearly not the intention of the Congress when DSHEA was passed in 1994, as is evident in reviewing the record of how FDA sought to regulate the products that are now regulated as dietary supplements prior to 1994 as well as the history of the law's adoption and language contained in the law itself. Implementation of the draft guidance as written would have the effect of returning new ingredients in this product class to a pre-DSHEA regulatory status, and would have the effect of stifling the supplement industry and reducing consumer choice and access.

AHPA reads the draft guidance, if implemented as written, as placing significant extra-legal burdens on dietary supplement companies that market products with or without NDIs. These additional burdens result from directives in the draft guidance that do not appear in the Act or that are contrary to the Act, as discussed in these comments.

In separate communications on the topic of NDI regulations FDA has stated its view that there is only a "minimal burden" on companies that need to generate data to meet the requirement to submit a NDI notification.[1] The agency explains its rationale for this evaluation by ignoring any effort required to develop the information on which an NDI manufacturer or distributor has based its conclusion that a dietary supplement that contains the NDI will reasonably be expected to be safe, and considering only the administrative processes involved in organizing and presenting already existing data as the only relevant burdens in submitting a NDI notification. AHPA refrains here from commenting on the accuracy of this burden evaluation by the agency, but notes that the burden created under the guidance if fully implemented would increase dramatically. AHPA notes also that there would be no concomitant benefit for consumers associated with this increased burden since compliance with the Act as written already protects consumers from supplements that are not reasonably expected to be safe.

AHPA notes that private label manufacturers may package the same or similar bulk liquid, powder, pill or other dosages for many different clients, labels or brands; as an example, one member company has informed AHPA they package the same bulk material under hundreds of different brand names or labels; and this represents just one of many hundreds of bulk products the member manufactures for private label. In other cases, companies package variations of the basic formula under different brands or labels, with minor changes made to the flavor, excipients, other dietary ingredients, or other specifications. AHPA further notes that FDA has estimated the cost of filing a NDI notification to be $410.[2] AHPA is not at this time commenting on the accuracy of FDA's estimates, although AHPA believes they may be too low. However, assuming the estimates are correct, if FDA were to insist on a separate NDI notice for each dietary

[1] 76 FR 32214 at 32215, June 3, 2011.
[2] 62 FR 49886.

supplement, one member company alone would be forced to spend in excess of $41,000 dollars on filing the NDI notices related to just one of their bulk products containing an NDI; and FDA would waste (at $224 per hour) many millions of dollars of the taxpayers' money filing these duplicative and pointless notices. This would be clearly inconsistent with the benefit-cost and small business analyses FDA performed in promulgating the regulation.

To restate AHPA's summary position, the draft guidance should be withdrawn in its entirety and FDA should issue new guidance, in the form of a revised draft. AHPA submits the comments here with one primary purpose to contribute the contained ideas toward the development of a revised draft guidance.

Legislative and regulatory background

The Food and Drug Administration (FDA or the agency) issued a Federal Register notice on July 5, 2011 (the July 5 notice) that announced the availability of a draft guidance for industry entitled, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (the draft guidance). The July 5 notice stated that this draft guidance was issued in compliance with section 113(b) of the Food Safety Modernization Act (FSMA). FSMA was signed into law on January 4, 2011, and section 113(b) established a requirement for FDA to issue draft guidance on specific aspects of NDI regulations within 180 days.

The July 5 notice stated that comments to any agency guidance may be submitted at any time, but directed that comments should be submitted by October 3, 2011, since extended to December 2, 2011, to ensure that they are considered before FDA begins work on a final guidance.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Dietary Supplement Health and Education Act (DSHEA) establishes certain definitions and requirements for new dietary ingredients (NDIs). More specifically:

- Section 413(d)[3] of the Act defines the term "new dietary ingredient" to mean, "a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."
- Section 413(a) of the Act establishes that a dietary supplement that contains an NDI is adulterated under section 402(f) of the Act "unless it meets one of the following requirements:

[3] Earlier documents referred to this paragraph as 413(c) but it was renumbered by an amendment included in FSMA. The draft guidance references the relevant cross-referenced section of 21 U.S.C. using the old numbering of 350b(c); this should be changed throughout to 350b(d).

(1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.

(2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe."

- Section 402(f)(1)(B) of the Act further establishes that a dietary supplement is 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."

FDA stated in the July 5 notice that the draft guidance, when finalized, will assist industry in two ways:

1. "…in deciding when a premarket safety notification for a dietary supplement containing a new dietary ingredient (NDI) is necessary"
2. "…in preparing premarket safety notifications"

Presentation of AHPA's comments

AHPA includes among its members companies that sell dietary supplements that consist only of pre-DSHEA dietary ingredients, and other companies that sell at least some dietary supplements that contain an NDI. AHPA and its members therefore have an interest in the draft guidance.

The order in which these comments are submitted should not be read to imply that the earliest provided comments are of greater importance than later submitted comments. Also, these comments do not retain the same order as is found in the draft guidance but instead group certain questions of the draft based on AHPA's view of a logical relationship among several separate questions.

In addition, due to the length of the draft, the complexity of the issues involved, and the numerous significant flaws in the draft guidance, AHPA has not in fact had time to review all sections of the draft. Thus the absence of comments on any portion of the draft guidance should not be taken to mean that AHPA agrees with that portion, unless

such agreement is specifically stated. In addition, AHPA intends to submit subsequent comments to the draft guidance at a later date, either to address issues not yet addressed in the comments submitted here or to clarify and expand on the current comments; such future comments are hereby incorporated by reference in these comments.

In order to make these comments most useful and to best clarify AHPA's intended meanings herein, in several places within these comments AHPA has provided suggested revisions to specific language within the draft guidance. In each such case, AHPA identifies language recommended for deletion with ~~strikethrough~~ text, and language recommended for addition in **bold underline font**.

Also, when these comments use the term "question" to refer to one or more specific question within the draft comments, the term is intended to include both the question or questions posed as well as the answer or answers provided.

Comment to "I. Introduction"

The Introduction to the draft guidance twice uses the term "premarket safety notifications," a term that does not appear elsewhere in this document or in either the Act or its implementing regulations. AHPA believes that there is no additional clarity in the draft guidance by the inclusion of this term, and therefore requests that FDA replace this term with the term "premarket notification," as is used in 21 CFR 190.6, or the term "new dietary ingredient notification" (short form "NDI notification"), as is used in section 113 of FSMA.

Comments to "II. Background"

The section of the draft guidance titled "Background" includes a list of the information that must be submitted with each NDI notification to comply with 21 CFR 190.6. This list, however, does not use precisely the same language as is found in the Act, in 21 CFR 190.6 itself, or in the preamble to the final rule wherein this regulation was promulgated.[4] Certain differences between the language of the Act and the language previously used by FDA in describing this rule and within this rule, on the one hand, and the language now used in the draft guidance on the other, are such that a person reading only the draft guidance could draw erroneous conclusions; for example, that all NDIs require a NDI notification; that a NDI notification can only be submitted for a single specifically described dietary supplement in which a NDI will be used; or that the manufacturer of every dietary supplement that contains a NDI must file a separate

[4] 69 FR 49886.

notification, even if its dietary supplement products were described in a notification submitted by the NDI's manufacturer or distributor.

AHPA therefore requests that this list and the immediately preceding paragraph be rewritten to include certain of the exact language in 21 CFR 190.6 and in the Federal Register preamble promulgating that regulation, and additional clarifications to conform to the language of the Act, as follows:

> To assist industry in complying with DSHEA, FDA issued a regulation in 21 CFR 190.6 (section 190.6 or the NDI regulation) to implement the FD&C Act's premarket notification requirements for dietary supplements that contain ~~a~~ **those** NDI**s which require premarket notifications** (62 FR 49886; September 23, 1997). **The Act stipulates that when a dietary supplement contains new dietary ingredients *other than* NDIs which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered, then a premarket notification to FDA is required.** The NDI regulation specifies the information the manufacturer or distributor **of the dietary ingredient or of the dietary supplement containing the NDI** must include in its premarket NDI notification (21 CFR 190.6(b)):
>
> - The name and complete address of the manufacturer or distributor **of the new dietary ingredient or of dietary supplement(s) that contains a new dietary ingredient,** 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 **specific** description of ~~the~~ **a** dietary supplement **or a general description of a range of dietary supplements** that contain~~s~~ **or will contain** the NDI, including:
>   - the level of the NDI in the dietary supplement**(s)**, and
>   - the conditions of use recommended or suggested in the labeling of the dietary supplement**(s) containing the NDI**, or if no conditions of use are recommended or suggested in the supplement's labeling, the ordinary conditions of use of the supplement**(s)**.
> - The history of use or other evidence of safety**, including any citation to published articles,** ~~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~~ **which is the basis on which the manufacturer or distributor has concluded that a NDI will reasonably be expected to be safe in one or more dietary supplements**.

AHPA also notes that 21 CFR 190.6 requires that the signature on a NDI notification be that of a person "designated by the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient." This is inconsistent with the Act and is not

possible when a NDI notification is submitted by the manufacturer or distributor of a new dietary ingredient that it intends to market to several manufacturers or distributors of dietary supplements, none of whom may be known to the ingredient company at the time the notification is submitted. AHPA notes also that FDA has accepted many NDI notifications submitted by the manufacturer or distributor of a NDI and signed by a person representing that ingredient company, such that FDA's actual practice differs from the regulation as written. AHPA also notes that Question V.A.17 correctly describes the person who should sign a notification as "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." AHPA therefore requests that the last bullet point in the list of regulatory requirements included in the Background section of the draft guidance be revised as follows:

- The signature of a person ~~authorized~~ **designated** by the manufacturer or distributor **of the new dietary ingredient or the dietary supplement that contains a new dietary ingredient** ~~to sign the notification on its behalf~~.

Comments to "III. Scope of the Guidance"

In the section of the draft guidance titled Scope of the Guidance FDA states that its goal in promulgating 21 CFR 190.6 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" (emphasis added).

This sentence misstates both the Act and what FDA stated in promulgating 21 CFR 190.6 and essentially attempts to rewrite history.

The Act states that a dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of two criteria:

1. The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or,
2. There is a 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, and the manufacturer or distributor provides FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

In promulgating the regulation implementing DSHEA, FDA stated:

> The Food and Drug Administration (FDA) is establishing the procedure by which a manufacturer or distributor of dietary supplements or of a new dietary ingredient is to

> submit under [the Act] the information on which it has concluded that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe. FDA is issuing this regulation to enable industry to comply with the requirements of [DSHEA]. 62 FR 49886.

The draft guidance should accurately reflect the language and intent of the law and the regulation, which is that the manufacturer or distributor – not FDA – bears the responsibility to determine the status of a NDI and the reasonable expectation of safety of supplements containing a NDI.

This discussion of the scope of the draft guidance also includes a statement that FDA has received approximately 700 NDI notifications since 1994 and estimates that there are 55,600 dietary supplements in the market. AHPA sees no relevance between these two numbers, as there is nothing in the Act or implementing regulations – or even in the draft guidance – that suggests that a NDI notification is required for every marketed dietary supplement. The number of dietary supplements in the marketplace thus does not predict the number of NDI notifications that should have been submitted since 1994.

This section also presents an even more irrelevant comment on the presence in the marketplace of products marketed as dietary supplements but that contain undeclared active ingredients. AHPA acknowledges the existence of illegal products masquerading as dietary supplements but which are spiked with undeclared and illicit drug ingredients or controlled substances, and AHPA has worked closely with FDA to address this problem.[5] But the NDI notification provisions have no bearing on the presence of such products in the marketplace and neither this regulation nor the draft guidance do anything to prevent or dissuade the unscrupulous from engaging in this international[6] criminal activity.

If FDA believes that the draft guidance should provide information that may actually be relevant to the number of dietary supplements in the marketplace, rather than implying that this data might have some relation to the number of NDI notifications or alluding to criminal practices the agency could instead acknowledge the extremely low number of

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[5] For example, AHPA and other associations appeared with Dr. Joshua Sharfstein, former FDA Principal Deputy Commissioner, at a press conference on December 15, 2010 where Dr. Sharfstein noted that FDA "is working with the dietary supplement industry's trade organization" to combat drug-spiking. See FDA Media Call: Tainted Products Marketed as Dietary Supplements; accessed on November 26, 2011 at http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM247280.pdf.

[6] Health agencies in Canada, Europe, Asia, Australia and the Middle East have used their law enforcement authority to remove such illegal products from those markets in the past several years. Examples can be seen at the AHPA maintained website, KeepSupplementsClean.org (http://keepsupplementsclean.org/intl_enforcement.html).

adverse event reports (AERs) observed in association with dietary supplements.[7] Fewer than 3,700 AERs have been reported to FDA as associated with dietary supplement use during the three year period from 2008-2010.[8] This calculates to just over 1,200 AERs each year and includes serious and non-serious adverse experiences. For the sake of comparison, adverse events reported for drugs ranged from 526,500 to 758,900 per year during the same timeframe.[9,10] While it is unknown how many of the 55,600 dietary supplements in the marketplace include one or more NDIs, the extremely low level of reported adverse events suggests that manufacturers and distributors of dietary supplements are doing an excellent job of ensuring there is in fact a reasonable expectation of safety for all the products they make or sell, including those that include a NDI.

When DSHEA was passed in 1994 the Congress found that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare." This is equally true today that it was 17 years ago. The Congress also found in 1994 that the federal government "should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products … to consumers." This admonition is still relevant, and FDA should not impose new and significant regulatory burdens on dietary supplements, a regulatory category that has established an excellent safety record.

Also included in this same paragraph is a statement that one purpose of the draft guidance is to "improve … the quantity of NDI notifications." The other purposes stated

[7] Since the end of 2007, all serious adverse events received by dietary supplement companies have been required to be submitted to FDA in accordance with the Dietary Supplement and Nonprescription Drug Consumer Protection Act. Some supplement companies also report non-serious adverse events to FDA and the agency also receives adverse event reports from consumers and medical professionals.

[8] This data was obtained from FDA by AHPA through a series of requests submitted under the Freedom of Information Act.

[9] Drug reporting data accessed December 1, 2011 at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm.

[10] FDA has from time to time cited a study that was "[b]ased on data for drug and vaccine reporting rates in other studies," and that concluded that for dietary supplements, illnesses that are reported "represent approximately 1 percent of total illnesses." 72 FR 34752 at 34922, June 25, 2007. This study (Walker AM. March 9, 2000. The relation between voluntary notification and material risk in dietary supplement safety) was published prior to the passage of Public Law 109-462 which mandated that serious adverse event reports (AERs) be submitted to FDA; AHPA is unaware of any updated analysis of the portion of supplement-associated AERs. In drawing the "1 percent" conclusion, Walker also concluded, however, that "…the rate of reporting of drug and vaccine adverse events, even in countries where there are well-advertised and effective systems for identifying events, is very low. *It is probably no more than one percent*, except when the event is readily recognized, severe, and clearly related to the exposure in the mind of the treating physician" (emphasis added). Any use of this single reference is thus apparently also applicable to estimating the portion of drug adverse events that are reported.

here are (1) to give manufacturers and distributors of NDIs information and recommendations to help them decide when a NDI notification is necessary, and (2) to improve the quality NDI notifications."

AHPA agrees that it may be useful for FDA to provide guidance on when a NDI notification is required to be filed, so long as such guidance is accurate and based on sound legal interpretations of the law. AHPA also agrees that FDA guidance may be useful to improve the quality of NDI notifications. It is unclear what FDA means by "improve…the quantity" of submissions; one possible reading – arguably the most likely reading – is that FDA means "increase…the quantity" of NDI notifications. AHPA does not agree that one purpose of the guidance should be to increase the number of NDI notifications, as FDA should only be interested in obtaining all required notifications, and should have no interest in receiving notifications that are not required. In addition, there is nothing in section 113(b) of FSMA that suggests that Congress intended this guidance to have as one purpose an increase in the number of NDI notifications.

