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DRAFT GUIDANCE FOR INDUSTRY (August 2016); DIETARY SUPPLEMENTS: NEW DIETARY INGREDIENT NOTIFICATIONS AND RELATED ISSUES

December 12, 2016

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A. BACKGROUND

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issued a Federal Register notice on August 12, 2016 (the August 12 notice) that announced availability of a revised draft guidance for industry titled, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (the 2016 revised draft guidance). This revised draft guidance replaced draft guidance of the same name initially issued by FDA in July 2011 (the 2011 draft guidance).

The August 12 notice stated that FDA intended the 2016 revised draft guidance to help dietary supplement manufacturers and distributors decide whether to submit an NDI notification, and to provide recommendations on how to conduct a safety assessment for an NDI notification and what to include in the notification. Related to these two purposes, in the 2016 revised draft guidance FDA identifies two goals of the guidance: to improve the rate of compliance with the NDI notification requirement and to improve the quality of notifications.

In the August 12 notice FDA also acknowledged that the 2011 draft guidance contained gaps and unclear statements that were subject to confusion and misinterpretation, and that the Agency had therefore decided to clarify and better explain its thinking on some critical issues, in addition to explaining their public health significance, and to request additional comments on these issues before publishing a final guidance. FDA also noted in the August 12 notice that it had revised certain questions and answers from those in the 2011 draft guidance and added a number of new questions and answers.

AHPA includes among its members companies that sell only dietary ingredients that were marketed in the U.S. prior to October 15, 1994 (i.e., old dietary ingredients, or ODIs; or pre-DSHEA dietary ingredients) or dietary supplements that consist only of

pre-DSHEA dietary ingredients; and other companies that sell NDIs or dietary supplements that contain one or more NDI. AHPA and its members therefore have an interest in the 2016 revised draft guidance and these comments are submitted on behalf of AHPA and its members.

The absence of comments on any portion of the 2016 revised draft guidance should not be taken to mean that AHPA agrees with that portion, unless such agreement is specifically stated.

B. SUMMARY OF POINTS

AHPA is identifying here numerous concerns on the content of the 2016 revised draft guidance and suggestions for improvements to any subsequent draft or final version of the Agency's NDI notification guidance. The most significant of these comments include the following views and suggestions:

- The revised draft guidance is unlikely to achieve the goals described by FDA in the guidance;
- The revised draft guidance is contrary to Congressional intent in numerous areas and would unnecessarily burden the dietary supplement industry and dietary supplement consumers, and is wholly inconsistent with the economic and small business analyses prepared in connection with the NDI notification regulations in 21 CFR § 190.6;
- FDA must refrain from declaring or implying that each dietary supplement that contains an NDI requires a separate NDI notification, and should instead encourage manufactures and distributors of new dietary ingredients to include in notifications very broad descriptions of the many dietary supplements that are expected to contain the subject NDI;
- Any list of FDA-recognized pre-DSHEA dietary ingredients should include all ingredients that are very likely to have been marketed in the U.S. prior to October 15, 1994, as well as traditional preparations of all such ingredients, and should not be limited to the actual ingredients proven to be sold at that time, but should be broadly described;
- FDA must clearly state that manufacturers and distributors of dietary ingredients and dietary supplements are not required to have documentation in their files proving that an ODI was marketed prior to DSHEA;

- Changes to manufacturing processes or products specification of an existing ingredient do not automatically create an NDI;
- Processing or specification modifications that lower impurities should not trigger an NDI notification requirement;
- The "chemical alteration" standard is not limited to conventional foods as FDA asserts, but rather applies to dietary ingredients as well;
- Conventional foods and other ingestible substances marketed within the U.S. prior to DSHEA are not NDIs unless they are chemically altered;
- Changes inherent in traditional food manufacturing processes are not "chemical alteration";
- Supercritical fluid extracts were marketed as food ingredients prior to DSHEA;
- FDA should implement the use of master files as an option;
- The draft guidance should not imply that shelf life dating is required, and should not impose impractical or unfeasible requirements with respect to the identification or presence of "degradants" in chemically complex ingredients;
- When interpreting toxicological data, FDA should not require new dietary ingredients to meet safety standards higher than those that existing foods would meet;
- Various definitions should be clarified; and
- A number of inaccurate or inappropriate statements in the current draft should be removed.

AHPA is providing this summary of the points made in these comments as a convenience to readers of this document. Note however that this summary section is not intended as a substitute for the more detailed comments presented below, which should be read in its entirety.

C. GENERAL COMMENTS

In submitting comments to the 2011 draft guidance AHPA identified significant concerns and offered numerous suggestions for improvement. In reviewing the 2016 revised draft guidance, AHPA recognizes some improvements when compared to the 2011 draft guidance, but also notes that many of AHPA's suggestions were not addressed or not accepted in the revised draft. More importantly, AHPA continues to have some of the same concerns about the content of the 2016 revised draft guidance, and also has additional concerns related to revisions in the 2016 revised draft guidance.

AHPA also believes that the 2016 revised draft guidance is unlikely to achieve the expressed goals identified in the guidance itself or the purposes identified by FDA in the August 12 notice. AHPA does not believe the 2016 revised draft guidance, as written, will improve the rate of compliance with the NDI notification requirement or improve the quality of notifications; nor is it likely to either help dietary ingredient and supplement manufacturers and distributors accurately decide whether to submit an NDI notification or to help or encourage such firms to implement many of the recommendations in that guidance on how to conduct a safety assessment for an NDI notification and what to include in the notification. AHPA furthermore believes the draft guidance contravenes the express will of Congress.

In order to better achieve these dual purposes and align with Congressional intent, AHPA recommends that FDA issue additional follow-up draft guidance that takes into account the concerns and suggestions presented in these and other comments submitted to the Agency. AHPA also requests that FDA reconsider some of the concerns and suggestions presented in comments submitted to the 2011 draft guidance that were not addressed or not accepted in development of the 2016 revised draft guidance,[1] and therefore incorporates by reference to the present comments the entirety of AHPA's earlier comments as submitted on December 2, 2011.

AHPA continues to view the 2016 revised draft guidance, much like the 2011 draft guidance, as seeking to erect extra-legal barriers to market entry and to transform the legal requirements for marketing of dietary supplements that contain NDIs from DSHEA's very limited notification process to a dietary supplement product specific FDA approval process. Instead of facilitating compliance with the NDI provision of the law, the 2016 revised draft guidance increases the burden on the supplement industry far beyond the intent of DSHEA with no concomitant benefit for consumers.

[1] AHPA additionally suggests FDA consider reorganizing any subsequent draft or final NDI guidance to treat separately (1) on the one hand, all of the included details that are the Agency's legal interpretations of the NDI provision of the Act, and (2) on the other hand, those details actually relevant once a firm has made the decision to submit a notification for an ingredient it has identified as an NDI. Such separation would assist companies that assign staff or consultants with expertise in legal issues, such as attorneys and regulatory staff, to evaluate and advise on legal matters, while on the other hand assigning persons with scientific expertise to the tasks associated with preparing the scientific information that is the basis of the submitting company's determination that a dietary supplement or supplements containing the NDI are reasonably expected to be safe.