Combining all of the points raised in the previous paragraphs, AHPA recommends that the first paragraphs of this section be rewritten as follows:

> FDA's goal in promulgating the NDI regulation was to **enable industry to comply with DSHEA by establishing when, and the procedure by which a manufacturer or distributor of dietary supplements or of a new dietary ingredient is to submit the information that is the basis on which it has concluded that** ~~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. Additionally, the~~ **The** Institute of Medicine **(IOM)** has estimated that 1,000 new dietary supplements are introduced to the market each year. **FDA does not know how many of the current dietary supplement products currently in the market or introduced each year may include a NDI, and notes that not all NDIs require premarket notification.** ~~These~~ **The IOM** figure~~s, coupled with recent concern by both the agency and~~

~~industry regarding the presence of undeclared active ingredients in products marketed as dietary supplements,~~ **may nonetheless** highlight the necessity for marketers of dietary supplements to **be aware of the laws and regulations for** submit**ting** NDI notifications **whenever these are required,** as **this is** 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 **or for which safety is not adequately documented. FDA also notes, however, that the number of adverse events reported in association with dietary supplement consumption is extremely low, which suggests that manufacturers and distributors of dietary supplements that contain a NDI are doing an excellent job of ensuring such products have a reasonable expectation of safety.**

The draft guidance has poorly defined the terms "component" and "constituent" and is inconsistent in its use of the former

AHPA notes that the word "component" is used 38 times in the text of the draft guidance. The draft guidance also provides a specific definition of the word in section VII, as follows:

> 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).

The "below" definition of "constituent" is given in the draft guidance as:

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

The word "component" is also used within the definition given in the draft guidance for the term "vitamin" ("An organic substance that is a minor *component* of foods…" (emphasis added)).

AHPA has observed that the use of the term "component" in the draft guidance is inconsistent and does not always have the same meaning. The term is sometimes used in a manner that has the meaning normally given to the term "constituent," as is the case in its usage in the definition for "vitamin." At other times the term's meaning approximates the meaning of the word "ingredient," for example, as used in Question VI.A.3: "For example, you might establish a specification to limit mold contamination of a *component* used to make your NDI (e.g., aflatoxin in corn)" (emphasis added). In this example, the component is corn, that is, the source ingredient of a NDI. Finally, the term "component" is also used in the draft guidance with the same meaning as is most familiar to the dietary supplement industry, which is as the term is defined in the current good manufacturing rule for dietary supplement operations, as follows:

> Component means any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Component includes dietary ingredients (as described in section 201(ff) of the act) and other ingredients.[11]

AHPA notes that the word "component" is used quite broadly throughout various other parts of Title 21 of the CFR. As far as AHPA is aware, however, the word is defined in regulation only in 21 CFR 111. It is almost certain that this definition and usage is the meaning of the word that is most familiar to the dietary supplement industry.

AHPA notes, however, that the word "component" as used in the draft guidance applies in some cases to dietary supplements and in others to conventional foods. This is consistent with the definition of food as it appears in Section 201(f) as "The term 'food' means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." AHPA therefore recommends that FDA replace the definition of the word "component" in the draft guidance as follows:

> Component. Any ingredient or other material used in the manufacture of a food, including a dietary supplement, including those that may not appear in the finished batch of the food or dietary supplement, and including dietary ingredients used in dietary supplements.

AHPA further recommends that the word "component" only be used in the draft guidance where it has the above meaning, and that the word be replaced with the word "constituent" where that is the intended meaning. AHPA further recommends that the word "constituent" be redefined as follows:

> Constituent. A chemical substance that is part of a food, food ingredient, dietary ingredient, or dietary supplement.

For purposes of these comments whenever these terms are used herein they have the meaning given in these revised definitions.

Traditional food preparation processes applied to pre-DSHEA ingredients do not produce NDIs

Section 413 (a)(1) of the Act includes the term "chemically altered" in identifying one of the two requirements that can be met to ensure that a dietary supplement that contains a NDI is not adulterated, such that a supplement is not adulterated if is contains "only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered." The draft guidance focuses a great deal of attention on the question of whether and when a dietary

[11] 21 CFR 111.3.

ingredient or article of food has been “chemically altered” and/or whether or when the chemical composition of such an ingredient has been changed, and how these changes may affect the regulatory status of the material.

The draft guidance seems to equate any change in the chemical bonds in an ingredient with “chemical alteration” (see for example Question IV.B.4), and seems to consider that any alteration in the chemical composition of an ingredient is chemical alteration for purposes of section 413(a), and so is likely to cause a pre-DSHEA ingredient to become a NDI (see for example Question IV.A.11).

AHPA agrees with certain aspects of FDA’s analysis but does not agree with FDA’s apparent view that any change in the chemical composition of an ingredient means that the ingredient has been chemically altered, as the term is used in the Act.

As discussed elsewhere in these comments, it is AHPA’s position that any substance that is described as a dietary ingredient in any of the paragraphs in section 201(ff)(1) and that was used as an ingredient in any food product, regardless of form, prior to October 15, 1994 is a pre-DSHEA dietary ingredient, and has been present in the food supply as an article used for food. AHPA also believes that any ingredient in the food supply prior to October 15, 1994 has historically been subjected to a wide range of traditional food preparation processes. Food ingredients have been prepared in any number of ways throughout history, using the materials and technology historically available. AHPA believes that the application of any traditional food preparation process to any food or dietary ingredient in the food supply produces a material which is itself a food or dietary ingredient in the food supply, and that application of any traditional food preparation process to any pre-DSHEA ingredient produces a material which is itself a pre-DSHEA ingredient .

A Statement of Agreement appearing in the Congressional Record on October 7, 1994 states that in the context of the Act, “the term ‘chemically altered’ does not include the following physical modifications: minor loss of volatile components, dehydration, lyophlization [sic], milling, tincture or solution in water, slurry, powder, or solid in suspension.” AHPA believes that this list is not intended to be all-inclusive, but merely provides examples of some of the physical modifications that do not result in an ingredient being chemically altered. AHPA also believes that other physical modifications to an ingredient accomplished through application of a physical process to the ingredient, especially such as those which are physically within the technological limits historically operating in a food kitchen (e.g., application of heat or cold, size reduction, dissolution, dispersion, emulsification, mixing or combining, etc.), should also be recognized as outside of the meaning of chemical alteration.

AHPA notes that the application of any of the physical modifications identified in the Congressional Statement on an ingredient cause changes in its chemical composition.

Use of other traditional food preparation processes similarly change the chemical composition of the original ingredient. For example, chemical bonds are extensively formed and broken during normal cooking processes; fermentation in the making of cheese, wine, or pickles involves microbiological transformation of numerous chemical constituents; and traditional extraction processes, in which a broad spectrum of soluble constituents of a food ingredient are extracted into a food liquid while insoluble constituents such as cellulose or fibrin are left behind, often naturally concentrate the soluble constituents by tens of times and also cause various chemical bond changes which naturally result from the extraction process.

Also, dehydration is often accomplished through the application of heat and/or vacuum, as is the making of a tincture or powder; lyophilization is certainly accomplished through application of cold under vacuum; and production of a slurry involves the physical processes of mixing or blending ingredients under various conditions. These are all physical processes historically used in food preparation[12] and most if not all of them result in significant changes in the chemical composition of the raw ingredients to which these processes are applied. This does not, however, render the resulting materials dangerous or unsafe, nor does it mean the safety profile of the resulting materials is unknown; nor is there any evidence that Congress intended that cooking or otherwise preparing a food ingredient (consistent with historical food preparation processes, as described further below) would raise any special safety concerns, or would transform a pre-DSHEA ingredient into a NDI. On the contrary, AHPA believes that the application of traditional food preparation processes to any pre-DSHEA ingredient, including any food or food ingredient, produces an ingredient that is itself a pre-DSHEA ingredient and thus does not in itself change the regulatory status of the material produced.

AHPA further notes that such non-specific and/or non-selective changes in chemical bonds and overall chemical composition as a result of traditional food preparation processes are a very different matter from the types of targeted, intentional chemical changes as are accomplished through the application of modern industrial chemical technology to a material (i.e., through the use of specialized reagents, solvents, columns, etc.) to intentionally effect a specific change in chemical bonds or in overall chemical composition.

Furthermore, AHPA notes that preparation of a tincture[13] (or other food, such as soup or salad dressing) in water and/or ethanol (as well as other traditional food liquids such as

[12] AHPA notes that the use of vacuum to prepare food dates back to at least 1799, when it was described by Sir Benjamin Thompson, and has been used in American food preparation since at least the 1960s.

[13] See below AHPA's separate discussion of solvents other than ethanol and water that may be used in the manufacture of tinctures, as well as a proposed revision to the definition of this word.

vinegar or milk) inevitably causes significant changes to the chemical composition of the ingredient through hydrolysis (in which water is added to a molecule, resulting in the breaking of some of the original chemical bonds in the molecule), esterification (in which an alcohol reacts with a carboxylic acid group to form an ester), transesterification (in which an ester is replaced by a different ester group donated by the alcohol), and various oxidation-reduction reactions (in which hydrogen or oxygen are added to or removed from a molecule due to exposure to atmospheric oxygen as well as to naturally occurring catalysts such as ascorbic acid or iron). AHPA can identify no logical or scientific basis to support the idea that some of these common food preparation processes result in "chemical alteration" of a food while others do not: They all equally result in the alteration of many chemical bonds and various changes in the chemical composition.

AHPA believes it is crucially important that application of any traditional food preparation process, including but not limited to the several examples identified in the Congressional Statement of Agreement, to conventional foods and dietary ingredients be explicitly and clearly acknowledged as processes which "change in the chemical composition" of the processed material but which do not "chemically alter" the ingredient for purposes of section 413(a)(1), and furthermore do not create NDIs in the first place.

To summarize, AHPA believes that any ingredient which is prepared from ingredients in the U.S. food supply prior to October 15, 1994 using traditional food preparation processes, is grandfathered as a pre-DSHEA dietary ingredient.

Further, AHPA is aware that certain non-traditional food preparation processes yield dietary ingredients which are chemically the same as those prepared in some traditional manner. For example, certain supercritical carbon dioxide extracts of botanicals are chemically indistinguishable from steam distillates of the same botanical.[14,15] AHPA believes that a dietary ingredient prepared by non-traditional food preparation processes may be a NDI, but if it is chemically (and microbiologically, in the case of

[14] See for example: Caredda A, Morongiu B, Porcedda S, Soro C. Supercritical carbon dioxide extraction and characterization of Laurus nobilis essential oil. March 2002. *J Agric Food Chem* 50(6):1492-6; and Morongiu B, Piras A, Porcedda S. Comparative analysis of the oil and supercritical CO2 extract of Elettaria cardamomum (L.) Maton. October 2004. *J Agric Food Chem* 50(6):6278-82.

[15] AHPA notes further that supercritical carbon dioxide, while not a traditional extraction solvent, does not pose many of the same concerns as other non-traditional extraction solvents: It typically does not modify covalent bonds in the extracted constituents and does not leave any solvent residues. AHPA further notes that certain types of supercritical fluid extracts may have been marketed in the U.S. for food use prior to October 15, 1994.

fermentations) indistinguishable from an existing food preparation or pre-DSHEA dietary ingredient, then it does not require a notification.

As a result of the above, AHPA recommends the addition of the following question:

> New Question: **Is a dietary ingredient a NDI if it is produced using traditional food preparation procedures from pre-DSHEA ingredients and/or other food ingredients?**
>
> **No. A dietary ingredient that meets the definition of 201(ff), including an ingredient that ingredient which is characterized by its constituent content or is a constituent, is not a NDI if it is produced through the use of any traditional food preparation process.**
>
> **A traditional food preparation process involves some or all of the following steps (not necessarily in any particular order):**
>
> - **Obtaining suitable crude botanical or other food material.**
> - **Drying, lyophilization, or other removal of moisture or other solvents.**
> - **Reducing the size as necessary, e.g., by milling, chopping, cutting, or grinding.**
> - **Fermentation or other microbiological processes alone or in combination with other food ingredients, using wild inoculations or specific, traditionally cultivated strains of microorganisms.**
> - **Heating, cooking, baking, frying, pressure cooking, roasting, grilling, steaming, smoking, cooling, refrigerating, freezing, or otherwise applying wet or dry heat or cold in any manner and in any combination with other food ingredients, at suitable conditions of temperature, pressure, and agitation.**
> - **Extraction by soaking, steeping, infusing, macerating, percolating, or steaming in or with water; wine, liquor, ethanol, or a hydroethanolic mixture; vinegar; glycerin; honey; a food oil; or other suitable liquid which is itself a food, at suitable conditions of temperature, pressure, and agitation.**
> - **Straining, filtering, pressing, or squeezing.**
> - **Peeling.**
> - **Coating.**
> - **Curing.**
> - **Distilling or rectifying.**
> - **Evaporating.**
> - **Mixing, combining, or emulsifying with other food ingredients by stirring, shaking, or other means.**
>
> **On the other hand, if the constituent has been synthesized; concentrated or chemically altered in a manner other than through traditional food preparation methods (as discussed above); or if its preparation omits steps traditionally used to detoxify a particular food, then it is an NDI. If the manufacture of a dietary**

ingredient includes non-traditional process steps, or uses non-traditional extraction solvents or fermentation inoculates, then the ingredient is a NDI. This applies especially to non-traditional process steps intended to concentrate a particular constituent or class of constituents, or to otherwise alter the chemical or microbiological composition of the food or ingredient in a manner inconsistent with traditional preparations of the material.

Furthermore, if the manufacture of a dietary ingredient omits steps traditionally used for a particular food ingredient which serve to detoxify the ingredient, then the dietary ingredient is a NDI. For example, potatoes are traditionally cooked to remove toxic glycosides; a dietary ingredient prepared from potatoes which did not include an appropriate cooking step would therefore be a NDI.

AHPA also recommends that certain other questions in the draft be revised to take into account this discussion on traditional food preparation processes. For example, the draft guidance states in Question IV.A.11 that if a change that is made in a manufacturing process alters the chemical composition or structure of a pre-DSHEA dietary ingredient the resulting compound is probably a NDI and a notification to FDA would be required.

It is up to the manufacturer or distributor of a dietary ingredient, including a pre-DSHEA dietary ingredient or a NDI that has previously been the subject of a NDI notification, to determine whether a change in a manufacturing process alters the chemical composition or chemical structure of the ingredient. If the manufacturer concludes that neither is altered, the manufacturer is free to market that ingredient.

Based on the fact that traditional food preparation processes applied to a pre-DSHEA dietary ingredient cannot result in a new dietary ingredient, and that non-traditional food preparation processes may yield an ingredient which is indistinguishable from the corresponding traditionally-prepared ingredient, AHPA believes the answer to question IV.A.11 should be revised to reflect this view. Note that this revision also suggests modification to the clause that directs firms to consult with FDA. AHPA does not believe that the draft guidance or resulting final guidance should recommend that companies consult with FDA on questions related to NDIs or NDI notification, unless this recommendation is extended to also recommend consultation with qualified counsel or consultants and unless FDA has the staff resources available to handle a large influx of questions on a daily basis.[16]

[16] This position is relevant not only to the discussion of a change in manufacturing process but to each time that the agency suggests that a firm consult with FDA on any matter relevant to NDIs. AHPA therefore requests that the same suggested language revision that follows here be applied also in Questions IV.A.12 and IV.B.2.a.

Question IV.A.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?

~~Yes~~ **It depends**. 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~~ **introduce only steps which are traditional food preparation processes as listed in the response to [new question #] the resultant ingredient is not a NDI. But if the changes introduce steps that are not traditional food preparation processes, or if the changes omit a step traditionally used to detoxify the particular ingredient for food use, then the ingredient manufactured by the revised manufacturing process is** 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.~~ **For example, using a solvent other than a food liquid or a hydroethanolic mixture to prepare an extract from a pre-DSHEA dietary ingredient creates a NDI. A notification to FDA is required for such an NDI unless it is chemically (and for fermentations, microbiologically) indistinguishable from an existing food, food ingredient, or pre-DSHEA dietary ingredient.**

Firms planning a manufacturing change are encouraged to consult with FDA **and/or with qualified counsel or technical consultants with expertise in NDI matters** on any questions as to whether such a change would create a NDI.

In addition to the above revised response to question IV.A.11, AHPA also notes that FDA uses here the phrase “chemical composition or structure of the ingredient.” It is not clear to AHPA what FDA means by the word “structure” but assumes FDA means “chemical structure”, as opposed to physical structures which might be altered by, say drying or grinding. AHPA therefore recommends that FDA be more specific with any future use of this phrase.

AHPA also notes that the discussion in Question IV.A.11 of “changes that alter the composition of the materials used to make the ingredient” and the example “using a different part of the plant” are confusing in relation to the discussion of manufacturing process changes; AHPA recommends this be addressed as a separate new question, as follows:

New question: **If I make changes that alter the composition of the raw materials used to make a pre-DSHEA dietary ingredient, does that make the ingredient produced from the altered materials a NDI?**

It depends. If the changes in your raw materials introduce materials which are not approved foods, food ingredients, or pre-DSHEA dietary ingredients then the

produced ingredient would be a NDI. For example, if the root (and only the root) of a particular plant is used to produce a pre-DSHEA extract of the root of the plant, and you change the raw material to use the leaves of the same plant, then the new ingredient, as an extract of the leaf of the plant, is a NDI. But if the changes to the raw materials are the result only of traditional food preparation processes then the produced ingredient is not a NDI.

Based on the views expressed here that traditional food preparation processes are not included in "chemical alteration," AHPA believes the answer to question IV.B.3 should be revised to read:

> Question IV.B.3: What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not ~~result in~~ chemical**ly** alter~~ation~~ **the ingredient for purposes of determining whether it is a NDI and whether a notification is required**?
>
> 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. **In addition, any traditional food preparation process as described in [new question #] does not chemically alter the ingredient.** Examples:
>
> - Leaves or roots of a plant **which are** consumed as conventional food (e.g., broccoli or carrots) are dried and ground for sale in powder form.
>
> *[AHPA comments here that inclusion of the words "which are" is important, otherwise the sentence can be read to mean that if a plant is consumed as a conventional food, then any part of that plant can be used in a dietary ingredient without causing a chemical alteration; which is not, AHPA believes, what FDA intends to say.]*
> - 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.

In addition, AHPA believes the answer to question IV.B.4 should be revised to read:

> Question IV.B.4: What are examples of processes that chemically alter an article of food present in the food supply to create a ~~dietary ingredient~~ **NDI**?
>
> **Any process which is a traditional food preparation process as defined in question IV.B.4 would not produce a NDI from an article in the food supply. Any process which is *not* a traditional food preparation process as defined in question IV.B.4; or which uses non-traditional or non-food solvents, microbial strains, or reagents; or which omits a step traditionally used to detoxify the particular ingredient for food use, *does* produce a NDI.** 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 dissolve in water (e.g., creation of a soluble salt) or during ingestion~~ **in the ingredient through the use of non-food chemicals or reagents, such as methyl bromide, sulfuric acid, or sodium hydroxide**,

- ~~Removal~~ **Concentration** of some ~~components~~ **constituents** of a tincture or solution in water **using processes other than traditional food preparation processes** (e.g., by chromatography, ~~distillation~~ or **chemically selective** membrane filtration)~~,~~ ~~which changes the chemical composition of the mixture~~.

  [AHPA comments here that "distillation" is a traditional food preparation processes, and membrane filters are commonly used in the manufacture of extracts to separate the crude botanical from the miscella.]
- [NOTE: AHPA's suggestions for revision of the point on use of solvents are provided at a separate part of these comments.]
- 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~~ **whose use is normally restricted to raw form**.

  [AHPA comments here that all historically-used food ingredients have been baked or cooked at some point, so the default presumption should be that baking or cooking of any ingredient does not yield a new ingredient. Only in cases where the use of the existing ingredient is affirmatively restricted to use in its raw form, should cooking or baking cause the ingredient to be "new."]
- Changing the manufacturing method for an ingredient such that the ~~chemical composition is significantly different~~ **revised manufacturing method includes steps which are not traditional food preparation processes** (e.g. ~~changes that alter the composition of materials used to make the ingredient~~, use of a ~~different~~ **non-food** solvent, use of a chromatographic matrix instead of a passive filter).
- **Changing the raw materials used in the manufacture of the ingredient to include raw materials which are not foods, food ingredients, food additives, or pre-DSHEA dietary ingredients (e.g., use of plant part other than the traditionally used part).**
- Application of nanotechnology to an ingredient ~~that results in new or altered chemical properties of the ingredient~~ **not previously sold in nano-scale form**.

  [AHPA comments here that it is not clear how the application of nanotechnology results in "new or altered chemical properties" of the ingredient, or even what FDA means by "chemical properties." AHPA agrees however that use of nanotechnology is not within the scope of traditional food preparation processes, and hence its use likely results in an ingredient which is "new."]
- Changing agricultural or fermentation conditions to alter the chemical composition of the ingredient, such as by ~~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.

  [AHPA comments here that sprouted garlic is routinely used as a food ingredient in the U.S. in home kitchens and Asian restaurants as well as potentially elsewhere.]

- 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~~).

  [AHPA comments here as follows: The growth of mushroom mycelium for food use is a traditional food preparation process. It has been FDA policy since 1976 that mushroom mycelium is suitable for food use so long as it is grown in acceptable media (i.e., media consisting of ingredients suitable for food use) and so long as the material is properly labeled to indicate use of mycelium.[17] *Therefore, there should be no presumption that mushroom mycelia are "likely" to be chemically altered. The only circumstance in which they would be chemically altered is if the fermentation medium is adjusted for the purpose of changing the chemical composition of the ingredient, as in the selenium yeast example cited above.]*

The draft guidance improperly narrows the range of "pre-DSHEA dietary ingredients"

The draft guidance takes several positions that, when read together, imply that pre-DSHEA dietary ingredients are NDIs. The draft guidance does this by improperly excluding ingredients marketed in or as conventional foods prior to October 15, 1994 (also referred to hereinafter as "pre-DSHEA dietary ingredients") as pre-DSHEA dietary ingredients; by inappropriately defining "marketing;" and by failing to recognize that ingredients made from pre-DSHEA dietary ingredients through traditional food preparation processes are still pre-DSHEA dietary ingredients. These positions by FDA are clearly inconsistent with the Act.

The Act defines a new dietary ingredient as follows:

> "…the term 'new dietary ingredient' means a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994." Section 413(d) of the Act.

But the Act does not make any reference in this definition to the food form or product category in which a dietary ingredient must have been marketed in order to be excluded from the term "new dietary ingredient." In other words, section 413(d) does **NOT** say the following, where the bold underlined words are added here for discussion:

[17] CPG section 585.525.

> "The term 'new dietary ingredient' means a dietary ingredient that was not marketed in the United States before October 15, 1994 **in a product intended for ingestion in a tablet, capsule, powder, softgel, gelcap, or liquid form and was not represented as a conventional food or for use as a sole item of a meal or the diet**; and does not include any dietary ingredient which was marketed in the United States before October 15, 1994, **so long as that ingredient was in a product intended for ingestion in a tablet, capsule, powder, softgel, gelcap, or liquid form and is not represented as a conventional food or for use as a sole item of a meal or the diet**." [18]

Yet the draft guidance is written in a manner that assumes that the food form of the product or products that contained a dietary ingredient that was, in fact, marketed in the U.S. prior to October 15, 1994, is a factor – and in fact a prerequisite – in determining whether an ingredient that was marketed in the U.S. before DSHEA was passed is now a NDI. The draft guidance thus proposes to add an additional requirement not found in section 413(d) by declaring that the dietary ingredient must have been marketed "in or as a dietary supplement, or for use in dietary supplements." But that is not what the law says, and there is nothing in the least unclear about what the words "does not include" mean in section 413(d) of the Act. The draft guidance should therefore be revised to accurately reflect the law.

Furthermore, there was no widely used definition of dietary supplement prior to the passage of DSHEA with which the term "dietary ingredient" as used in section 413(d) can be aligned. FDA had variously attempted to regulate vitamins, minerals, amino acids and botanicals as either drugs or food additives. The fact that FDA in the period preceding the passage of DSHEA attempted to regulate ingredients such as black currant oil as food additives to be added to conventional foods supports the conclusion that the marketing of ingredients in conventional foods pre-DSHEA satisfies the prior marketing standard of 413(d).

It is completely contrary to principles of statutory construction to assume that Congress intended to limit the "new dietary ingredient" definition to ingredients included in "dietary supplements" when prior to DSHEA there was no "dietary supplement" category. Congress enacted DSHEA in order to secure consumer access to dietary ingredients on the market at the time of its passage. By making clear that dietary supplements are a class of food under the Act, Congress clearly intended that food ingredients then on the

[18] The language cited here references section 411(c) of the Act, in which restrictions were established on the forms and representation of products which would be marketed (after enactment of the Act) as dietary supplements.

market could be dietary ingredients and defined what the properties of those ingredients must be, e.g., a vitamin, a mineral, an herb or other botanical, etc.

Furthermore, AHPA notes that foods and food ingredients exist in the marketplace not only in grocery stores, health food stores, convenience stores, etc. but also in restaurants, catering trucks, ballparks, etc.; therefore, documentation related to the operation of the latter businesses also qualifies as evidence of marketing (e.g., menus). Finally, AHPA believes it is reasonable to suppose that every food or food ingredient has at some point appeared for sale at a restaurant and thereby has been in commerce, whether or not documentation of that sale is readily available. AHPA therefore believes that any evidence of the food or food ingredient being present in the food supply prior to October 15, 1994 serves to document the material as a pre-DSHEA ingredient.

Also relevant here is the fact that the draft guidance defines “marketing” as the term applies to ingredients in the U.S. prior to October 15, 1994 in a manner that excludes use of an ingredient in conventional foods. The Congress did not include any language that suggested such limitation on the meaning of the term “marketing” for this application, even though elsewhere in DSHEA the term “conventional food” is included as a limitation to the definition of a dietary supplement. Clearly then if the Congress also intended pre-DSHEA marketing of a dietary ingredient to exclude use in conventional foods the Congress would have said so.

Based on the preceding paragraphs it must be concluded that DSHEA did not mean the phrase “marketed in the United States before October 15, 1994” to mean “marketed in the United States *as a dietary ingredient as defined herein* before October 15, 1994,” nor did it mean “marketed in the United States *as an ingredient in a dietary supplement* before October 15, 1994.” Rather, the phrase meant exactly what it said and all that needs to be done to ascertain whether an ingredient that fits the definition of 21 U.S.C. 321 (ff)(1) is “new” or “old” is to determine whether that ingredient was “marketed in the United States before October 15, 1994,” and that the context of such marketing was dietary, that is, for ingestion. It is thus apparent that any substance that is described as a dietary ingredient in any of the paragraphs in section 201(ff)(1) and that was used as an ingredient in any food product prior to October 15, 1994, including a conventional food product as well as a food product intended for ingestion in the form of a tablet, capsule, powder, softgel, gelcap, or liquid, or any other form that is in conformity with section 411(c) of the Act, is a pre-DSHEA dietary ingredient.

As is also discussed in these comments, it is AHPA’s view that the application of any traditional food preparation process to any pre-DSHEA dietary ingredient produces a material which is itself a pre-DSHEA ingredient. AHPA also restates that some confusion exists in the draft guidance due to its unclear or inconsistent use of the words “component” and “constituent.” With regard to the present section of these comments, AHPA believes that FDA meant “constituent” where it stated “component” in Question

IV.A.4, and has provided comments below as though the question pertains to constituents as AHPA has proposed that term to be redefined.

In order to address the issues raised here, the draft guidance should be revised in several areas, including the following:

> Question IV.A.3: Is an ingredient that was used to make a conventional food marketed before October 15, 1994 a NDI if the ingredient was not **also** ~~a dietary ingredient~~ marketed in the U.S. before October 15, 1994 **as or in, or for use in, a products for ingestion in the form of a dietary supplement as established by DSHEA**?
>
> ~~Yes~~**No**. The use of an ingredient **(other than an ingredient used solely as a food additive or color additive which is not a dietary ingredient as defined in 201(ff)(1) of the Act)** in a conventional food before October 15, 1994 ~~does not determine whether the ingredient is a NDI~~ **constitutes marketing of a dietary ingredient** ~~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. **The mere presence of a substance as an ingredient of a food that was marketed before October 15, 1994 establishes that the substance was marketed as a dietary ingredient before that date, so long as the ingredient meets the definition of a dietary ingredient.** Therefore, an ingredient that was used to make a conventional food before October 15, 1994 is **not** 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.)
>
> *[NOTE: With the above revisions the two subquestions that follow – IV.A.3.a and IV.A.3.b – are irrelevant and should be stricken in their entirety.]*
>
> Question IV.A.4: Is a substance that was a ~~component~~ **constituent** of a conventional food marketed before October 15, 1994, a NDI if the ~~component~~ **constituent** was not a dietary ingredient **in a product** marketed in the U.S. before October 15, 1994 **and intended for ingestion in a form described in section 411(c)(1)(B)**?
>
> ~~Yes, assuming the component meets the definition of a dietary ingredient.~~ **It depends.** The mere presence of a substance as a ~~component~~ **constituent** of a conventional food that was marketed before October 15, 1994 ~~does not~~ establish**es** 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) **it is not a NDI irrespective of whether it** ~~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~~. **In addition, a constituent that is produced from a pre-DSHEA dietary ingredient or from a food ingredient by a traditional food preparation process 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**, and [New Question #] on how processing with traditional food preparation processes affects the NDI status of constituents**.)

Question IV.A.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 **or in** a **conventional food or a** dietary supplement, (2) in bulk as **an ingredient for use in a conventional food or** ~~a dietary ingredient~~ for use in dietary supplements, or (3) as an ingredient in a blend or formulation of **ingredients for use in conventional foods or** ~~dietary ingredients~~ for use in dietary supplements. A dietary ingredient may be "marketed" by physically offering the ~~article~~**, ingredient, or a conventional food or dietary supplement containing the ingredient,** for sale at a retail establishment **or at an establishment engaged in the cooking or serving of foods or the manufacture or packing of foods or dietary supplements;** listing it**, or a food or supplement product containing it,** for sale in a **menu,** catalog or price list, or through advertising or other promotion, if the promotion makes clear that the article is available for purchase **either by consumers or by companies engaged in the manufacture of conventional foods or dietary supplements**. "Coming soon" advertisements would not qualify.

Question IV.A.9: Is marketing an ingredient for any use prior to October 15, 1994, sufficient to conclude that it is ~~not a NDI~~**a pre-DSHEA dietary ingredient**?

No. The marketing of an ingredient ~~as a conventional food,~~ as **or in** a **new** drug **approved under section 505 of the Act**, or ~~for any other non-food use~~ **not for ingestion** cannot be used as evidence that an ingredient is ~~not a NDI~~**a pre-DSHEA dietary ingredient**. Unless the ingredient was marketed ~~as a dietary ingredient~~ for use **as or** in a **conventional food or** dietary supplement prior to October 15, 1994, it is a NDI. **Note however that marketing of an ingredient as or in a new drug or for not for ingestion does not automatically classify it as a NDI or disqualify it from use as a dietary ingredient, so long as it was also marketed in a conventional food or dietary supplement use before October 15, 1994.**

Identification of a constituent in analytical chemistry is not relevant to its NDI status

In Question IV.A.4 FDA asserts that "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." As is obvious from the context of this sentence, the use of the word "component" means "constituent" in both uses in this sentence.