In submitting these comments AHPA therefore strongly recommends additional significant revisions to the 2016 revised draft guidance, and calls on FDA to make additional changes as needed to ensure that any subsequent draft or final NDI guidance is consistent with DSHEA by incorporating the revisions suggested in these and AHPA's earlier 2011 comments.

D. LEGISLATIVE AND REGULATORY FRAMEWORK

AHPA considers the draft guidance to be contrary to Congressional intent and to create an undue burden on industry and on supplement consumers.

DSHEA established a regulatory framework for dietary supplements as a separate class of foods and amended the law to end FDA's capacity to classify ingredients now in this class as unapproved food additives, thereby requiring food additive approval. Even before DSHEA, Congress had taken away FDA's power to regulate vitamins and minerals above certain daily consumption 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, comply with a wide variety of regulations covering facility registration, good manufacturing (and warehousing) practices, product labeling, adverse event reports, and other operations, as well as filing required NDI premarket notifications to FDA when a new ingredient is introduced to the marketplace.

Into this settled regulatory environment, the 2016 revised draft guidance would place numerous extra-legal requirements on manufacturers and distributors of dietary ingredients and dietary supplements, including at least the following:

- Such firms would be required to establish the pedigrees and even the detailed manufacturing processes of all old dietary ingredients, even though there is no such requirement in the Act;
- Submission of NDI notifications would be expected for many if not every supplement containing a new dietary ingredient;
- These notifications, if not based on entirely historical use, would need to be supported by safety documentation that meets or exceeds food additive

requirements and appears to be, to some degree, modeled on the safety evaluations and manufacturing information required for drugs, even though these are the very requirements DSHEA sought to strike from the dietary supplement regulatory paradigm;

- Many ingredients that were marketed in the U.S. prior to October 15, 1994 (i.e., old dietary ingredients, or ODIs) would be reclassified as NDIs.

Such extra-legal requirements are all clearly inconsistent with the intention of the Congress when DSHEA was enacted 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 2016 revised draft guidance as written would have the effect not only of stifling innovation in this nearly $40 billion supplement industry, but also driving many existing ODIs and dietary supplements out of the marketplace and suppressing the use of ODIs by new market entrants, thereby reducing consumer choice and access.

On several occasions FDA has stated its view that there is only a "minimal burden" on companies to meet the requirement to submit an NDI notification.[2] The Agency explains its "minimal burden" rationale by ignoring any effort required of the NDI manufacturer or distributor to develop the information described in the revised draft guidance and considering only the expense associated with the administrative processes involved in organizing and presenting pre-existing data. As is discussed elsewhere in these comments,[3] AHPA's view is that the burden created under the 2016 revised draft guidance, if fully implemented, would increase dramatically from that contemplated by DSHEA.

It is the considered view of Congress, as memorialized in the accompanying Senate Report[4] (the DSHEA Senate report) and cemented in DSHEA, that consumers have a right to access the broadest possible range of dietary supplements so long as they do not present a significant or unreasonable risk of illness or injury, and that the Federal

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[2] Examples include 70 FR 6444, February 7, 2005; 76 FR 32214, June 3, 2011; and 78 FR 52773, August 26, 2013.

[3] See comments # E1, E3, E5, and E9 in particular.

[4] Senate Report 103-410, October 8, 1994.

government must not take any action to slow, limit, or impede the flow of safe dietary supplements to the public. It is therefore incumbent upon FDA to ensure it does not promulgate NDI guidance that imposes unnecessary burdens on firms marketing or using dietary ingredients, whether new or old.

E. KEY ISSUES AND CONCERNS

While there are numerous details in of the 2016 revised draft guidance that could be improved to better meet the Agency's stated goals and the purposes identified in the August 12 notice, AHPA has identified several specific issues addressed in the revised draft guidance as of most significance to AHPA and its members and is addressing each of these below.

1. Duplicative dietary supplement filings should be discouraged

1.1 FDA's approach is flawed

AHPA continues to have significant concerns that the 2016 revised draft guidance, like the 2011 draft guidance, implies that a separate notification is necessarily required for potentially every dietary supplement that contains an NDI, or at least many different supplements containing the same NDI. This implication is conveyed through statements scattered throughout the document and various provisions requiring excessive levels of specificity and detail regarding the dietary supplement(s) that will contain the NDI.

For example, the draft guidance contains the following statements; note the emphasis on the singular form of the terms *dietary supplement* or *product* throughout:

- Section VI Question A11: "You should state the identity and level of each ingredient in the *dietary supplement*, including both dietary ingredients and other ingredients, such as those used for a technical or functional effect in the *product* (e.g., binders, fillers, and color additives). You should also describe how the ingredient combination in the mixture relates to the history of safe use or other evidence of safety of the *dietary supplement* in which the NDI will be used. The dietary supplement safety narrative should address bioavailability of the ingredients as formulated, including use of any binders or fillers that affect bioavailability of any of the dietary ingredients in the *dietary supplement*."

- Section VI Question C3: "If the *supplement* contains dietary ingredients other than the NDI, the dietary supplement safety narrative should identify the NOAEL and ADI for each ingredient…, describe the toxicity data or adverse events that were the basis for determining the NOAEL, state the basis for the margin of safety for each ingredient, and discuss whether there is any possible synergy or interaction among any or all ingredients that could affect the safety of the *dietary supplement*. For each dietary ingredient other than the NDI, the dietary supplement safety narrative should concisely evaluate known safety concerns and describe how the notifier concluded that the combination of ingredients will reasonably be expected to be safe. If the formulation of the *product*, including other ingredients, affects the bioavailability of dietary ingredients, then the safety narrative should include a discussion of the effective per-serving intake level of the dietary ingredient(s) in the products compared to per-serving intake levels or dosages described in the history of use or other evidence of safety….The safety narrative should also describe the function of each food additive, color additive, and GRAS substance (i.e., each non-dietary ingredient), including the technical effect and the quantity needed to achieve that technical effect. References to the applicable food additive regulation, color additive regulation, GRAS regulation, or GRAS notification are also recommended…."

AHPA disagrees with an approach to NDI notifications and evaluations that assumes separate NDI notifications are required for every dietary supplement that contains an NDI; such an approach is inconsistent with the statute and is wholly impractical and economically impossible. It is also completely inconsistent with the economic and small business analyses conducted in connection with 21 CFR §190.6, as discussed elsewhere in these comments.[5] The law clearly does not intend NDI notifications to require detailed information, data, and analysis for every possible combination of dietary ingredients, dosage forms, excipient profiles, etc. And contrary to FDA's assertion, nowhere does the law contemplate that "a combination of two NDIs is itself an NDI."[6]

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[5] See comment # E9. To summarize these analyses briefly, FDA estimated submission of between 0 and 12 NDI notifications per year; between 0 and 12 small businesses affected per year; and no more than one notification required per NDI.

[6] Section IV Question C5, Scenario 6. This scenario cites, as support for this assertion, the extreme example of a combination of a *Nerium oleander* ingredient and a *Convallaria majalis* ingredient; however, as discussed elsewhere in these comments (see comment # F3). AHPA believes this example to be unrealistic and implausible.