AHPA disagrees that a constituent found in a pre-DSHEA food or food ingredient by analytical chemistry procedures is not a dietary ingredient, except in the case of contaminants. For example, AHPA agrees that just because lead has been found to be present in wheat, that does not qualify lead as a dietary ingredient. However, in all cases other than contaminants, AHPA believes that any chemical constituent found in a food or food ingredient is necessarily a dietary ingredient (either a pre-DSHEA ingredient or a NDI).

AHPA also holds that the date on which a constituent is identified as present in a pre-DSHEA food or food ingredient is irrelevant to determining whether the constituent or an ingredient containing the constituent is a NDI. Foods and food ingredients are quite chemically complex and few, if any, have been completely chemically characterized. The mere fact of identifying or quantifying a constituent within a food or food ingredient does not change the chemical composition of the food or food ingredient. If through new research a company or academic institution succeeds in identifying or quantifying a chemical constituent in a food or food ingredient, companies may decide to use the presence of that constituent in describing the manufacture or composition of their foods, ingredients, and dietary supplements. The use of new descriptive language does not automatically render said foods, ingredients, or dietary supplements "new." The only thing that would in fact make them "new" is if the actual chemical composition of the foods, ingredients, or supplements is altered in a manner inconsistent with traditional food preparation processes (e.g., if the constituent is synthesized, concentrated using specialized chromatography, etc.).

The draft guidance inappropriately suggests that every change to the specifications of a NDI requires submission of a new NDI notification

In Question IV.A.12, FDA states that a new NDI notification should be submitted if a change in the manufacturing process for a NDI results in any change to the specifications needed to describe the ingredient. This is too broad a requirement. Only changes which would alter the identity or specifications of the NDI to the degree that the information originally submitted to support the submitters safety conclusion is no longer quantitatively and qualitatively related to the NDI should trigger a new NDI notification. These would be limited to (1) any material change to the chemical composition or chemical structure of the NDI; (2) raising the allowed levels of any contaminant or introducing new potential contaminants; or (3) changing the particle size to the nanoscale range. Other changes, including, for example, changing the bulk density, the particle size distribution in the micron range, lowering the allowed levels of an existing contaminant, etc. should not trigger a new filing requirement.

AHPA therefore recommends that question IV.A.12 should be revised to read:

> Question IV.A.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~~ **It depends. If** the manufacturing change does not change the chemical ~~properties~~ **composition or chemical structure** of the dietary ingredient ~~or the specifications needed to describe the ingredient~~ **in any material way there is no need to submit a new NDI notification**. **On the other hand, if the changes in your manufacturing process do result in a material change to the chemical composition or chemical structure of the NDI, a new notification may be required.** For example, a change in the manufacturing process for a NDI intended to ~~produce particles in~~ **reduce the particle size from the micron range to** 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~~ **the same** substance manufactured without using nanotechnology and, therefore, would likely require a NDI notification. **In addition, if the changes in your manufacturing process result in a material upward adjustment of any contaminant specification or the introduction of new potential contaminants, a new notification may be required.**
>
> Manufacturers planning a manufacturing change are encouraged to consult with FDA **and/or with qualified counsel or technical consultants with expertise in NDI matters** on any questions as to whether such a change would be viewed as having created a different NDI.

FDA must continue to permit submitting companies to identify trade secret or confidential commercial information and should also establish a process to allow notifiers to permit other companies to incorporate by reference an ingredient notification in a later dietary supplement notification

In Question V.A.16 of the draft guidance, FDA addresses the issue of information contained in a NDI notification that is a trade secret or confidential commercial information (CCI).

Under section 413 of the Act, FDA is required to place on public display any information submitted in a NDI notification as the basis for the submitting firm's conclusion that a dietary supplement is reasonably expected to be safe, including any citation to published articles, and except for matters in the information which are trade secrets or otherwise CCI.

The draft guidance identifies certain information that FDA believes is trade secret or CCI and other information that it believes is not. Of particular interest to AHPA is that FDA expresses its view that information about the history of use or other safety information related to the dietary ingredient, including both published and unpublished studies, are

generally not trade secrets or CCI, and therefore would be available for public disclosure.

AHPA strongly objects to FDA making any unpublished studies identified as trade secret or CCI publicly available without the explicit consent of the submitter and, where applicable, the company that funded the study. The nature of studies performed on an ingredient or supplement, the methods used in the studies, the institutions where the studies were conducted, and the data and results produced by the studies (among other things), may all constitute confidential commercial information. For example, a company may conduct studies to determine the use of a particular food or food ingredient in the diet of certain populations, which may form part of the evidence upon which the company relies to establish a reasonable expectation of safety for its NDI; this information would be the property of the company which conducted the study and should appropriately be used solely for its own commercial advantage, not made public for its competitors to use.

Of additional interest in the discussion on trade secret and CCI in the draft guidance is that the agency suggests that the submitter clearly identify any information in the notification that is believed to be trade secret or CCI and also provide an explanation for the basis for this belief. FDA's practice to date has been to accept whatever designation is made by the submitting firm to identify which parts of a notification are trade secrets or CCI. With one particular notification, for example, the agency redacted the entire notification with the exception of the name of a consulting firm, such that not even the name of the submitting firm or of the ingredient itself were disclosed in the material made public, and all of the information submitted as the basis for the company's safety conclusion was also redacted.[19]

AHPA believes that FDA should continue to allow the submitter of a NDI to identify any part of its notification as trade secret or CCI, with the possible exceptions of the name of the submitting firm, the identity of the NDI, and published studies. While AHPA is not opposed to FDA's suggestion that a submitting firm should provide an explanation for its belief that submitted information is trade secret or CCI, AHPA also believes that FDA should accept almost any reason as acceptable, including, for example, a company's expressed view that disclosure of the material identified as such would create a business disadvantage of any sort, and should therefore presume to honor any such request with respect to any information that has not previously been made public. AHPA suggests that FDA also establish a policy whereby the agency notifies the submitter in advance any time it determines to place on public display any of the information that

[19] Report number 326 received by FDA on January 3, 2006; Brock Scientific Consulting LLC is the named consulting firm.

was requested to be identified as trade secret or CCI, so as to allow the submitter to take appropriate legal action if it disagrees with FDA's decision to do so.

AHPA therefore requests that the second and also the final paragraphs in Questions V.A.16 be revised as follows:

> Question V.A.16: How should I identify information that I believe is trade secret or confidential commercial information?
>
> …
>
> 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. **FDA will generally accept any request to recognize designated non-public information as trade secret or CCI, even, for example, if the explanation is simply that you believe disclosure of the information will is likely to cause harm to your competitive position. Should the agency determine that the designated information is not, in fact, trade secret of CCI, we will notify you in advance of placing such information on public display.**
>
> …
>
> 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 **or under section (1) of this paragraph**.

AHPA also believes that FDA should establish an option to allow a company that submits a NDI notification for an ingredient to both identify virtually all of its notification as trade secrets or CCI and at the same time allow another company that intends to use the NDI in a new dietary supplement to incorporate the original ingredient notification by reference into a subsequent NDI notification for the supplement.

As discussed elsewhere in these comments, some NDI manufacturers or distributors may have sound business reasons to submit a notification for its newly developed NDI that is intended to address the safety of a range of dietary supplements that will contain or that may come to contain the NDI. There may also be sound reasons for such an ingredient company to want each supplement company that will use its NDI to file a separate notification while it also chooses to refrain from disclosing all of its proprietary

knowledge to each of its customers. Such a system would allow the submitter of a NDI notification for an ingredient to give permission, at its sole option, for specific dietary supplement manufacturers or distributors to reference its NDI file, but not to access or view the contents of the file. Any such authorized supplement manufacturers or distributors would then be required to use the specific NDI which is the subject of the NDI file in the dietary supplements they manufacture or distribute. AHPA notes that FDA has used such a master file system for other regulated product categories.

AHPA notes that its support of such a NDI file system is contingent upon the owner of the NDI file retaining full control over the use of its file by other companies; and further that any such system must not preclude a manufacturer or distributor of a NDI from submitting a NDI notification which describes in general terms, as opposed to highly detailed and specific terms, the types of dietary supplements which will or may come to contain the NDI.

The draft guidance places a burden on companies that market only pre-DSHEA ingredients where the Act places no such burden

The Act establishes what a company intending to market a new dietary ingredient must do to conform to its NDI provisions. The Act does not, however, place any NDI-related burden whatsoever on companies that market only pre-DSHEA dietary ingredients. And for companies that market some dietary supplements that contain a NDI, the Act limits their NDI-related burden to just those products that contain an NDI.

On the other hand, the draft guidance strongly implies that companies that market dietary supplements that contain only pre-DSHEA dietary ingredients have an affirmative burden to prove or to have evidence that each of these ingredients was marketed in the U.S. before October 15, 1994, and is therefore not a NDI. This implication is apparent where the draft guidance identifies the kind of documentation that a company would “need to” show that an ingredient was marketed before October 15, 1994, and what such documentation “should” consist of or include.

But the Act does not require marketers of dietary supplements that consist only of pre-DSHEA dietary ingredients to have documentation that these ingredients were marketed in the U.S. before October 15, 1994. If there were such a requirement it is apparent that companies that were in business before DSHEA was passed in 1994 would have a competitive advantage over companies that were founded after that date, as only those earlier businesses could have such pre-DSHEA records readily in their possession. AHPA does not believe the Congress intended to pass a law that would give a competitive advantage to one class of companies solely because those companies were already in business when the law was passed.

The draft guidance also takes the position that affidavits attesting to a recollection of the marketing of dietary ingredients before October 15, 1994 are inadequate. This position

is contrary to the manner by which proofs are made in the courts of the United States. Moreover, this advice has the potential of sending companies on unnecessary and costly hunts for information that may be unobtainable. And to the extent that FDA is implying that companies had an obligation to maintain records of old ingredients, such a position would be inconsistent with all other State and Federal principles and requirements of business recordkeeping. No law requires records to be kept for the seventeen years that have passed since DSHEA became law.

It is up to the manufacturer or distributor of a dietary supplement to ascertain the status of the dietary and other ingredients used in its product. If the company chooses to market a product of old dietary ingredients only, it is entitled to rely on whatever information it is wishes to ascertain the status of those ingredients. That may be catalogs and general descriptions of old products, the lists developed by industry trade associations after DSHEA was passed, advice of persons familiar with the dietary supplement industry pre-DSHEA, or general knowledge that many of the substances identified in section 201(ff)(1) of the Act were marketed at the time DSHEA was passed. There is no requirement that a manufacturer establish the pedigree of the dietary ingredients it intends to use or to establish as well that each of these ingredients is identical to ingredients sold pre-DSHEA.

The draft guidance should therefore be corrected as follows. Note that this revision also addresses, with the last struck through phrase in the first paragraph below, AHPA's previously stated position that the draft guidance improperly narrows the range of pre-DSHEA dietary ingredients:

> Question IV.A.8: What documentation would ~~I need to~~ show that my dietary ingredient was marketed prior to October 15, 1994?
>
> **There is no requirement in the law that manufacturers or distributors of dietary ingredients or dietary supplements have documentation** ~~Documentation~~ to show that a dietary ingredient ~~is not a NDI~~ **was marketed prior to October 15, 1994. For companies that nevertheless wish to do so, examples of such documentation** ~~sh~~**c**ould consist of **but would not be limited to** written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994. **Specific examples** ~~Examples~~ **could** include **, but are not limited to, any of the following records for a specific ingredient or for any food, regardless of form, which contained an ingredient: purchase or** sales records, manufacturing records, **inventory records, menus, recipes found in cookbooks,** commercial invoices, magazine advertisements, mail order catalogues, or sales brochures**, and any other record that documents the use of the dietary ingredient in the food supply**. Documentation ~~should~~ **may also** include adequate information to establish that marketing took place in the U.S., **and** 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.~~

In addition, and in order to completely clarify that the Act does not place any NDI-related burden whatsoever on companies that market only pre-DSHEA dietary ingredients, and that the NDI-related burden is limited to only those products that contain a NDI for companies that market some dietary supplements containing a NDI and others that contain only pre-DSHEA ingredients, an additional question should be added to the draft guidance, as follows:

New Question: **Am I required to have documentation that my pre-DSHEA dietary ingredients were marketed prior to October 15, 1994?**

No. The Act does not require a dietary ingredient or dietary supplement manufacturer or distributor to have documentation to show that its marketed dietary ingredients or the dietary ingredients included in its marketed products are pre-DSHEA dietary ingredients. Such companies should nonetheless understand that FDA may take the position that an ingredient is a NDI and could do so based upon representations made by the manufacturer of the ingredient or dietary supplements containing the ingredient.

FDA should acknowledge the value of published and industry-submitted ingredient lists of pre-DSHEA dietary ingredients

The draft guidance takes the position that there is not an authoritative list of pre-DSHEA dietary ingredients. FDA also states in the draft guidance that it does not accept the inclusion of an ingredient on any of the lists of such pre-DSHEA dietary ingredients created by industry trade associations shortly after DSHEA was passed as proof that such an ingredient was in fact marketed in the U.S. prior to October 15, 1994.

In 1992 AHPA published a document titled *Herbs of Commerce* which listed approximately 550 species of plants, the majority of which were sources of articles used at that time as food ingredients, although some of the listed species were identified at that time as “used only as drug plants.” In 1997 FDA incorporated *Herbs of Commerce* (1992 edition) by reference in its final rule establishing requirements for the identification of dietary supplements and for their nutrition labeling and ingredient labeling in

response to DSHEA, 21 CFR 101.4(h).[20] *Herbs of Commerce* (1992 edition) did not include the part or parts of the plant generally used in trade for the listed plant species.

In discussing records of pre-DSHEA dietary ingredients, FDA should clearly state that this reference is incorporated by reference in Title 21 of the Code of Federal Regulations. Even though 21 CFR 101.4(h) was promulgated after October 15, 1994, *Herbs of Commerce* (1992 edition) itself was published before that date. In issuing the final rule in which this document was incorporated by reference into Federal regulation, FDA did not express any concern as to its validity as a true and accurate record of some of the herbal ingredients that were marketed in the U.S. at its time of publication in 1992. No such concern has arisen in the meantime, such that it should be acknowledged that all of the plants listed therein were articles in trade at the time of publication. Moreover, FDA proposed to add *Herbs of Commerce* (2000 edition) to this regulation on August 28, 2003. Food Labeling: Ingredient Labeling of Dietary Supplements That Contain Botanicals: Proposed Rule, 68 FR 51738.

In 1996 and 1998 several trade associations submitted lists of ingredients that were identified as believed to be marketed in the U.S. before October 15, 1994. These included a submission by the National Nutritional Foods Association (NNFA; now the Natural Products Association, or NPA) on April 26, 1996 of approximately 836 ingredients; a submission by AHPA on September 17, 1996 of approximately 1,679 ingredients; and a submission by the Council for Responsible Nutrition dated September 1998 of approximately 1,234 ingredients. Some ingredients were listed in more than one of these lists, such that AHPA calculates that the total number of non-duplicated ingredients included in any of these lists is approximately 3,011.

The NNFA list was organized into several categories, and so included, for example, 9 “drug” ingredients and 53 “capsule and tablet ingredients.” AHPA notes that the NNFA list included somewhat over 200 “botanical” ingredients and that though many of these did identify the part of the listed plant, others did not. AHPA understands that the NNFA list was compiled from already existing records in that organization’s “TruLabel” program, which was a compilation of the ingredients listed on product labels in the marketplace.

The CRN list relisted most of the ingredients in the NNFA list and also listed more than 300 additional ingredients. In submitting its list, CRN stated that it included ingredients from the NNFA list and added other ingredients that its members had “asserted were in use prior to October 15, 1994.”

[20] 62 FR 49826 at 49847.

The AHPA list consisted almost exclusively of names of plants though it also included the names of 33 non-plant ingredients, consisting of animal species, animal-sourced ingredients, and mineral ingredients used in traditional Chinese formulas believed to be marketed in the U.S. before October 15, 1994. AHPA acknowledges that its list included some plant species that are no longer allowed to be sold in dietary supplements, including, for example, six species of *Ephedra* and two species of *Symphytum*. AHPA's list also did not include the part or parts of the plant generally used in trade for the listed plant species.

The AHPA and CRN letters to FDA that accompanied submissions of their pre-DSHEA dietary ingredient lists each included some form of disclaimer. AHPA stated in its 1996 submission that it believed the submitted list to contain "only herbs meeting the criteria stated above," that is, herbs marketed as dietary supplements or dietary ingredients before October 15, 1994, but also acknowledged that it had not "independently verified the list." Similarly, CRN stated that its list "does not constitute verification that any specific dietary ingredient was or was not marketed as a dietary supplement before October 15, 1994," and that it had not "independently verified that ingredients on this list were in fact in use prior to October 15, 1994."

The draft guidance makes much of these disclaimers, specifically citing the above statements in the CRN letter. The draft guidance also notes that the CRN letter stated that there "is no definitive list of 'grandfathered' dietary ingredients." The draft guidance states, "*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" (emphasis added).

AHPA also notes that it submitted comments to the agency on February 1, 2005 to respond to a Federal register notice dated October 20, 2004 in which FDA solicited comments on its premarket notification program for new dietary ingredients as it existed at that time. Among other things, AHPA informed the agency in these comments that it had subsequently published in 2000 a second edition of *Herbs of Commerce*. AHPA noted that *Herbs of Commerce* (2000 edition) included a statement in its introduction that clarified that this reference serves as an update on its 1996 submission to FDA. Specifically, the introduction to *Herbs of Commerce* (2000 edition) states:

> "This work represents a compilation of submissions from companies involved in the trade of products containing botanicals and from experts in this class of trade. These were in response to written requests from AHPA that specifically stated that only dietary ingredients marketed prior to October 15, 1994 should be included in such submission. In addition, the editors included species that were thought to have been overlooked in this process. To the best of our knowledge, only plants marketed prior to this date are included herein, though neither AHPA nor the editors have expended any effort in independent verification of this assumption. The listing of a particular

> species of plant in this work is not, therefore, in and of itself, evidence that such species was marketed in the United States prior to October 15, 1994."

AHPA stated in its above-cited 2005 comments its position that any plant species included in *Herbs of Commerce* (2000 edition) can be presumed to have been in commerce in the United States on October 15, 1994, "at least in the form of 'an herb or other botanical' in conformity with 21 U.S.C. 321(ff)(1)(C)" (section 201(ff)(1)(C) of the Act) and that the presence of a plant in this reference creates a presumption of presence in the marketplace prior to October 15, 1994. AHPA restates these positions here and notes that the preface to *Herbs of Commerce* (2000 edition) provides additional information that clarifies that this publication was, in fact, a compilation of pre-DSHEA dietary ingredients, as is obvious form the following:

> "In February of [1995], AHPA solicited its members to identify all of the plants that were ingredients in their products at the time that DSHEA was passed, so that these could be clearly differentiated from 'new dietary ingredients,' as defined by DSHEA. This first call resulted in a tripling of listed species. Additional submissions were received as AHPA members reviewed a draft circulated in late 1997. As might be expected of a task that relied solely on voluntary effort, the taxonomic and technical review of the information received has taken over three years to complete."

FDA should take into account the processes whereby these lists and publication were compiled, as well as the spirit in which they were compiled. As stated in the cover letter to AHPA's submission of its list in 1996, the list "represents a compilation of the submissions received from AHPA members as well as non-members in response to a written request from AHPA [that] specifically stated that only herbs marketed as dietary supplements or dietary ingredients before October 15, 1994, were to be included in any submissions made to AHPA." The introduction to *Herbs of Commerce* (2000 edition) clarifies that this same process was used, along with input from the editors, and that AHPA's belief was that "only plants marketed prior to [October 15, 1994] are included herein."

AHPA strongly disagrees that the fact that trade associations told the truth about how their compiled and submitted lists and publications of pre-DSHEA were or were not reviewed constitutes evidence that they should "therefore" be dismissed out of hand.

Again, FDA states in the draft guidance that there is not an authoritative list of dietary ingredients that were marketed in the U.S. before October 15, 1994. AHPA agrees that there is not a single list that identifies every single ingredient that was marketed in the United States before this date. But AHPA also believes that better questions could be asked that would identify the relevance of AHPA's *Herbs of Commerce* (both the 1992 and 2000 editions) and of the lists compiled by trade associations and submitted to FDA in the years immediately following the passage of DSHEA.

AHPA restates here its position that there is no requirement in the Act for supplement companies to "prove" that pre-DSHEA dietary ingredients were marketed before October 15, 1994, as the Act's NDI provisions are limited only to what marketers of new ingredients must do and place no NDI-related burden whatsoever on marketers of pre-DSHEA dietary ingredients.

Taking into account all of the above discussion on the relevance of published and compiled lists of herbs and other dietary ingredients, AHPA suggests the following revisions to the draft guidance:

> Question IV.A.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")?~~ **What is the NDI status of the ingredients included on published lists of "old dietary ingredients" and AHPA's *Herbs of Commerce*?**
>
> ~~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," these lists have not been verified by FDA and ~~are~~ not **every ingredient listed on them is** backed by evidence that ~~the ingredients listed were~~ **it was** 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 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.~~
>
> **FDA has been informed, however, that the "old dietary ingredient" lists submitted to FDA by trade associations FDA in 1996 and 1998 [add footnote to identify submissions by AHPA, NNFA, and CRN] were compiled through processes that included requests that these associations' members identify only dietary ingredients that were marketed in the U.S. before October 15, 1994 and review of certain association records of such ingredients. FDA has no reason to believe that these requests were not honored or that these reviews were not conducted in a manner that would be likely to list only ingredients marketed in the U.S. before this date.**

FDA is also aware that the American Herbal Products Association (AHPA) published a document in 1992 titled *Herbs of Commerce* which listed approximately 550 species of plants. The majority of these plants were sources of articles used at that time as ingredients in products then classified as foods, although the reference states that some of the listed species were identified as "used only as drug plants." In 1997 FDA incorporated *Herbs of Commerce* (1992 edition) by reference in its regulation on the ingredient labeling for dietary supplements, 21 CFR 101.4(h).

AHPA published a revision to its *Herbs of Commerce* in 2000, which lists slightly more than 2000 species of plants. FDA has been informed that *Herbs of Commerce* (2000 edition) was compiled through processes that included requests that AHPA's members identify only dietary ingredients that were marketed in the U.S. before October 15, 1994. FDA has no reason to believe that these requests were not honored.

Neither edition of *Herbs of Commerce* identifies the part or parts of each of the listed plants generally used in trade. In addition, these references include some plants that may not be sold as dietary supplements under current law because they have been determined by FDA to represent a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or under ordinary conditions of use.

In general and except as discussed below, FDA considers an ingredient listed on any of the above-cited industry lists, as well as the part or parts generally used from each of the plant species that is included in any of these lists or in *Herbs of Commerce* (1992 or 2000 edition), to be a pre-DSHEA dietary ingredient.

FDA cautions, however, against any reliance on these lists or publications with respect to any of the following ingredients even if included therein:

- **Ingredients that would present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or under ordinary conditions of use, including, for example, ingredients that have been banned in the years since 1994, such as ephedrine alkaloid-containing botanical ingredients.**
- **Ingredients that are drug ingredients or drug excipient ingredients, if they do not also qualify as dietary ingredients under section 201(ff) of the Act.**
- **Botanical ingredients that are derived from plant species included on any of the lists but that are parts of these plants for which there is not a history of use in foods or dietary supplements.**
- **Ingredients that are vaguely described or that are not clearly described as dietary ingredients.**
- **Ingredients that FDA has ruled are not pre-DSHEA dietary ingredients.**

FDA should more accurately clarify when a change in manufacturing process of an ingredient creates a NDI and when a notification is needed

The draft guidance states that if a change that is made in a manufacturing process alters the chemical composition or structure of a pre-DSHEA dietary ingredient the resulting compound is probably a NDI and a notification to FDA would be required.

AHPA believes that it is up to the manufacturer or distributor of a dietary ingredient, including a pre-DSHEA dietary ingredient or a NDI that has previously been the subject of a NDI notification, to determine whether a change in a manufacturing process alters the chemical composition or chemical structure of the ingredient. If the manufacturer concludes that neither is altered, the manufacturer is free to market that ingredient.

AHPA also believes it is sometimes but not always accurate that a change in a manufacturing process that alters the chemical composition or structure of a dietary ingredient necessarily results in production of a NDI. AHPA also believes that a notification is not necessarily required to be submitted when this type of compound is, in fact, a NDI.

The resulting ingredient would not be a NDI, for example, if this ingredient, produced by one manufacturer which uses a new manufacturing process that alters the chemical composition of its own ingredient, if the newly altered ingredient is one that was marketed in the U.S. before October 15, 1994, either by the same ingredient manufacturer or by any other manufacturer or distributor of the ingredient or a dietary supplement or conventional food that contained the ingredient.

Even if the resultant ingredient is a NDI, however, a notification would not be required to be submitted if the altered ingredient is itself an article used for food, even if the date on which the ingredient was first used as a food was after October 15, 1994.

In addition, AHPA does not believe that the draft guidance or resulting final guidance should recommend that companies consult with FDA on questions related to NDIs or NDI notification, unless this recommendation is extended to also recommend consultation with qualified counsel or consultants.[21]

AHPA therefore suggest that the following changes be made in the draft guidance:

> Question IV.A.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 **chemical** structure of the ingredient, does that make the ingredient a NDI?

[21] This position is relevant not only to the discussion of a change in manufacturing process but to each time that the agency suggests that a firm consult with FDA on any matter relevant to NDIs. AHPA therefore requests that the same suggested language revision that follows here be applied also in Questions IV.A.12 and IV.B.2.a.

~~Yes~~**It depends**. If the changes in your manufacturing process alter the chemical composition or **chemical** 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 **could** create~~s~~ a NDI ~~because~~ **if** 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.~~ **But the resulting ingredient would not be a NDI if the altered ingredient itself is one that was marketed in the U.S. before October 15, 1994, either by the same ingredient manufacturer or by any other manufacturer or distributor of the ingredient or a dietary supplement or conventional food that contained the ingredient.**

When such altered ingredient is, in fact, a NDI, in many cases a notification to FDA would be required to be submitted. But a notification would not be required if this NDI itself is an article used for food and the alteration to its chemical composition or structure is not a further alteration to that food ingredient. Also, see question IV.B.3 for information on the types of processes that do not result in chemical alteration.

Firms planning a manufacturing change are encouraged to consult with FDA **and/or with qualified counsel or technical consultants with expertise in NDI matters** on any questions as to whether such a change would create a NDI.

New question: **If I make changes that alter the composition of the raw materials used to make a pre-DSHEA dietary ingredient, does that make the ingredient produced from the altered materials a NDI?**

It depends. If the changes in your raw materials introduce materials which are not approved foods, food additives, food ingredients, or pre-DSHEA dietary ingredients then the produced ingredient would be a NDI. For example, if the root (and only the root) of a particular plant is used to produce a pre-DSHEA extract of the root of the plant, and you change the raw material to use the leaves of the same plant, then the new ingredient, as an extract of the leaf of the plant, is a NDI. But if the changes to the raw materials are the result only of traditional food preparation procedures then the produced ingredient is not a NDI.

The list of solvents that do not result in chemical alteration should be expanded

The draft guidance provides a list of processes that it would consider to chemically alter an article of food present in the food supply. Included in this list is an example of the use of solvents “other than water or aqueous alcohol (tincture) to make an extract.”

As noted elsewhere, the October 2, 1994 Congressional Statement of Agreement recorded certain physical modifications that should not be considered to be chemical alteration when making a determination as to whether a notification is required for a NDI that is an article used for food. The law exempts from the notification requirement an NDI that is also an article used for food, so long as the food is in a form in which it has not been chemically altered. One of the exceptions to chemical alteration recorded in the above-cited Statement of Agreement is "tincture."

The draft guidance provides a definition for the term "tincture" as an "aqueous alcoholic solution." In addition, citing the October 7, 1994 Congressional Statement of Agreement, the draft guidance notes that water and aqueous ethanol are specifically excluded from processes that chemically alter a food.

AHPA notes that water and ethanol and mixtures thereof (i.e., aqueous ethanol) are not the only solvents that are used to make an extract of an herb or other botanical that does not necessarily result in chemical alteration, for example, by making or breaking chemical bonds. Other such solvents include, for example, glycerin, vinegar, and vegetable oils such as olive oil. Each of these solvents, like water and aqueous ethanol, will produce an extract of an herb or botanical that includes a broad spectrum of the constituents found in the starting plant material. AHPA can identify no logical or scientific basis to support an idea that an herb or other botanical that is extracted in water or aqueous ethanol does not chemically alter the starting material botanical but that extracting the same starting material in one of these solvents would, in fact, result in chemical alteration.

In addition, water and ethanol are not the only solvents used in the manufacture of products that have been known as tinctures. For example, one contemporary reference defines a tincture to be, "A plant extract made by soaking herbs in a liquid (such as water, alcohol, vinegar or glycerine [sic]) for a specified period…."[22] In addition, examples can be found in historic pharmacopoeial references tinctures that include glycerin as a solvent, such as Cinnamon Tincture[23] and Compound Cardamom Tincture.[24]

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[22] Skidmore-Roth, L. 2009. *Mosby's Handbook of Herbs and Natural Supplements*, 3rd edition. St. Louis, MO: Mosby Elsevier.

[23] American Pharmaceutical Association. 1946. *The National Formulary*, 8th edition. Easton, PA: Mack Printing.

[24] United States Pharmacopoeial Convention. 1950. *The Pharmacopoeia of the United States of America* XIV. Easton, PA: Mack Printing.

In addition, AHPA notes that there are some inaccuracies in the definition of "tincture" provided in the Definitions in section VII of the draft guidance. AHPA therefore suggests the following changes to the draft guidance:

> Question IV.B.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.
>
> - …
> - Use of solvents other than water or aqueous ethanol (tincture)**, or other traditionally used solvents, such as glycerin, vinegar or vegetable oils, etc.,** to make an **herbal or botanical** extract. Water and aqueous ethanol are specifically excluded from processes that chemically alter a food in the official legislative history of DSHEA. **The other solvents listed here can also be used to extract a broad spectrum of a plant's naturally-occurring constituents.** Other solvents **that** alter the composition of the extract in significantly different ways, ~~usually~~ **for example** by extracting different types of constituents than are extracted using water**,** ~~and~~ aqueous ethanol**, or other traditionally used solvents, or by selectively extracting only certain constituents, or by breaking or making new chemical bonds, would be considered to be chemical alteration**.
>
> Section VII. Definitions: Tincture: An **ethanol or** aqueous **ethanol**~~alcoholic solution (e.g., an aqueous alcoholic~~ extract of ~~leaves or other plant material)~~ **an herb or other botanical**. A tincture ~~is~~ **may be** characterized by the ratio ~~of~~ **between** the weight of the dried botanical **raw material extracted and** ~~to~~ the volume ~~or weight~~ of the finished ~~product~~**extract**. A 1:5 ratio**, for example,** ~~is one part botanical to 5 parts alcohol~~ **indicates that 1 kilogram of an herb or botanical was used to manufacture 5 liters of the tincture**.

The draft guidance is inaccurate in its discussion of when separate NDI notifications are needed, and should clarify that a generally-described dietary supplement is acceptable in a NDI notification

The Act requires that a manufacturer or distributor, of either the contained NDI or of each dietary supplement, file a notification to provide the information on which it has based its conclusion of that a dietary supplement containing the dietary ingredient will reasonably be expected to be safe. There is nothing in the Act however that dictates that a separate NDI notification must be submitted for each and every dietary supplement.