AHPA also disagrees with the Agency's assertions that are presented as the basis for this flawed approach to establishing the safety of finished supplement products by assuming the need for separate NDI notifications for every supplement that contains an NDI. Thus, AHPA completely disagrees with FDA's expressed opinion (in Section VI Question B1) that "it is not possible" to draw conclusions that combining dietary ingredients that are each reasonably expected to be safe will produce a finished supplement that is also reasonably expected to be safe; nor does AHPA find at all credible the Agency's advice (in Section VI Question C3) to include in an NDI notification discussions of "any possible synergy or interactions among any or all ingredients," except as a rare and unlikely circumstance. These ideas are completely contrary to the basic and logical premise that, except in rare and unlikely circumstances, combining safe food ingredients will with near certainty produce safe foods. As discussed elsewhere in these comments,[7] FDA may call attention to the occasional need to consider whether other ingredients in combination with an NDI may result in a legitimate safety concern, but this theory must be presented as the exception and not the rule.

Both the law and the contents of the DSHEA Senate report are emphatically clear that FDA is to regulate dietary ingredients and dietary supplements as foods; and there is no precedent in the realm of food regulation for safety evaluations to require consideration of a wide variety of permutations (much less every possible permutation) of ingredient combinations, the physical form of the food (e.g., tablet vs. capsule vs. liquid), and the effects of excipients and minor ingredients included in a food for some technical purpose. Congress certainly saw no need for such evaluations in connection with ODIs, despite the fact that many ODIs (like conventional foods) contain naturally-occurring toxins and/or produce physiological effects of various types; there is no reason to expect Congress would deem them necessary for NDIs. Not even food additive petitions, which are designed to evaluate substances that may have no history of use whatsoever in the human diet, contemplate such an enormous volume of data.[8] The closest analog comes from drug regulation, where parameters such as specific active ingredient combinations, physical form, and excipient usage are scrutinized closely –

[7] See comments # E3 and F3 in particular.

[8] AHPA grants that food additive petitions may require consideration of the cumulative intake of chemically or pharmacologically related substances in the diet, if relevant to safety. This is different, however, from a requirement to examine every potential combination of food ingredients.

but, as has been repeated many times by both Congress and industry, FDA is required by law to regulate dietary supplements *as foods and not as drugs*.

For over 20 years, dietary supplements have exhibited a generally excellent track record of safety, with fewer adverse events reported than for conventional foods or drugs,[9] despite their commonly combining multiple dietary ingredients in a wide range of variations. This is clear evidence that, except under rare circumstances, there is no reason to expect that detailed consideration of specific ingredient combinations is necessary to protect the public health.

Furthermore, as discussed elsewhere in these comments, [10] it is not in the interest either of industry, consumers, or FDA itself for large numbers of pointless NDI notices to be filed. AHPA estimates conservatively that the current draft guidance could trigger filing of tens of thousands of notices, which will put a tremendous strain not only on industry but also on the Agency and will likely result in a severe constriction in the range of dietary ingredients available in the marketplace. This would be economically wasteful and an inefficient use of government resources, and is precisely the opposite of Congress' intended goal.

1.2 Solutions that will support the goals of guidance

The best solution to prevent excessive and duplicative submissions of NDI notifications for each dietary supplement that contains an NDI would be for FDA to encourage, in any subsequent draft or final NDI guidance, manufacturers or distributors of dietary ingredients to make sure to provide general descriptions of the many dietary supplements that may contain the NDI. AHPA therefore requests FDA to provide, as a central tenet of any subsequent guidance, specific training and encouragement for manufacturers and distributors of new dietary ingredients to provide in their notifications broad descriptions of all of the dietary supplements that will include or may include the NDI, so long as the information submitted provides the basis for the submitter's

[9] AHPA notes that the Center for Disease Control reports foodborne illness to cause a monthly average of 780,000 adverse events and 4,700 hospitalizations, while the most recently available data from FDA indicate a monthly average of 72,200 drug adverse event reports (AERs). In contrast, the most recently data available from FDA indicate an average of only 412 AERs each month associated with dietary supplements.

[10] See comment # E3 in particular.

conclusion that the dietary supplements containing the NDI will be reasonably expected to be safe.

For example, an NDI notification could reasonably describe dietary supplements that may contain the NDI to be marketed "in the form of a tablet, capsule, softgel, gelcap, powder, or liquid," as long as the information that is the basis of the NDI manufacturer's or distributor's conclusion that the dietary supplements containing the NDI will reasonably be expected to be safe applies to each of these forms.

Similarly, an NDI notification could reasonably describe dietary supplements that may contain the NDI to be "formulated to contain the NDI as the sole dietary ingredient, or to contain one or more additional dietary ingredients," as long as the information submitted provides the basis of the NDI manufacturer's or distributor's conclusion that dietary supplements containing the NDI will reasonably be expected to be safe applies to all such described dietary supplement products.

Finally, AHPA encourages FDA in any subsequent draft or final NDI guidance to make liberal use of the clarifying phrases "if applicable to safety" or "if relevant to safety," rather than stating broad and unrestricted requirements.

2. FDA should not develop an authoritative list of ODIs unless it (1) is prepared to acknowledge as "old" the 1000s of dietary ingredients marketed prior to 1994 and the fact that those specific ingredients are likely not available and that comparable forms presently available are included in the coverage of such a list and all traditional preparations of the dietary ingredients likely marketed prior to 1994; and (2) acknowledges that documentation of ODI-status is not required.

2.1 A recognized list of dietary ingredients that were very likely marketed pre-DSHEA would be of value

In the 2016 revised draft guidance, FDA stated that it is prepared to develop "an authoritative list[11] of pre-DSHEA ingredients, based on independent and verifiable data." In developing the list, the two main factors FDA proposes to use for placing an ingredient on such a list would be: (1) adequate documentation of marketing for use as

[11] AHPA objects to describing such a list as "authoritative" because this implies the list is complete. As FDA acknowledges in the draft guidance, it is unlikely such a list can ever be complete. A better description would be to call the proposed list a "list of FDA-recognized ODIs."

or in a dietary supplement in the U.S. before October 15, 1994: and (2) a precise description of the identity of the ingredient marketed. In addition, FDA states in the revised draft guidance that documentation to show that a dietary ingredient is not an NDI "should consist of written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994," and that examples could include "sales records, bills of lading, sales contracts, manufacturing records, commercial invoices, magazine advertisements, mail order catalogs, or sales brochures."

In AHPA's view the effort described by FDA to create a so-called "authoritative list" of ODIs or pre-DSHEA ingredients is a bound-to-fail enterprise that is described in such restrictive terms so as not to be viable. FDA seems bent on identifying only those few ingredients for which there is absolute proof from company-specific records of pre-DSHEA marketing, 22 years after the passage of DSHEA and 20 years after the Agency failed to act on, or even respond to, the substantive lists of ingredients submitted to FDA by industry trade groups and identified contemporaneously as ingredients believed to have been marketed in the U.S. before October 1994. This idea as described must be rejected as a very poor use of the Agency's limited resources.

Nevertheless, AHPA believes there could be significant value in creating a list of dietary ingredients that are acknowledged as very likely to have been marketed in the U.S. as of October 15, 1994. FDA would need to abandon its very narrow criteria, however, and would need to clearly state its acceptance of all comparable ingredients identified as very likely to have been marketed as ODIs for purposes of the Act's NDI provisions.

2.2 Numerous authoritative references should be recognized

Some of the best resources to identify dietary ingredients that are very likely to have been marketed in the U.S. as of the enactment of DSHEA include each of the lists of ingredients submitted between 1996 and 1998 by trade associations that serve the supplement industry[12]. FDA has previously dismissed these lists because each includes some ingredients that are not dietary ingredients or are vaguely described; or because,

[12] "NNFA List of Dietary Supplement Ingredients In Use Before October 15, 1994;" submitted in April 1996 by the National Nutritional Foods Association; "Herbs in Commerce in the United States as Dietary Ingredients prior to October 14, 1994;" submitted by the American Herbal Products Association on September 17, 1996; and "CRN List of Dietary Ingredients 'Grandfathered' Under DSHEA;" submitted by the Council for Responsible Nutrition in September 1998.

in the case of herbal ingredients, specific plant parts and extract types are not identified; or because these submissions included honest statements to clarify that the trade associations had compiled their lists with presumed honest input from the trade but had not required absolute proof. It should also be noted that some of the ingredients included present significant safety concerns.

AHPA recommends that FDA completely transform its view of these documents and their usefulness in creating a list of FDA-recognized ODIs. The limitations FDA has previously identified with these could be readily overcome, for example by removing from the list drug ingredients (e.g., acetaminophen), as well as herbal ingredients that are known to be highly toxic (e.g., *Nerium oleander*) or that are no longer allowed to be sold as dietary ingredients (e.g., various species of *Ephedra* known to contain ephedrine alkaloids). Similarly, there is readily available information to inform which parts of almost all of the plant species included in any of the industry lists are (and can be assumed, were in 1994) generally available in the market a dietary ingredients, and this information can be applied to make these lists useful resources to indicate dietary ingredients that were or were likely marketed in the U.S. before 1994.

Additional resources that identify botanical dietary ingredients that are very likely to have been marketed in the U.S. as of the enactment of DSHEA are AHPA's publications, *Herbs of Commerce*, 1st edition (1992)[13] and *Herbs of Commerce*, 2nd edition (2000).[14]

In the 2016 revised draft guidance, the Agency opined that "[a]lthough references published before October 15, 1994, such as the 1992 edition of *Herbs of Commerce*, may be supportive, [the Agency is] unlikely to regard a listing in *Herbs of Commerce* as being solely determinative of whether a dietary ingredient was marketed as such before October 15, 1994 because this listing may not specify necessary information such as the plant part and/or extract type." AHPA requests and strongly recommends that FDA abandon the thinking indicated by this statement, as refusal to accept this reference, as well as the other references identified in this section of AHPA's comments, will leave the Agency and industry mired in the current situation and will miss an important opportunity

[13] Foster S (ed.). 1992. *Herbs of Commerce*. Austin TX: American Herbal Products Association.

[14] McGuffin M, Kartesz JT, Leung AY and Tucker AO (eds.). 2000. *Herbs of Commerce*, 2nd ed. Silver Spring MD: American Herbal Products Association.

for progress that will allow regulatory attention to the Act's NDI provision to focus where it should – on truly novel ingredients.

Herbs of Commerce, 1st edition is without question an authoritative record published prior to enactment of DSHEA in 1994. FDA's rejection of this reference as an authoritative list because it does not state plant parts puts the cart before the horse. There was no plant-part designation required pre-DSHEA and FDA's description of this as disqualifying disrespects DSHEA's mandate regarding dietary ingredients on the market at the time of enactment. The 2nd edition, although published after 1994, represented, as is clearly described in its introduction, "a compilation of submissions from companies involved in the trade of products containing botanicals and from experts in this class of trade … 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 submissions [as well as] species that were thought to have been overlooked in this process" by the editors.[15]

Herbs of Commerce 1st and 2nd editions both have some of the same shortcomings already mentioned in relation to the trade association lists submitted to FDA in 1996-1998, as there are species listed that should not be marketed in dietary supplements (again including such taxa as *Nerium oleander* and *Ephedra* spp.[16]) and the text does not identify plant parts or details on the types of extracts made for these plant species that were already in the market. Nevertheless, AHPA believes they contain much useful information which can and should, with a modicum of review and editing, be formally

[15] The introduction to this text also includes a disclaimer stating, "the listing of a particular species of plant in this work is not … in and of itself, evidence that such species was marketed in the United States prior to October 15, 1994," since "neither AHPA nor the editors have expended any effort in independent verification" of the assumption that only pre-DSHEA ingredients were included. But that disclaimer, read in the context of AHPA's honest effort to create an accurate record of the botanicals marketed in the U.S. at that time, does not take from the fact that this reference does, in fact, provide valuable evidence that each of the listed herbs was very likely to have been marketed in the U.S. before October 15, 1994. Seen in this light, *Herbs of Commerce* 2nd edition will support AHPA's above suggestion that FDA move away from its prior insistence on proof positive and instead acknowledge as ODIs all such ingredients so long as they meet the definition of "dietary ingredient."

[16] In suggesting that these and other toxic plant species included in these references may generally be inappropriate for inclusion as ingredients in dietary supplements, and so would be appropriately excluded from any list of FDA-recognized ODIs, it must be acknowledged that such ingredients may have applications in which inherent safety concerns are removed. For example, in the 2016 revised draft guidance FDA envisions a scenario in which the agency would reply to an NDI notification for an extract of *Nerium oleander* with "an acknowledgement letter without objection," apparently in recognition that an extract of this toxic plant can conceivably be made that removes the cardiac glycosides.

captured for use by industry and the Agency alike. While these *Herbs of Commerce* editions do not list the plant parts used, this information is readily available in authoritative references. As for FDA's objection that extract types were not specified in industry lists, AHPA believes that, for each botanical, a variety of extracts made with (at a minimum) water and/or ethanol (and most likely a wide range of other food grade solvents) were available in the marketplace. Comparable ingredients available today should be deemed included in any FDA-recognized list of ODIs.

Additional valuable resources for compiling a list of FDA-recognized ODIs are found in various parts of Title 21 of the Code of Federal Regulations that list articles recognized as food ingredients before 1994.

2.3 Traditional preparations of ODIs should also be recognized as ODIs

As discussed in AHPA's comments to the 2011 draft guidance, it can be reasonably assumed 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. See also related discussions in comment # E10 below.

Congress itself acknowledged that many of these traditional food preparation processes do not raise any new safety concerns by including Sec. 413(a)(1) in DSHEA (the "chemical alteration" standard) and by stipulating that the following, at least, do not constitute "chemical alteration" for purposes of this standard: physical modifications such as minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, powder, or solid in suspension. The items on this list are examples of traditional food preparation processes. Congress does not state that this list is exhaustive, and FDA likewise recognizes that it is not exhaustive; AHPA believes a more comprehensive list will provide clarity to both regulators and industry.