AHPA notes that FDA has previously estimated that NDI notifications submitted annually would be very few in number and provided commentary that strongly suggested that only one notification would be required for each NDI. In the economic analysis that accompanied proposed 21 CFR 190.6, the agency expressed an

assumption that "the number of new ingredients will vary [and that] [t]he plausible range is estimated to be 0 to 12 new ingredients per year." The agency also stated, "The total number of businesses affected by the proposed rule will be small—no more than the number of new ingredients (estimated to be 0 to 12 per year)."[25] In other words, the agency assumed that *only one business would be affected for each new dietary ingredient*, an assumption that clearly implied that each NDI would require only one notification, irrespective of how many companies used the NDI in their dietary supplements. FDA repeated these same assumptions in promulgating the final rule.[26] Although the agency has subsequently increased its estimate of the annual number of NDI notifications it will receive to 55,[27] it has never before – prior to issuance of the draft guidance – made any statement that can be read as contradicting its initial assumption that the total number of businesses that are required to submit a NDI notification is exactly the same as the number of NDIs that come into the market each year. Thus, the only position that FDA has ever previously stated is that it expects only one notification for each NDI.

AHPA believes that separate notifications are not required when the initial notification filed for the NDI provides a description of a dietary supplement or a range of dietary supplements that would include the NDI. There is nothing in either the Act or the implementing regulations to prevent such an approach, and in fact 21 CFR 190.6 appears to envision such an option as it requires a notification to include a "description of the dietary supplement **or dietary supplements** that contain the NDI" (emphasis added). Moreover, FDA's actual practice has been to file without objection premarket notifications that describe the NDI specifically but that only generally describe dietary supplements that will contain the dietary ingredient.

There are sound business reasons for an ingredient company to submit a notification for its newly developed NDI that is intended to address the safety of a range of dietary supplements that will contain or that may come to contain the NDI. At the time of introduction into the marketplace that manufacturer or marketer of a NDI is unlikely to know all of the potential customers for the ingredient. If that company has information that is the basis for its conclusion that many dietary supplements that will contain or that may come to contain the NDI will reasonably be expected to be safe, the company may submit a single NDI notification that describes this range of dietary supplements. This may be accomplished by quite specifically describing these possible dietary supplements or by providing a general description of these possible products, so long as the described range of products are those that the submitting company has

[25] 61 FR at 50774 at 50776, September 27, 2006.
[26] 62 FR at 49886 at 49890-1, September 23, 2007.
[27] For example, 76 FR 32214 at 32215, June 3, 2011.

concluded will reasonably be expected to be safe. This is already an established practice.

For example, Martek Biosciences Corporation submitted a NDI notification on November 11, 2010 for an ingredient it identified as a NDI, and specifically as "DHA and EPA Algal Oil," which the company stated was derived from *Schizochytrium* spp. The notification's section on conditions of use stated that the ingredient "will be used as a source of DHA and EPA in dietary supplements … at up to 3 grams of DHA and EPA / person / day to supplement dietary intake of DHA and EPA." The level of use was reduced to 2 grams / person / day in a follow-up communication, and the company also described a cautionary statement that will be applied to labels of products that contain the NDI. FDA acknowledged receipt of this notification without identifying any objections and clarified in its letter of acknowledgement that Martek had informed FDA that it "intend[s] to market … [the NDI] ... in bulk form for third party manufacturing of dietary supplements in suitable dosage forms." Thus, in this case the agency found no objections to a filing for a NDI in which the submitting firm, as an ingredient supplier, provided the information that is the basis for its conclusion that a range of dietary supplements containing the ingredient will be reasonably expected to be safe under the described level and other conditions of use.

There is nothing in the Act, in implementing regulations, or in FDA's history of responses to NDI notifications to suggest that every marketer of a dietary supplement that comes to contain the above-described Martek ingredient is required to submit a separate NDI notification if its product is labeled to limit daily intake to 2 grams of DHA and EPA per day and to provide the described cautionary statement on labeling. Because the Martek notification addressed the safety of any and all dietary supplements which comply with the described level and conditions of use, there is no legal requirement for the downstream supplement company to do a separate filing. AHPA notes also that this Martek filing is offered here as an example only, and that this sort of general description of dietary supplements that will come to contain a specific NDI is not at all uncommon in the NDI notification docket, and that it is also not uncommon for FDA to acknowledge such notifications without identifying substantive objections.

There are also sound business reasons for a manufacturer or marketer of a NDI or a dietary supplement that will contain the NDI to submit a notification that is specific to a single dietary supplement. A submitting ingredient company might choose this option if it has or intends to have an exclusive relationship with the marketer of a specific supplement brand. And a submitting supplement company might choose this option to establish that only its supplement product, uniquely formulated, manufactured, and described, has complied with the NDI notification requirement under the Act. There are numerous examples of NDI notifications that are specific to a specifically described NDI, including one filed on March 6, 2010 by Sun-Chlorella USA for an ingredient identified

as a NDI and specifically as "*Agaricus blazei* Murrill (ABM)." This notification, to which the submitter provided additional information on a number of occasions, was quite specific in describing a single dietary supplement product that will combine this ingredient with one other dietary ingredient in a formulation specified in the notification and that will be distributed under the company's own brand name and under the conditions of use identified in the notification. It is AHPA's understanding that any other manufacturer or distributor of a dietary supplement that contains Sun-Chlorella's specific NDI would need to file a separate notification to comply with the Act's NDI provisions.[28]

It bears repeating that Section 413(a) of the Act states:

> "A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 342(f) [i.e., 402(f) of the Act] of this title unless it meets one of the following requirements:
>
> (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.
> (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe." Section 413(a) of the Act.

With respect to dietary supplements containing a Section 413(a)(2) NDI, one of the following must occur at least 75 days prior to introduction or delivery of the dietary supplement into interstate commerce:

- The manufacturer of the dietary ingredient must provide the Secretary with information, including any citation to published articles, which is the basis on which it has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.
- The distributor of the dietary ingredient must provide the Secretary with the above described information; or

[28] Notwithstanding this expressed view, AHPA is taking no position here as to whether *Agaricus blazei* Murrill was marketed as a food or dietary supplement in the U.S. prior to October 15, 1994.

- The manufacturer of the dietary supplement must provide the Secretary with the above described information; or
- The distributor of the dietary supplement must provide the Secretary with the above described information.

The draft guidance as written, however, is not clear that only one of the above four options is required and has indicated to the industry that FDA believes that a NDI that is used in, for example, one hundred separate dietary supplements would necessarily be the subject of one hundred separate NDI notifications.

The draft guidance, for example, states that a company that "intend[s] to market" a dietary supplement that contains a NDI must submit a separate NDI even if "another manufacturer or distributor" has already submitted a notification for the same NDI. This may be true in some cases and is inaccurate in others. If that previous submitter is the manufacturer or distributor of the very NDI that is included in a dietary supplement – or one hundred different dietary supplements – that one or more companies intend to market, these supplement companies will not need to file separate notifications in most cases. In fact, in this scenario it is possible for a single submission for just the NDI itself to provide sufficient information that can serve as the basis for the NDI's manufacturer or distributor to conclude that all of these dietary supplements containing such NDI will reasonably be expected to be safe.

AHPA believes that the draft guidance should be revised to clarify when separate notifications are not required for both a NDI and for each and every dietary supplement that contains the NDI. Separate notifications are not required when the initial notification filed for the NDI provides a description of a dietary supplement or a range of dietary supplements that would include the NDI. There is nothing in either the Act or the implementing regulations to prevent such an approach, and in fact 21 CFR 190.6 appears to envision such an option as it requires a notification to include a "description of the dietary supplement **or dietary supplements** that contain the NDI" (emphasis added). Moreover, FDA's actual practice has been to file without objection premarket notifications that describe the NDI specifically but that only generally describe dietary supplements that will contain the dietary ingredient.

AHPA further believes that the most useful guidance that FDA could provide in this specific matter would be to suggest how those who wish to submit a premarket notification that would apply to a broad range of dietary supplements containing a NDI may do so. In addition, AHPA repeats here its view that the draft guidance should be revised to remove any indication that FDA's evaluation of submitted NDIs will transform the legal requirements for marketing of dietary supplements that contain NDIs from the notification process described under law to an FDA approval process.

To address the issues raised above AHPA suggests that the following revisions and additions be made to the draft guidance:

New Question: **Is a manufacturer or distributor of a NDI allowed to include a description of more than one dietary supplement that contains or will contain the NDI?**

Yes. Section 413(a)(2) of the Act states that a NDI notification must include the information that is the basis for the submitter's conclusion that "a" dietary supplement containing the NDI will reasonably be expected to be safe. If the Congress had intended a notification to be required for each and every dietary supplement that contains a NDI the Act would have used the definite article, "the" instead of the indefinite article, "a" in this phrase. In addition, 21 CFR 190.6 (b)(3) specifies that a notification shall include a description "of the dietary supplement or dietary supplements" that contain the NDI.

New Question: **May a manufacturer or distributor of a NDI submit a NDI notification for its NDI even if it does not know, at the time of submission, the exact brand or formula of a dietary supplement that will contain the dietary ingredient?**

Yes. FDA has received numerous NDI notifications from the manufacturer or distributor of a NDI in which the description of the dietary supplement that will contain the NDI is not specifically described or that is somewhat broadly defined. FDA believes that such a notification may comply with 21 CFR 190.6 (b)(3) so long as it includes a description of a dietary supplement or range of dietary supplements that may later contain the NDI.

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

It depends. If you **or the manufacturer or distributor of a NDI** have already submitted a NDI notification for **the same NDI or** a dietary supplement containing ~~a~~ **the same** 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, **whether those were specifically or generally described in the earlier 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, **and** (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~~**.**

Question IV.C.2: If ~~another~~ **a** manufacturer or distributor **of a NDI** 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~~ **It depends**. 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~~ **any one of four parties**: **the** manufacturer or distributor **of the NDI or the manufacturer or distributor of the dietary supplement**. **If the original notifier was the manufacturer or distributor of a particular NDI and conducted its safety evaluation based on the characteristics and intended use of a variety of dietary supplement products, including supplements that conform to a range of composition and labeling specifications that the notifier was proposing to market or have marketed, then any manufacturer or distributor who wishes to market its own dietary supplement containing the same NDI should not submit a NDI notification to FDA as long as the dietary supplement it will market also conforms to the specifications described by the original notifier for the variety of dietary supplements that were the subject of the original safety evaluation.**

On the other hand, if the ~~The~~ original notifier**, as the manufacturer or distributor of a particular NDI,** conducted its safety evaluation based on the characteristics and intended use of ~~the~~ **one** specific **dietary supplement** product under review, including the **specific** composition and labeling of the dietary supplement that the notifier was proposing to market**, then any**~~. 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 be expected to be safe" under the conditions recommended or suggested in the new product's labeling. **One exception to this would be if the original notifier has licensed you to manufacture the same dietary supplement, in which a separate notification would not be needed.**

Notwithstanding the above, in the case of certain NDIs, such as crude botanical NDIs whose only processing consists of dehydration and/or size reduction, the first NDI notification submitted for that botanical is applicable to all subsequent companies who choose to market that NDI in any dietary supplement which conforms to the level and conditions of use established in the original NDI notification.

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. *[AHPA notes that the last two sentences here might be best moved to a separate question.]*

New Question: **Should I submit a separate NDI notification for a dietary supplement that I manufacture or distribute containing a NDI that was already the subject of a NDI notification submitted by the manufacturer or distributor of another dietary supplement that contains the same NDI?**

It again depends. Because the notification requirement is specific to the a reasonable expectation of safety of the dietary supplement that contains a NDI, you should submit a separate notification if the dietary supplement that you will market containing the NDI does not conform to the description of the dietary supplement identified in the notification submitted earlier by the other dietary supplement company.

Question IV.C.4: Can you provide 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.

[NOTE: AHPA recommends the following changes to the left column in the table included in this question.]

- A dietary ingredient that was marketed in the U.S. before October 15, 1994**, including any conventional food, conventional food ingredient, or any preparation thereof which is made by traditional food preparation procedures**
- 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
  a) not been chemically altered**, as defined in the response to question IV.A.4**
  b) been chemically altered**, as defined in the response to question IV.A.4**
- A dietary ingredient that was NOT marketed in the U.S. before October 15, 1994 AND is NOT present in the food supply as an article used for food.

Question V.A.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~~ **accept** 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~~ **one or more** dietary supplement **that will or may come to contain the NDI** with the information required by 21 CFR 190.6(b), **including by identifying a general dietary supplement**

and (2) provided the history of use or other evidence of safety on the basis of which the notifier concluded that the dietary supplement would reasonably be expected to be safe under its labeled conditions of use. **See Question V.A.4 for more information about how generally-described dietary supplements may be addressed.**

Question V.A.4: How should the notification describe the dietary supplement **or dietary supplements** in which the NDI will be used?

The notification should contain a description of the dietary supplement **or dietary supplements** in which the NDI will be used **or may come to be used**, including (1) the **highest** level of the NDI in ~~the~~ **any** dietary supplement**, stated both per serving and per day as calculated by the conditions of use of the supplements**; **and** (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 **that will be** recommended or suggested in the labeling of the dietary supplement **or dietary supplements**, 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~~ **any** dietary supplement **that may contain the NDI**. 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.

The description of the dietary supplement or dietary supplements in which the NDI will be used should also include the identity and level of any other dietary ingredients and non-dietary ingredients (e.g., excipients and fillers) in the dietary supplement or dietary supplements, if the presence of other ingredients is relevant to the submitter's conclusion that a dietary supplement that contains a NDI is reasonably expected to be safe. If, however, the submitter is the manufacturer or distributor of the NDI and has concluded that a wide range of dietary supplements containing the NDI will reasonably be expected to be safe, a statement to that effect, or to the effect that the NDI may be combined with other dietary ingredients and non-dietary ingredients would be sufficient.

In addition, the notification should include information about the manufacturing process or specifications of the dietary supplement, but only if such information is relevant to the submitter's conclusion that a dietary supplement that contains a NDI is reasonably expected to be safe..

When a NDI notification is submitted by the manufacturer or distributor of a specific dietary supplement all of the above information may be provided for the specific dietary supplement. On the other hand, when a NDI notification is

submitted by the manufacturer or distributor of a NDI all of the above information may be provided for a generally-described dietary supplement. A general description may include, for example, statements to the effect that a dietary supplement containing the NDI may be in the form of a tablet, capsule, powder, softgel, gelcap, or liquid, or any other form that is in conformity with section 411(c) of the Act; that any such generally-described dietary supplement will be manufactured with or without other dietary ingredients and food excipients; and that any such generally-described dietary supplement will be manufactured and labeled in a manner that ensures that the level of the NDI and all conditions of use described in the notification are met.

Question VI.A.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**, either provided in a manner that specifically identifies each such ingredient when the NDI will be used in a single dietary supplement or in general terms when the NDI will be used or may come to be used in more than one 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.~~

Question VI.A.10:

[NOTE: With the above revisions the Question VI.A.10 is largely irrelevant and should probably be stricken in its entirety. Should the question be retained AHPA suggests the following revisions.]

What additional identity information should I submit if ~~my~~ **the described dietary supplement** product contains a mixture of ingredients?

If your NDI notification describes a specific dietary supplement you~~You~~ should state the identity and level of each **dietary** ingredient in the dietary supplement. **Other** ingredients, such as those used for a technical or functional effect in the product, including binders, fillers, and color additives**, should also be identified but only if identification of these other ingredients is relevant to your safety conclusion**. **On the other hand, if your notification describes a general dietary supplement you may state the identity and level of the NDI, but describe other ingredients that may be included in a dietary supplement containing the NDI in general terms, such as, "with or without other dietary ingredients and other components, as established**

in a master manufacturing record and manufactured under current good manufacturing practice." You should also describe how the combination of all the **dietary** 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 **if, in fact, the combination of dietary ingredients is relevant to your safety conclusion**. 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**, but only if this bioavailability information is relevant to your safety conclusion**.