In organizing any list of FDA-recognized ODIs AHPA therefore requests FDA to specifically acknowledge in such list (1) any ingredient that is itself an ODI (based on inclusion in one of the references AHPA has identified here or other credible or authoritative documents), and (2) any ingredient derived from such recognized ODIs through any of the following processes, at a minimum, or a combination of such processes:

- Minor loss of volatile components;
- Drying, lyophilization, or other removal of moisture or other solvents;
- Reducing the size as necessary, e.g., by milling, chopping, cutting, or grinding;
- Extraction (including tinctures) 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;
- Solution in water, slurry, powder or solid in suspension;
- 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;
- 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.

AHPA believes that each ODI present in the marketplace prior to DSHEA was available in a wide variety of forms (whole, chopped, milled, extracted in water, extracted in other food grade solvents, etc.) whose manufacture involved a wide variety of these traditional food preparation techniques, even if commercial documents to prove these

details cannot readily be produced. In order to focus attention on ingredients that are truly novel and therefore merit additional scrutiny as NDIs, FDA should accept the ODI status of ingredients processed by these methods. This will facilitate efficient enforcement by regulators and avoid pointless paperwork exercises by industry. Furthermore, it will provide a level playing field for industry; otherwise companies that have been in existence since before 1994 (and therefore have access to detailed manufacturing process records) enjoy an enormous advantage over newer entrants.

2.4 Any list of FDA-recognized ODIs must bear an appropriate disclaimer as to its completeness

AHPA appreciates that FDA has explicitly stated in discussing this idea in the 2016 revised draft guidance, "The mere fact that an ingredient is not on the list would *not*, however, establish that the ingredient is an NDI or that dietary supplements containing that dietary ingredient are adulterated for failure to notify. Rather, the omission of an ingredient from the list would be regarded as neutral and would not affect the ingredient's regulatory status." AHPA believes this clarification is important and should be retained in future communications and documents regarding any such proposed list.

2.5 FDA must clarify that documentation of ODI status is not a statutory requirement

In addition, AHPA strongly believes that FDA must directly inform the regulated community that manufacturers and distributors of dietary ingredients and dietary supplements are under no statutory obligation whatsoever to document that any of their ingredients are ODIs. The law requires certain actions by companies that bring to market NDIs and dietary supplements that contain NDIs, but the law does not require companies that sell only ODIs to prove that fact.

AHPA therefore requests that FDA explain this fact with absolute clarity. AHPA proposes that this request could best be met by adding one question and answer to any subsequent draft or final NDI guidance, possibly for inclusion in Section IV between Questions A8 and A9, as follows:

> Question xx: What documentation is required to show that that a dietary ingredient was marketed prior to October 15, 1994?
> A: There is no requirement in the law that manufacturers or distributors of dietary ingredients or dietary supplements have documentation to show that a dietary ingredient was marketed prior to October 15, 1994.

…or:

> Question xx: Is a manufacturer or distributor of a dietary ingredient or dietary supplement required under the law to have documentation to show that a marketed dietary ingredient, or the dietary ingredients in its dietary supplement, were marketed prior to October 15, 1994?
> A: No, there is no such requirement in the law.

3. Changes to manufacturing processes or specifications are not germane unless they alter the food in a manner with material relevance to safety

The 2016 revised draft guidance sends mixed messages with respect to the degree and type of changes that would change a conventional food into an NDI, an ODI into an NDI, or an NDI into a new NDI.

In Section VI, "What to Include in an NDI Notification," the draft guidance sets forth instructions indicating that information regarding the identity, manufacturing, and specifications for an NDI should be limited to details relevant to safety. For example:

- In Section VI Question A2, FDA recommends establishment of identity specifications that "are relevant to establishing the basis for the safety of the dietary supplement."
- In Section VI Question A3, FDA states "You should identify any points in the process that you know to be relevant to the safety of the dietary supplement. Detailed descriptions of manufacturing can be limited to those portions relevant to safety and identity, if they can be identified….You may describe the entire process and all specifications or select only those that are relevant to the identity and safety information that provides the basis for the safety of your NDI."
- In Section VI Question A4, FDA states "the specifications should include critical safety attributes and may omit attributes not relevant to safety or identity."
- In Section VI Question A5, FDA states "Your notification should list and explain the role of those specifications that are relevant to the identity of the NDI and to the safe consumption of the dietary supplement containing the NDI."

The instructions above indicate that NDI notices will be focused on information and data relevant to the identity and safety of the NDI, with the implication that changes in

processing or specifications that do not affect any of the submitted information or data do not trigger the need for a new or revised notification. This should also apply generally; i.e., any change in processing or specifications that does not affect the identity or safety of the food does not change it from a conventional food to an NDI, an ODI to an NDI, or an NDI into a new NDI.

This is consistent with FDA guidance for other categories of food, which states "The manufacturing process of a food substance is considered for the purposes of safety assessment only insofar as it may affect the properties and safety of the finished product."[17] AHPA believes this to be appropriate.

However, other sections of the draft guidance are written in a manner that implies nearly any change in processing or specifications will create an NDI and/or require an NDI notification. For example:

- In Section IV Question A12, FDA states with respect to ODIs, "Manufacturing changes that alter the physicochemical structure or properties, purity and impurities, or biological properties (such as bioavailability or toxicity) of the ingredient result in an NDI. For example, using a solvent to prepare an extract from a pre-DSHEA dietary ingredient creates an NDI because the final extract contains only a fractionated subset of the constituent substances in the original dietary ingredient. A manufacturing change which changes the ingredient in a way that leads to alteration of the serving level or conditions of use of the product is another example of a significant change which is likely to create an NDI."
- In Section IV Question B13, FDA states with respect to NDIs for which a notice has already been filed, "If the manufacturing change does not alter the chemical or molecular composition or structure of the dietary ingredient or the specifications needed to describe the ingredient, it is not necessary to submit a second NDI notification," which obviously implies that a second NDI notice is required if these criteria are not met.
- In Section V Question A3, FDA states that NDI notices should "describe the manufacturing process used to make the NDI, including process controls"; FDA

[17] Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives, FDA, June 2014.

fails to indicate this is limited to those process controls relevant to identity or safety.

- In Section V Question A4, FDA directs that NDI notices should "contain a description of the dietary supplement in which the NDI will be used, including: (1) the level of the NDI in the dietary supplement; (2) the identity and level of any other dietary ingredients and non-dietary ingredients (e.g., binders and fillers) in the dietary supplement; (3) a description of the manufacturing process of the dietary supplement, including process controls; (4) a specification sheet for the dietary supplement that describes its critical safety attributes; and (5) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, a discussion of the ordinary conditions of use of the dietary supplement. The conditions of use should include the serving form (e.g., tablet, capsule, powder, etc.)…."

AHPA believes these statements are overly broad and should be revised to stipulate in each case that only those parameters with a significant impact on safety (1) have any bearing on whether the material has been changed into an NDI or new NDI; and (2) need be disclosed in an NDI notice where such notice is required.[18] For example, AHPA believes it unlikely that formulation as a tablet vs. a capsule would have a material effect on product safety, nor would the process controls used during encapsulation or tableting be particularly relevant to safety. Such excessive levels of extraneous detail should not be considered.

AHPA is aware based on feedback from its members that the draft guidance, in its current form, is being interpreted by some in industry to require filing of an NDI notice as a result of nearly every manufacturing change. AHPA has also heard reports that FDA itself has told industry members that unless a firm can prove an ODI is currently being manufactured by precisely the same manufacturing process as was used prior to DSHEA, an NDI notice is required.