Use in conventional food production or in live form is not a prerequisite for a bacterial or yeast ingredient to be a dietary ingredient

In Question IV.C.3 FDA discusses bacterial ingredients in dietary supplements, stating that "not all bacterial microorganisms are dietary ingredients." FDA adds, "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)." As an example, FDA notes that certain bacteria used to produce fermented foods that are eaten without cooking or pasteurization "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))." The implication of FDA's response appears to be that the agency believes that such an ingredient must be in the conventional food supply in order to be a dietary ingredient, and furthermore that they must be consumed in live form in order to qualify as a dietary ingredient.

AHPA assumes this discussion is intended also to cover yeast used in food and dietary supplements (e.g. brewer's yeast); or if not, then for clarity yeast ingredients should be included in this question.

It is AHPA's view that this position fails to recognize that there were bacterial and yeast microbial ingredients present in the marketplace prior to the passage of DSHEA that are not necessarily used to produce fermented foods. Various species of probiotic and other dietary ingredients were firmly a part of the food and/or "dietary supplement" industries prior to DSHEA becoming law (e.g., acidophilus milk; brewer's yeast used as a source of B vitamins and micronutrients). The NNFA (now NPA) list of dietary ingredients on the market prior to DSHEA becoming law listed several such ingredients, including several species of *Bifidobacterium* and one of *Saccharomyces*.

Furthermore, many bacterial and yeast ingredients are not consumed in live form (e.g. the wild yeast used in sourdough starter). AHPA notes that either live or killed bacterial and yeast ingredients may be suitable as dietary ingredients, although use of the live

form of a microorganism that was previously only consumed killed, would likely be a NDI.

AHPA's position is that subparagraph (E) of the section 201(ff)(1) was meant to capture the many dietary ingredients then on the market that did not fit into the (A) to (D) categories. AHPA also asserts that and yeast ingredients are covered by subparagraph (C) since, as unicellular fungi these are "other botanicals." AHPA therefore recommends the following modifications to this question:

> Question IV.C.3: Should I notify FDA about a **bacterial or yeast** microbial ingredient in my dietary supplement?
>
> ~~Yes, if~~ **It depends. 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)) **a notification should be made**. **In addition, in the case of bacteria or yeast which were previously consumed in food only in cooked or otherwise killed form, use of the microorganism in a dietary supplement in live form would require a NDI notification**.
>
> 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. **Also,** ~~Bacteria~~ **bacteria or yeast** that have never been consumed as food are unlikely to be dietary ingredients.
>
> A bacterial **or yeast** microorganism is a dietary ingredient**, however,** if it is ~~a dietary substance (~~an ~~intentional constituent of~~ **ingredient in** food~~)~~ or otherwise falls within one of the dietary ingredient categories listed in 21 U.S.C. 321(ff)(1)**, or if it is in any of the classes of bacterial or yeast ingredients, such as probiotics and brewer's yeast, that were marketed prior to the enactment of DSHEA in products intended for ingestion in the form of a tablet, capsule, powder, softgel, gelcap, or liquid, or any other form that is in conformity with section 411(c) of the Act**. ~~For example,~~ **While FDA does not have a separate regulatory category or definition for dietary ingredients consisting of live or viable microorganisms, we recognize that** 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)). **And since yeasts are classified as fungi, these are "other botanicals" as defined in section 201(ff)(1)(C) of the Act (21 U.S.C. 321(ff)(1)(C)).** ~~FDA does not have a separate regulatory category or definition for dietary ingredients consisting of live or viable microorganisms.~~
>
> **Any of these bacterial or yeast microorganisms that conform to the dietary ingredient definition and that are in the food supply do not require a NDI notification.**

Human-synthesized constituents of botanicals which are the same as those synthesized by botanicals are dietary ingredients

In the draft guidance FDA takes the position that a synthetically-produced compound that is a copy of a constituent found naturally in an herb or other botanical is not a dietary ingredient under section 201(ff)(1)(F) of the Act. Stated another way, the position that FDA is taking is that a compound synthesized by humans that is chemically identical to a constituent synthesized by an herb or other botanical is not a dietary ingredient under this section. AHPA disagrees.

FDA's interpretation of the phrase "constituent … of [an herb or other botanical] ingredient" ignores the fact that a chemical entity can be the same whether synthesized by a person or by a plant. In fact, in highly purified form, the substances in question derived by humans or from nature are most likely indistinguishable by modern chemical analyses and characterization, and in their biological functions.

Human-synthesis of a compound found in a plant may produce an ingredient that contains varying degrees of impurities, but it is also possible for human-synthesis to produce a material that contains a lower level of contaminants than may be found in nature. In addition, a salt form of a material is not the same chemical entity as that material as a free base, although both the free base and salt forms very well may function equivalently when consumed. Also, some laboratory-synthesized chemicals exist as mirror-image stereoisomeric enantiomers or diastereomers in racemic mixtures, while compounds synthesized within organisms typically will exist in only one enantiomeric form, and only the matching laboratory-produced enantiomer can be considered to be the same chemical entity. It may be reasonable to consider such manufactured ingredients to be NDIs, and a NDI notification may need to address these issues to conclude that a dietary supplement containing such a human-synthesized nature-identical ingredient is reasonably expected to be safe.

What is not reasonable is to consider that these could not possibly be dietary ingredients. There is no valid scientific or toxicological reason to suppose that a human-synthesized, bio-identical copy of a naturally-occurring constituent will exhibit any different biological function *in vivo* than the purified naturally-occurring constituent itself, barring the presence of any toxic impurities (the possibility of which can be suitably addressed by the company submitting a NDI notification). The fact that synthetic copies of natural substances are equivalent to the original substance in safety and in supplementing the diet is amply demonstrated through the fact that many such substances are already in the food supply, such as synthetic caffeine, vitamin E, lycopene, taurine, etc. Furthermore, there is no reason to suppose that the Congress intended to exclude synthetic copies of any of the items listed Section 201(ff)(1). For

FDA to exclude the possibility of synthetic copies in the case of 201(ff)(1)(F) and (F) alone, is arbitrary and capricious.

Aside from the fact that a human-synthesized constituent is the same constituent when it naturally occurs, and so meets the dietary ingredient definition in section 201(ff)(1) of the Act, there is nothing to prevent a human-synthesized constituent from coming into the conventional food supply as an article that is generally recognized as safe for its intended use in whatever food may contain that human-made constituent and in fact there are such "synthetic botanical constituents" already in the food supply. They would thus meet the definition of a dietary ingredient as described in section 201(ff)(1)(E) of the Act, and could therefore be present in a dietary supplement as a dietary substance for use by man to supplement the diet by increasing the total dietary intake.

AHPA therefore requests that FDA revise the draft guidance as follows:

> Question IV.D.2: Is a ~~synthetic~~ **human-synthesized** copy of a constituent or extract of an herb or other botanical a dietary ingredient?
>
> ~~No~~**Yes**. A**lthough a human-synthesized** ~~synthetic~~ copy of a constituent of a botanical was never part of the botanical**, as long as it is an exact copy of a constituent that is naturally-synthesized in a botanical – i.e., that it is in fact an exact "synthetic copy" of the constituent and so is literally chemically identical – it meets the definition of a "constituent" of the botanical under 201(ff)(1)(F)** ~~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~~. **In addition, as long as the botanical itself is marketed in the food supply, its naturally-synthesized constituents, which are clearly included in 201(ff)(1)(F), are also dietary substances for use by man to supplement the diet, as described in 201(ff)(1)(E), and the constituent, whether botanically-synthesized or human-synthesized, could increase the total dietary intake of the constituent.**

Further clarification is needed that a prior marketed dietary ingredient that is approved or authorized for investigation as a new drug may continue to be marketed as a dietary ingredient

The draft guidance discusses in several questions the possible dietary ingredient status of a substance that is also an article that is approved or authorized for investigation as a new drug. Of particular interest for these comments are Questions IV.D.9 and IV.D.11. The former addresses a substance that is both a new drug or subject to investigation as a new drug and also a constituent of a plant that has never been marketed as a food or as a dietary supplement, while the latter addresses the related issue of a new drug or investigational substance that is itself or is found in a dietary ingredient that was already marketed.

Question IV.D.9 includes a statement that as written appears to be applicable to all dietary ingredients and constituents thereof that may be new drugs or subject to investigation, irrespective of whether an ingredient or constituent is currently or has previously been marketed as a dietary ingredient. In addition, Question IV.D.11 is inaccurate in stating that the presence of a new drug or investigational drug substance in a food as a constituent would not be enough to show that the substance was marketed. The Act, in fact, is clear that a substance may continue to be marketed as or in a dietary supplement if the substance was already marketed as or in a food or dietary supplement when approval of such a substance as a new drug or publicity about investigation of such a substance as a new drug occurs.[29] This is true even when the substance is a naturally-occurring constituent of a dietary ingredient, irrespective of whether the prior marketing of that dietary ingredient identified the contained constituent in labeling or marketing. If this were not true, then publicity about an IND for, for example, menthol for investigation for any drug purpose would force the removal of peppermint from the market, contrary to the clear language of the Act.

In order to clarify and correct these points AHPA therefore believes both of these questions need to be revised and offers the following revisions as the most straightforward way to do so.

> Question IV.D.9: ~~How do I determine whether a dietary ingredient is an article that is approved or authorized for investigation as a new drug?~~ **Can I manufacture and sell a dietary supplement containing a dietary ingredient that was not marketed as or in a food or dietary supplement before it was approved as a drug, licensed as a biologic, or authorized for investigation under an IND?**
>
> **No.** Either an entire product or a ~~component~~ **constituent** 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. For example, assume that Substance A, which is a constituent of a plant ~~and~~ has never been marketed as **or in** an article of food or as **or in** a dietary supplement, ~~is~~ **might come into the market as** a botanical dietary ingredient under section 201(ff)(1)(~~C~~**F**) 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 that is being studied for its possible therapeutic action. Any compound that **was not previously in the food supply and** delivers Substance A is excluded from being used in a dietary supplement. **See question IV.D.11 for an example that clarifies situations in which a new drug or investigational substance**

[29] Section 201(ff)(3)(A) of the Act.

that was previously marketed in or as a food or dietary ingredient may continue to be marketed as a dietary supplement.

Question IV.D.11: Can I manufacture and sell a dietary supplement containing a dietary ingredient that was marketed as **or in** 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 this case, assume that Substance B is a constituent of a plant, Plant C, and has previously been or is currently marketed as or in 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; and a drug company is studying a salt of Substance B, "Substance B hydrochloride," as an investigational new drug under an IND. In this case, the relevant article for purposes of whether Substance B can be used in a dietary supplement is again Substance B itself. But because Plant C was marketed prior to the initiation of the described investigation of Substance B as a new drug, Plant C can continue to be marketed as a dietary ingredient, even if it contains a level of Substance B consistent with traditional food preparations of Plant C.**

In considering whether a substance **is an article that** has been "marketed as a **food or as a** dietary supplement ~~or as a food~~," FDA looks for evidence of one of the following:

- 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~~**B** supplement" would establish the marketing of Substance ~~A~~**B** as a dietary supplement. Similarly, business or other 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.
- **Evidence that an ingredient in which the substance is naturally occurring 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 dietary ingredient or dietary supplement catalog listing an ingredient or product identified as "Plant C" would establish the marketing of the plant as well as all of its contained and naturally-occurring constituents, whether or not such listing identified Substance B, as a dietary supplement. Similarly, business records documenting that the ingredient Plant C was offered for sale or sold as an ingredient for use in manufacturing a conventional food would establish the marketing of the ingredient and all of its contained and naturally-occurring constituents, whether or not such listing identified Substance B, as a food. Thus, merely showing that the substance was present in a food as a constituent would be enough to show that the substance was "marketed," but FDA considers this marketing history to be relevant only to the ingredient in forms prepared using traditional food preparation techniques or in any other form in which the ingredient was offered prior to the approval or investigation of**

a new drug. For example, if an extract of Plant C that contained the new drug substance was already marketed it would be allowed to remain on the market. On the other hand, if a marketer developed a new extract with the express purpose of increasing the level of Substance B, that new extract would not be allowed to be marketed.

- Evidence that the substance was a ~~component~~ **constituent** 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. 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. ~~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.~~

Any recommended template for organizing a NDI notification should include an option to describe more than one dietary supplement, including a generally described dietary supplement

The draft guidance at Question V.A.2 provides a recommended template for organizing a NDI notification. AHPA notes that this template is written in a manner that assumes that any NDI notification will be submitted for a single dietary supplement.

As noted elsewhere in these comments, AHPA believes that a NDI notification may be submitted in a manner that identifies more than one specific dietary supplement, or in a manner that describes in general terms a range of dietary supplements that may contain a NDI that is the subject of notification. Such an approach is particularly relevant when a notification is submitted by the manufacturer or distributor of a dietary ingredient as opposed to a dietary supplement.

AHPA therefore recommends that the template be rewritten to provide these options for use especially when the manufacturer or marketer of a NDI submits a notification, and expects or intends for the NDI to be used in more than one dietary supplement.

Information to describe an NDI that is or is derived from an herb or other botanical should more clearly take into account the form of the NDI

The draft guidance includes information on FDA's view of how a NDI should be described in a notification. This information is presented in Question V.A.3 in a manner that seems to imply that such a description can be standardized for any dietary ingredient. This question also refers to section VI.A of the draft guidance, where more specific information is provided.

AHPA believes that Question V.A.3 and the questions in section VI.A should provide consistent information. AHPA believes that the most effective way to do so would be to

simply remove Question V.A.3 or to reduce its answer to one that clarifies that the descriptive information depends on the specific dietary ingredient category and that refers the reader to section VI.A, as follows:

> Question V.A.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. **Additional information to describe the NDI depends to a significant degree on the specific category, form, and identity of the NDI.** ~~; (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.

In reviewing section VI.A, AHPA's comments are largely limited to those sections that are relevant to NDIs generally or to ingredients that are or are derived from herbs or other botanicals. In refraining from commenting on other sections of section VI.A, AHPA is not implying that these other sections may not also need revision.

AHPA recognizes that it is essential for a NDI notification to accurately and precisely describe the NDI. AHPA is concerned, however, that the questions relevant to botanical ingredients in section VI.A are in some cases imprecise or suggest that a notification for such an ingredient needs to provide information that may not necessarily be needed to adequately identify the NDI for the purpose of ensuring that FDA will be able to know with certainty the identity of the NDI.

For example, there is some redundancy in Questions VI.A.11 and 12, as both of these suggest that the part of the plant be identified. AHPA agrees that the part of the plant is essential information with regard to establishing identity, but this needs only one mention in the guidance. In addition, much of the data identified for submission in Question VI.A.12 is unnecessary to identify a NDI that is a botanical ingredient and should not be requested unless relevant to the ingredient's identity or safety determination. Thus, if a NDI is derived, for example, from garlic, it will be sufficient to identify the plant source as the bulb of *Allium sativum* L. Inclusion of a voucher specimen would not assist FDA in understanding or establishing the identity of the NDI, and neither would information that discloses whether the garlic is grown in India or Indiana, for example, nor whether the garlic is grown in the ground or in a greenhouse. While there is some possibility that such factors have some safety relevance, this information should not be described in any manner that suggests that it should always be submitted. AHPA notes also that FDA has received and acknowledged without substantive objection many NDI notifications that did not include a voucher specimen or information on conditions of cultivation or propagation; it thus appears that the record of

the last 17 years indicates that this information is seldom needed to ensure accurate identity of botanical ingredients.

AHPA also suggests that Question VI.A.13 should more bluntly state that botanical ingredients that are raw agricultural commodities or simply dehydrated plant parts will generally not need to describe "production methods," and that Question VI.A.14 should more precisely identify when toxins that may be present in related plants may actually be relevant to a specific NDI. In addition, in reviewing Question VI.A.15 AHPA suggests that greater clarity be provided in addressing standardization and adulterants, and, to be consistent with AHPA's position on the issues of synthetic botanical ingredients as addressed at Question IV.D.2, that the last point in Question VI.A.15 be deleted.