[18] See related discussion in comment # E10.

These interpretations have no basis in law; to the contrary, they fly in the face of Congressional intent. DSHEA was premised in part on recognition by Congress of repeated attempts by FDA to require premarket safety evaluations of pre-DSHEA supplement type products on the spurious bases of their being drugs or unapproved food additives.[19] As discussed elsewhere in these comments,[20] both the law and the DSHEA Senate report make it abundantly clear that FDA is to treat dietary supplements and dietary ingredients as foods; that they, like other foods, enjoy a presumption of safety over a broad range of conditions of use; that FDA is to refrain from any action that impedes, delays, or limits consumer access to supplements except where an actual safety problem exists; and that FDA is precluded from implementing requirements for premarket safety review (i.e., an NDI notification) except where an ingredient or supplement is substantively new.

AHPA notes it is in no one's interest for NDI notice requirements to be triggered on the basis of trivial or immaterial manufacturing changes. The NDI notice requirements outlined by FDA will impose extreme costs on industry, requiring perhaps tens of thousands of dollars to prepare a notice where safety is established on the basis of historical use and up to several millions of dollars where formal safety studies are required.[21] If these notice requirements are applied broadly or indiscriminately, as FDA may intend based on this draft guidance, consumers will lose access to many or even most dietary ingredients currently available. This is precisely the opposite of the

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[19] Senate Report 103-410, October 8, 1994.

[20] See comment # E5 in particular.

[21] FDA has stated elsewhere its view that there is only a "minimal burden" associated with meeting the requirement to submit an NDI notification; see, for example, 70 FR 6444, February 7, 2005; 76 FR 32214, June 3, 2011; and 78 FR 52773, August 26, 2013. The Agency explains this view by opining that the burden on industry to generate data to meet the NDI notification requirements of the premarket notification program is minimal "because the agency is requesting only that information that the manufacturer or distributor should already have developed to satisfy itself that a dietary supplement containing a new dietary ingredient is in full compliance with the act." Such an argument is disingenuous. There is no reason to suspect that, for example, chamomile flower water extract is not safe for human consumption, since it has been in the food supply for thousands of years with very few if any adverse effects; yet under FDA's current guidance, it would likely be considered "chemically altered" and thus potentially unsafe since its manufacture very likely includes a filtration step. Thus an NDI notice would be required, and AHPA can envisage no credible NDI notice being filed without the input of various lawyers, scientists, and other experts, all of which will cost many thousands of dollars. Similarly, the existing draft guidance would create thousands of spuriously "new" ingredients for which this preparation cost must be borne.

outcome contemplated by Congress, which deemed access to the widest possible range of safe supplements to be a right enjoyed by consumers and which FDA must not infringe.

It is, furthermore, not in FDA's interest to require an unnecessary volume of NDI notices. Over the first 20 years the NDI notice provision has been in effect, FDA has received only a few dozen notices per year on average, and the economic and small business analyses performed in connection with 21 CFR § 190.6 contemplated only 0-12 notices per year. If FDA persists in requiring a notice for every change in manufacturing or specifications, whether relevant to safety or not, AHPA believes FDA could be faced with tens of thousands of notices per year.[22] This would put a tremendous strain on the FDA budget and staffing resources, and would be a useless waste of taxpayer money.

AHPA notes that many of the dietary ingredients and supplements currently in the marketplace are made with manufacturing processes and specifications that are not exactly the same as those used pre-DSHEA. Nevertheless, dietary supplements have proven themselves to be among the safest of all FDA-regulated categories, with fewer adverse events reported than for conventional foods or drugs.[23] This is clear evidence that many variations in manufacturing processes and specifications do not affect safety and do not require scrutiny by FDA.

AHPA therefore encourages FDA to rewrite the guidance to maintain a strict focus on only those parameters and variations that are substantively relevant to safety, both when discussing factors that may create an NDI or transform an NDI into a new NDI, as well as when discussing what information need be included in NDI notices.

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[22] AHPA notes there are around 89,000 FDA-registered food manufacturing facilities worldwide as of 2016, a number which AHPA expects to increase as awareness spreads of the "farm mixed-type facility" category established under FSMA. If a mere 5% of these facilities process dietary ingredients, and each dietary ingredient facility processes 25 different dietary ingredients, this would represent 111,250 dietary ingredients that could be interpreted as requiring the filing of an NDI notice. The numbers of notices would increase exponentially if FDA continues to insist that every new combination of one NDI with another NDI creates a new NDI, and that a separate notice is required for a supplement containing an NDI under conditions that were not explicitly mentioned in the ingredient NDI notice.

[23] As mentioned elsewhere, AHPA notes that the Center for Disease Control reports foodborne illness to cause a monthly average of 780,000 adverse events and 4,700 hospitalizations, while the most recently available data from FDA indicate a monthly average of 72,200 drug adverse event reports (AERs). In contrast, the most recently data available from FDA indicate an average of only 412 AERs each month associated with dietary supplements.

4. Changes to processes or specifications that serve to lower impurities should not trigger an NDI notice requirement

To minimize the burdens on both industry and the Agency and to further the intent of the law, AHPA encourages FDA to state explicitly that changes to manufacturing processes or specifications that serve to lower impurity levels should not trigger the need for an NDI notice. For example, if the manufacturer of an existing dietary ingredient (whether an ODI or an NDI that has been previously the subject of a notice) finds that the levels of residual solvent in its product can be reduced through adjustments to the drying process, this should not trigger a requirement to file an NDI notice. Similarly, if the manufacturer of an existing ODI or NDI botanical ingredient finds that by adjusting its sourcing of the herbal raw material it can lower the specifications for a naturally-occurring undesirable constituent in its product (say, furanocoumarins in a celery dietary ingredient), this should not trigger an NDI notice requirement. These types of adjustments will not make the ingredient less safe, so there is no reason they require additional safety review by FDA. Furthermore, industry should not be disincentivized from making these changes by the onerous prospect of an NDI filing requirement.

5. The "chemical alteration" standard applies to dietary ingredients as well as conventional foods

Section 413(a) of the Act states,

> "IN GENERAL. - A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) 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…."

This "chemical alteration" provision stands in distinction to Section 413(a)(2), which requires a premarket safety review by FDA for new dietary ingredients that do not meet the standard of Section 413(a)(1). The following types of processing are explicitly deemed by Congress not to constitute "chemical alteration" for purposes of this standard: physical modifications such as minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, powder, or solid in suspension. It is clear from the existence of Sec. 413(a)(1) that Congress considers that such processing does not present new safety concerns requiring premarket review.

In Section IV Question A12 ("If I change the manufacturing process for a dietary ingredient that was marketed in the U.S. prior to October 15, 1994, does that make the ingredient an NDI?"), FDA comments on this provision as follows:

> "The 'chemically altered' standard in section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) governs only the manufacturing of dietary ingredients that have been 'present in the food supply' as articles 'used for food' (*i.e., conventional foods and their ingredients*) [emphasis added] and is applied to determine whether an NDI notification is required for a conventional food ingredient that was not marketed as a dietary ingredient before October 15, 1994."

AHPA finds this interpretation to be wholly without basis either in law or in logic.

The plain language of the law's provision includes no such limitation to conventional foods or conventional food ingredients. As is evident from the Findings of the Act,[24] Congress was clearly aware of the presence in the 1994-era marketplace of thousands of pre-DSHEA dietary supplement foods and their pre-DSHEA dietary ingredients that were then components of food; furthermore, the DSHEA Senate report on DSHEA explicitly states that a "supplement is a substance that already exists in the food supply."[25] If Congress had intended the "chemical alteration" standard to exclude these then existing foods then Congress would have said so (e.g., by stating "… as an article used for **conventional** food…"). The fact that Congress did not so limit this provision is a clear indication that Congress did not intend any such limitation.

Furthermore, such a limitation would run contrary to the basis for and intent of the law. As Congress stated in 1994, dietary supplements and dietary ingredients are safe within a broad range of intakes and rarely pose safety problems. Since 1994, this has been borne out by more than two additional decades of safe consumption. Indeed, dietary supplements have proven themselves to be among the safest of all FDA-regulated

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[24] For example, the Findings state that as of 1994 "the estimated 600 dietary supplement manufacturer in the United States produce approximately 4,000 products, with total annual sales of such products alone reaching at least $4,000,000,000."

[25] Senate Report 103-410, October 8, 1994, page. 14.

categories, with fewer adverse events reported than for conventional foods or drugs.[26] As a result of such safety, it was the stated intent of Congress in passing DSHEA to clarify once and for all – since FDA had continually resisted previous legislative attempts to establish this principle – that dietary supplements and dietary ingredients are foods that are presumed to be safe and legal, and that FDA cannot interfere with such products being brought to market by speciously claiming them to require safety review beforehand.

In related discussions under Section IV Question B1, FDA states:

> "Interpreting 'food supply' to include dietary supplements for purposes of this exemption from the NDI notification requirement would expand the exception to the point that it would risk swallowing the rule, as prior use in even one dietary supplement manufactured in small quantities and distributed over a small area would exempt all dietary supplements containing the NDI from the notification requirement, even if the intake level and conditions of use were much different. Moreover, such an interpretation would not make sense in light of the purpose of the NDI notification requirement, which is to ensure that dietary ingredients that have not been widely consumed receive a safety evaluation before reaching the marketplace."

AHPA believes this analysis to be faulty. Nowhere does the law or the DSHEA Senate report state or imply that the purpose of the NDI notification requirement is to ensure that dietary ingredients that "have not been widely consumed" should receive a safety evaluation before reaching the marketplace. Nor does the law or the DSHEA Senate report state or imply that differences in dietary ingredients' intake levels[27] or conditions of use should necessitate a premarket safety evaluation. If Congress doubted the safety of foods that are dietary supplements or dietary ingredients, Congress would not have granted them the presupposition of safety. To the contrary, the law is predicated on the fact that dietary supplements and dietary ingredients, like any other foods, are safe within a broad range of intakes and in various combinations and are unlikely to pose

[26] As mentioned previously, AHPA notes that the Center for Disease Control reports foodborne illness to cause a monthly average of 780,000 adverse events and 4,700 hospitalizations, while the most recently available data from FDA indicate a monthly average of 72,200 drug adverse event reports (AERs). In contrast, the most recently data available from FDA indicate an average of only 412 AERs each month associated with dietary supplements.

[27] By "intake level" AHPA here refers to the intake of a particular dietary ingredient or conventional food ingredient in a form that has not been "chemically altered" as defined for purposes of Sec. 413(a)(1).

safety problems. In addition, the law and the DSHEA Senate report take great pains to emphasize that the burden is not on manufacturers of dietary supplements to prove to FDA the safety of those foods either before or after going to market, but rather that the burden is on FDA to remove food products that are unsafe, and that FDA has full authority to do so.

AHPA furthermore notes that, if FDA maintains the interpretations stated in this draft, the resulting deluge of NDI notices will overwhelm the economic and small business analyses FDA performed in connect with 21 CFR § 190.6.[28] As discussed elsewhere in these comments,[29] AHPA estimates that the current draft could trigger the filing of (at least) tens of thousands of NDI notifications. FDA's proposal to limit the "chemical alteration" standard to conventional foods would exacerbate this problem by triggering a filing requirement under circumstances where premarket safety review of an NDI is not necessary to ensure safety. For example:

- Dietary ingredient A was sold in the U.S. prior to DSHEA in the form of dried powder, but a company now wants to sell it as a slurry.
- Dietary ingredient B was sold in the U.S. prior to DSHEA in the form of a dried powder, but a change to the drying process now results in an additional loss of minor volatile components.
- Dietary ingredient C was sold in the U.S. prior to DSHEA in dried, chopped form for making tea, but a company now wants to sell it as a water extract.
- Dietary ingredient D was sold in the U.S. prior to DSHEA as a spray dried water extract, but a company now wants to sell it as a lyophilized water extract.

There is no reason to believe that any of these circumstances require premarket safety review by FDA, any more than would be the case for a conventional food or conventional food ingredient.[30]

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[28] See comment # E9. To summarize these analyses briefly, FDA estimated submission of between 0 and 12 NDI notifications per year; between 0 and 12 small businesses affected per year; and no more than one notification required per NDI.

[29] See comment # E1 and E3.

[30] AHPA notes that conventional foods and conventional food ingredients are themselves not perfectly safe; they may contain a wide range of deleterious and/or pharmacologically active substances.

Congress states in DSHEA's Findings that "although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take *any actions* to impose unreasonable regulatory barriers *limiting or slowing* the flow of safe products…to consumers" and "legislative action that protects the *right* of access of consumers to safe dietary supplements is necessary" [emphasis added throughout]. By these statements Congress made clear its intent not merely to permit consumer access to safe dietary supplements, but to establish such access as a *right* which the government must protect. It was Congress' clear intent to ensure consumers have access to the broadest possible range of safe dietary supplements while strictly minimizing unnecessary regulatory barriers.

It would be wholly illogical, in this context, for Congress to have deemed dietary ingredients to be safe, and to have deemed processing that does not result in chemical alteration to be safe, but then to have intended for dietary ingredients used in a new but chemically unaltered form to be burdened with a premarket safety evaluation by FDA.

In view of all the above, AHPA believes it untenable for FDA to posit that the "chemical alteration" standard is limited to conventional foods and conventional food ingredients. Rather, interpretation consistent with the plain language and intent of the law requires dietary supplements and dietary ingredients to be included in the "articles used for food" to which the "chemical alteration" standard applies. AHPA believes the responses to Questions A12 and B1 must be rewritten to reflect this fact.