AHPA therefore recommends that the following revisions be made to take into account the above comments:

> Question VI.A.11: What ~~identity~~ information should I submit **to identify and describe** ~~if~~ my NDI **if it** 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.
>
> **We recommend that you also provide the following:**
>
> - **The part of the plant from which the ingredient is derived.**
> - **Conditions of propagation, but only if they involve deliberate manipulation of propagation in a manner that is significantly different than common plant propagation and breeding practices;**
> - **Conditions of cultivation (e.g., wild harvest, field, or greenhouse), and geographical origin of plant material, but only if this information is essential to accurately identify the NDI or is relevant to your determination that the ingredient is reasonably expected to be safe;**
> - **Period during which the botanical is cultivated and/or harvested (season or month(s) and/or age of plant) and/or the stage of maturity of the harvested plant part, if this information may affect the identity or safety of the NDI.**
>
> **You may, in addition, provide a common or usual name for your botanical ingredient.**
>
> Question VI.A.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.~~

Question VI.A.13: Should I describe the production methods for my botanical **or cultured** NDI?

~~Yes~~ **It depends**. **If a botanical NDI is a raw agricultural commodity or simply a dehydrated plant part and is cultivated and/or wildcrafted under standard agricultural and collection conditions then no information on production methods is needed to clearly identify the NDI. But if the NDI is, for example, a botanical extract, a purified constituent, or a cultured microorganism, you** ~~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 **or microbial** 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.

Question VI.A.14: How should the identity section of my NDI notification deal with toxins in **a plant or microorganism from which a botanical NDI is derived or 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 **identified or** unidentified) known to be present in ~~the~~ **a plant or microorganism from which a NDI is derived.** ~~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 **itself**, 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 **microbial** strain designation) can be relevant to the safety determination when some varieties or strains of a species are known to contain toxins. **You should also identify toxins or other deleterious constituents of related plants**

or microorganism in the same species (if the NDI is derived from a taxon identified below the species level) or in a family or genus that is phylogenetically related to the NDI, but such information would not be needed if it is well established that the toxin or constituent is not present in the species that you are using. For example, although toxic pyrrolizidine alkaloids (PAs) are known to be present is some species of *Asteraceae*, there would be no need to document the absence of toxic PAs in every NDI derived from every plant in this extensive plant family, such as dandelion root, sunflower seed, or chamomile flower.

Question VI.A.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 (either specifically names or generally described), 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 **quantified** marker substances, **if applicable to your safety conclusion. The marker content may be** 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**, if such standardization is an element of the NDI's manufacture** ~~and how adulterants such as non-food solvents, pesticides, heavy metals, and filth are excluded~~.
- **How adulterants that are potentially present due to production methods, such as non-food solvents, are excluded.**
- **How adulterants that are potentially present in raw materials from which a NDI is derived, such as pesticides, heavy metals, and filth are controlled. FDA advises that a statement that the product is manufactured in accordance with current good manufacturing practice, citing either 21 CFR 110 or 111, would generally be sufficient for this purpose.**
- If **non-food** 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.

Question VI.A.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 **and any specifications for the production organism in the finished NDI, particularly if the production organism is not inactivated and/or removed.**, the **The** fermentation vessel(s), the fermentation conditions, the methods used to harvest the NDI from the fermentation mixture**, and** Post**post-fermentation harvest and processing (including filtration, washing, and preservation methods) should also be described if these are relevant to the identity and/or safety of the NDI.**, 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.

The guidance should better clarify that no information about a claim for the NDI or dietary supplement containing a NDI is needed in a notification

The draft guidance includes one question that clarifies that data or information used primarily to substantiate a claim about the efficacy of the ingredient or supplement is not useful in a NDI notification unless it also contains information that pertains to safety.

AHPA agrees, but suggests that the question would provide greater clarity if it also stated that there is no need to even mention such claims in a NDI notification, as follows:

> Question V.A.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, **descriptions of claims that may be made for a dietary supplement that may contain a NDI or** data or information that is used primarily to substantiate a claim about the efficacy of the ingredient or supplement is not useful unless ~~it~~ **these** also contain~~s~~ 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. 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.

The draft guidance should refrain from restating manufacturer's requirements under 21 CFR 111 or from imposing new manufacturing requirements not envisioned in 21 CFR 110 or 111

At several places in the draft guidance FDA brings up issues that are required to be addressed by dietary supplement manufacturers under current good manufacturing practice regulations, and specifically under 21 CFR 111, but that are either not relevant to NDI notifications or have been addressed elsewhere in the draft guidance. One such example, Question VI.A.18 on supporting data for product expiration dates, should be completely removed from the draft guidance. This is strictly a cGMP issue and is unlikely to be the kind of information that a manufacturer or distributor would use as the basis for its conclusion that one or more dietary supplements containing a NDI are reasonably expected to be safe. Furthermore, Question VI.A.18 includes language that would require companies to show that "no new degradants" will be formed during a product's shelf life. AHPA strongly objects to the notion that food manufacturing companies, including dietary ingredient and supplement manufacturers, bear any responsibility to identify or quantify degradation products in their goods or that such information is important to ensure the safety of foods or dietary supplements.

AHPA therefore proposes the following revisions and addition to address cGMP related issues.

> Question VI.A.3: How much detail should my description of the **NDI** 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~~ **In addition, you** should identify any points in the **manufacturing** process that you know to be ~~relevant to~~ **necessary to ensure** the safety of ~~the~~ **a** dietary supplement **that will contain the NDI**. Detailed descriptions of manufacturing should be limited to those portions relevant specifically to **the** safety **of the NDI, as opposed to requirements that apply generally to foods to make them fit for human consumption**. ~~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~~ **but FDA recommends that you** select only those that are relevant to the identity and safety information that provides the basis for the safety of your NDI.

New Question: **How much detail should my description of the dietary supplement manufacturing process contain?**

As a rule a NDI notification does not need to describe the manufacturing process for a dietary supplement that will contain the NDI that is the subject of notification and it is usually sufficient to simply state that such dietary supplement will be manufactured under current good manufacturing practice. Nonetheless, if there are any points in the manufacturing process of a dietary supplement product that contains or will contain a NDI that you know to be necessary to ensure the safety of the dietary supplement and that are directly related to the presence of the specific NDI, or which fall outside of the scope of traditional food manufacturing procedures, you should identify these points.

Question VI.A.4: ~~What is a specification?~~ **What specifications should be disclosed in a NDI notification?**

[NOTE: In recommending that Question VI.A.4 be rewritten AHPA also suggests that the term "Specification" be added to Section VII, Definitions, and that it be defined as, "A specification is a set of standards developed by the manufacturer or distributor of a material (e.g., a NDI or a dietary supplement). An appropriate specification must be established for each of the components of the material, and for the material as a whole." AHPA notes that a single specification document will generally not include standards for more than one item, i.e., the standards for components are not generally listed in the same document as the standards for the finished product.]

~~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~~ **appropriate** specification**s for the ingredient itself** should **be included, and specifications for components used to manufacture the NDI and/or a dietary supplement that will contain the NDI may be included if such**

specifications are not generally addressed under current good manufacturing practice and are relevant to the safety of the NDI. Specifications identified in a NDI notification, which may be presented in the form of a specification sheet, should include critical safety attributes, and may omit attributes not relevant to safety or identity ~~The specification sheet~~**. A NDI notification** should provide a list of tests, the acceptance criteria for each test, and **references to the** analytical methods used to support the acceptance criteria **for any stated specification**. 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 **referenced in the specification** 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**, evaluate, and/or quantify** the analyte **or other tested parameter**.

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 **or band** matches (both height**, area, intensity** and location**as applicable**) or there is a description of which ~~peak or~~ peak**(**s**) or band(s)** 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 **or bands**, but does require matching sufficient numbers of peaks **or bands** ~~across the entire spectrum or chromatogram~~ to assure the validity of the test result. ~~Components~~ **Constituents** that are known to be toxic can be identified by a single acceptance criterion (e.g., "less than")**. Other**~~, but~~ acceptance criteria ~~for other components should be expressed as a range~~ **may be expressed as a minimum, maximum, or range, as applicable to the tested parameter**. The source and authenticity of analytical standards **or other reference materials** should also be documented.

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

If you are ~~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).

On the other hand, if you are a manufacturer or distributor of a NDI you are not required by regulation to establish the above specifications. It may nonetheless be common industry practice for NDI manufacturers and distributors to establish some such specifications.

Irrespective of whether you are a manufacturer or distributor of a NDI or of a dietary supplement that will contain a NDI, you ~~You~~ should describe in your notification those specifications**, whether for the NDI, the components used to manufacture the NDI, or the dietary supplement containing the NDI,** 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.~~ **If relevant to your conclusion that a dietary supplement containing a NDI will reasonably be expected to be safe, you should also include**~~, 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, **and, if relevant to product safety,** 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~~ **information** 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.

~~Question VI.A.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.~~

FDA should not assume that all dietary supplements will be used for the entire lifetime of each consumer

In Question VI.A.19 the draft guidance states that FDA will assume "daily lifetime use by all age groups at the highest recommended serving size" as described in the conditions of use for a dietary supplement that contains a NDI. This approach does not take into account usage levels that may vary over the lifetime of a user.

It is possible for the described conditions of use to suggest a lower recommended serving size for certain age groups, for example a smaller serving size than the adult serving size for children. This approach was taken in a notification submitted by Embria Health Sciences, LLC on December 14, 2010 (received by FDA on January 3, 2011) for its NDI identified as "Dried Fermentate (made using *Saccharomyces cerevisiae*)" in which the level of use was described as up to 3 grams per day for adults but only 500 mg per day for children over the age of 4. It would clearly be inappropriate to assume that the daily use of this ingredient will be 3 grams per day throughout the lifetime of all users, including users that begin use while children at a daily consumption of 500 mg.

In addition, although some supplements may be used on a daily or nearly daily basis for many years, that should not be assumed to be the norm. To the best of APHA's knowledge, it is rare for consumers consistently to consume the same food or dietary supplement daily over the course of more than a few months or years (except for certain staples such as wheat, potatoes, or rice).

AHPA therefore requests that this sentence be stricken from the question, as follows:

> Question VI.A.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).

FDA's discussion of "other evidence of safety" must not overstate the amount of data required by the law, either explicitly or implicitly

In section VI.B of the draft guidance, FDA provides useful information on the role of "history of safe use" and on the role of "other evidence of safety" in a NDI notification. AHPA believes, however, that FDA has overly and inappropriately relied on the extent

and types of safety evidence required for new food additives. As FDA has acknowledged, Congress established different requirements for safety evidence for NDIs than for food additives. But FDA's draft guidance pays only lip service to this important point.

Furthermore, FDA's discussion of "other evidence of safety" appears to presuppose that, if there is inadequate "history of safe use" information to establish a reasonable expectation of safety for the dietary supplement(s) containing the NDI under the recommended conditions of use, then the notifier is required to conduct food additive type safety studies of its own to provide the necessary evidence; when in fact the only data the law explicitly requires be provided in such a NDI notification is "any citation to published articles" which the notifier relies upon in determining there is a reasonable expectation of safety.

As stated at the outset of these comments, AHPA intends to submit subsequent comments to the draft guidance at a later date, which should be considered to be hereby incorporated by reference in these comments. One of the key purposes of AHPA's future comments will be to provide comments on section VI.B. In the interim, AHPA requests that FDA delete in their entirety from within section VI.B both "Table 2: Safety Testing Recommendations Matrix" and questions 20-25. This table and these questions are overly prescriptive and likely to cause confusion. AHPA believes that any such lists or table will inevitably be interpreted by regulators, notifiers, and others to mean that the "proper" way to establish a reasonable expectation of safety in each of the identified cases is to perform all of the studies listed. AHPA believes that any such interpretation, whether explicit or implied, is contrary to and goes far beyond the intent of the law and is wholly unnecessary and inappropriate in many cases to establish a reasonable expectation of safety.

If FDA retains these questions and table, AHPA requests the word "Recommended" be stricken from the description of the table, the clause "What types of data would help…" be replaced by "What types of data may be helpful…", and that the answer to each question begin with the following clear disclaimer: "FDA provides the following list for informational purposes only. It is not intended to state or imply that any or all of these items is necessary in an NDI notification to establish a reasonable expectation of safety for the dietary supplement(s) containing the NDI under the recommended conditions of use."

Section VI.C, Summary of the Basis for Your Conclusion of Safety, should be largely removed

It is AHPA's view that almost all of Section VI.C is overly prescriptive and is predicated on a level of evidence inconsistent with the law, and should therefore be removed, with the possible exception of Question VI.C.29.

FDA's definition of an Amino acid is flawed

In section VII Definitions of the guidance, FDA defines "Amino acid" as "An alpha-amino carboxylic acid used as a constituent of proteins or peptides." AHPA believes this definition to be fundamentally flawed and inconsistent with the intent of Congress. There is nothing in the text of the law or the Congressional record which suggests that Congress intended so limited a definition of "amino acid." The term "amino acid" normally refers to any organic molecule containing an amino group (NH2), and a carboxylic group (COOH). There are over 200 amino acids that have been found to occur naturally, of which only about 20 are used in making protein. FDA commissioned a review of amino acids used as dietary supplements, which was published in 1992 and which states "Amino acids are the individual structural units of proteins and are precursors for or may function as biologically active molecules." [30] Various non-proteinogenic and non-standard amino acids were in the food supply in purified form at the time DSHEA was passed into law, such as carnitine, GABA, and selenomethionine, Therefore if Congress intended to limit 201(ff)(1)(D) to only proteinogenic amino acids, they would explicitly have said so. AHPA therefore recommends the definition of Amino Acid be revised as follows.

> "An organic molecule containing an amino group (NH2) and a carboxylic group (COOH) used biologically as a structural unit of proteins or as precursors for, or which function as, biologically active molecules."

FDA's definitions should not simply reference earlier portions of the document.

In section VII Definitions of the guidance, FDA defines "Chemically altered" and "Marketed" by referring the reader to the text of one of the questions discussed previously in the document. FDA should instead reproduce the relevant portion of the document in the applicable definitions.

[30] "Safety of amino acids used as dietary supplements," Life Sciences Research Office Federation of American Societies for Experimental Biology, July 1992.

Additional miscellaneous comments

AHPA submits here comments on several additional details.

The draft guidance should not solicit "voluntary" NDI notifications for ingredients that are not NDIs.

The draft guidance states at Question IV.B.2 that voluntary NDI notifications may be advisable for ingredients that are generally recognized as safe or approved as a direct food additive in the U.S. The draft also states at Question IV.B.2.a that FDA intends to continue to review voluntarily submitted notifications for NDIs that are exempt from notification requirements.

AHPA does not believe that FDA should solicit or accept notifications for NDIs for which notifications are not required, nor for dietary ingredients that are not NDIs. With regard to the former, AHPA notes that section 413(b) of the Act provides a mechanism for submission of a petition proposing the issuance of an order prescribing the conditions under which a new dietary ingredient under its intended conditions of use will reasonably be expected to be safe. AHPA believes that use of this mechanism would be more appropriate for any company that wishes to submit to FDA information regarding a NDI for which no notification is required, and suggests that the two above-cited references to voluntary NDI notifications should be removed from the draft guidance.

The function of a botanical marker substance may be irrelevant to a safety evaluation of a NDI.

Question VI.A.15 identifies how an extract of a botanical or dietary substance should be described, and includes that such description should include a description of "whether a marker is a marker of efficacy, toxicity, or surrogate marker." AHPA notes that with the exception of markers of toxicity, such information is probably irrelevant to a safety evaluation and suggests that the phrase be amended, for example, by adding the words, "if relevant to your safety conclusion."

Conclusion

AHPA has provided these comments to express the views of the organization and its members on FDA's draft guidance on new dietary ingredients. AHPA has taken this exercise seriously and has expended considerable resources to offer specific suggestion about how the guidance should be revised. AHPA staff and counsel will make themselves available at any mutually convenient time to discuss any of the topics addressed herein and to contribute in any way possible to creating more useful guidance that is consistent with the law.

Respectfully submitted,

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