6. Conventional foods and other ingestible substances marketed within the U.S. prior to DSHEA are not NDIs unless they are chemically altered

In Section IV Question A5 ("Is a substance that was a component of a conventional food marketed before October 15, 1994, an NDI if the component was not a dietary ingredient marketed in the U.S. before October 15, 1994?") FDA opines,

> "Yes, assuming the component[31] meets the definition of a dietary ingredient. The mere presence of a substance as a component of a conventional food that was

[31] AHPA reiterates its objection, expressed in previous comments to the 2011 draft guidance, to the needlessly-confusing use of the word "component" in this guidance. The word "component" has a specific meaning as defined in 21 CFR §111.3: "*Component* means any substance intended for use in the

> marketed before October 15, 1994, does not establish that the substance was marketed as a dietary ingredient before that date. Similarly, the fact that a minor component may have been isolated as part of an analytical chemical procedure to examine the composition of the previously marketed food before October 15, 1994, is not sufficient to establish that the component is a pre-DSHEA dietary ingredient…"

In Section IV Question A10 ("Is marketing an ingredient for any use prior to October 15, 1994, sufficient to conclude that it is not an NDI?") FDA opines,

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

AHPA believes these statements to be contrary to the plain language and intent of the law, which defines "new dietary ingredient" as follows:

> "**DEFINITION. -** For purposes of this section, 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."

This provision makes no requirement that the ingredient have previously been marketed *as a dietary ingredient* (a category that did not even exist prior to the law's passage), or even that it have been marketed as a food rather than as a drug (although AHPA grants an implicit requirement that it must have been marketed for human consumption).

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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." For FDA to use this word with a wholly different meaning in the context of this guidance, which is aimed at the same regulated industry that has been taught the earlier meaning established by regulation, runs contrary not only to common sense and courtesy but also to logic and good guidance practices. AHPA encourages FDA to use the word "component" as a synonym for "ingredient" and to use the word "constituent" (meaning "a part of the whole") to refer to chemical substances contained within a component. This usage of the word "constituent" is consistent with established practice in the natural products industry and related academia.

To the contrary, the DSHEA Senate report repeatedly discusses the benefits and relative safety of conventional foods containing beneficial substances and dietary supplements containing those same substances.[32] The DSHEA Senate report furthermore repeatedly discusses the use of various ingestible materials with respect to their effects on diseases – a usage that, technically under the law, renders the ingestible material a "drug"; but it was the manifest intention of Congress to facilitate, not to impede, the use of such ingestible materials as dietary ingredients (rather than disqualify them as being drugs) so long as they have a history of safe human consumption.[33]

In fact, AHPA notes that in paragraph (3) of the definition of "dietary supplement," Congress takes pains to specifically discuss a product being "marketed *as a dietary supplement or as a food*" in contradistinction to having been "approved *as a new drug*" or "investigated *as a new drug*." Congress therefore specifically crafted the definition to avoid precluding old drugs from being used in dietary supplements; that is to say, old drugs are permitted to be marketed as supplements if they meet the other criteria required of supplements. These facts lend further support to the interpretation that, since Congress did not choose to specify in the definition of "new dietary ingredient" that the substance must have been marketed in any particular regulatory category, Congress did not intend the regulatory category (dietary supplement, conventional food, or drug) to have any effect for purposes of the NDI definition.

As a result, AHPA believes that a correct interpretation of the NDI definition requires any ingredient to be classified as an ODI so long as it meets the definition of "dietary ingredient" and was safely marketed within the U.S. for human consumption prior to DSHEA, and that this assumed ODI classification is not disqualified by virtue of the ingredient's use for any other purpose or in a separate regulatory category, even if such other use was the only known pre-DSHEA use.[34]

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[32] Senate Report 103-410, October 8, 1994, page 7.

[33] AHPA does not mean to imply that Congress intended to allow foods containing such ingredients to bear claims for disease treatment or prevention, as the law clearly precludes such labeling; only that there is no evidence Congress intended such ingredients to be excluded from the category of ODIs.

[34] AHPA furthermore believes that ingredients meeting the definition of "dietary ingredient" if marketed safely for human consumption *outside* the U.S., are covered by Section 413(a)(1) and therefore exempt from Section 413(a)(2).

7. Supercritical fluid extracts were marketed as food ingredients prior to 1994

In the 2016 revised draft guidance FDA opines that "supercritical fluid extraction was not commonly used prior to 1994, and there is no evidence of extracts like this having being marketed as food prior to 1994." AHPA notes, however, that commercial availability of supercritical extracts of a variety of food ingredients is recorded at least as early as 1989, including, for example, basil, ginger, pepper, and others.[35]

8. FDA should implement use of master files as an option and clearly identify other options to reduce unnecessary or redundant notifications

In the 2016 revised draft guidance, FDA introduced the idea of optional use of a confidential "NDI master file" which would contain information needed to completely describe a dietary ingredient that is the subject of an NDI notification. As presented in the draft, other firms that obtain the NDI from the submitting manufacturer or distributor, presumably for use as an ingredient in a dietary supplement not identified in the original NDI notification, could be authorized to reference the contents of a master file.

AHPA supports the use of an NDI master file as one option that can help eliminate duplicative filings, provide an efficient path to compliance for responsible companies and, significantly, also protect the intellectual property of those investing in costly safety studies and interpretive reports.

AHPA cautions, however, that FDA must avoid identifying its proposal to allow use of master files as the best or only solution to reduce the number of unnecessary and redundant NDI notifications for every dietary supplement that contains any specific NDI. AHPA has suggested in these comments[36] alternative approaches to reducing this regulatory burden and restates here the recommendation that FDA encourage, in any subsequent draft or final NDI guidance, manufacturers or distributors of dietary ingredients to make sure to provide descriptions of the many dietary supplements that may contain the NDI; and to provide, as a central tenet of any subsequent guidance, specific training and pointed encouragement for manufacturers and distributors of new

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[35] Eggers R and Sievers U. "Current State of Extraction of Natural Materials with Supercritical Fluids and Developmental Trends." In Johnston KP and Penninger JML (eds.). 1989. *Supercritical fluid science and technology.* Washington DC: American Chemical Society.

[36] See Comment #E1.

dietary ingredients to provide in their notifications quite broad descriptions of all of the dietary supplements that will include or may include the NDI, so long as the information submitted provides the basis for the submitter's conclusion that the dietary supplements containing the NDI will be reasonably expected to be safe.

Further, AHPA requests that detailed information concerning any safety studies conducted in relation to the NDI should be kept confidential to the maximum extent possible; only the conclusions concerning the safe use of the ingredient in humans should be made public. The specifics of the research, if released publicly, may put companies at a significant disadvantage in the marketplace. If FDA insists on making public the details of the research conducted, it will discourage companies from conducting the relevant research and/or will provide a disincentive to file required NDI notifications. Even where the data exists and an NDI notification is filed, the threat of such disclosure will discourage companies from sharing the data with FDA if other data can be relied upon (such as historical use).

9. The draft guidance is wholly inconsistent with the economic analysis and small business impact analysis prepared in connection with 21 CFR §190.6

AHPA finds that the draft guidance is wholly inconsistent not only with the intent of Congress but also with FDA's own intent as expressed in promulgating the NDI notification regulations in 21 CFR §190.6.[37] At that time when there were estimated to be already thousands of dietary supplements in the marketplace and hundreds of supplement manufacturers, FDA estimated the number of NDI notices to range from 0 to 12 per year, and the number of small businesses affected to range from 0 to 12 per year. FDA furthermore stated that "the number of new ingredients will vary, but will not be greatly different from the past year [in which 6 notices were filed]….FDA expects the number of new ingredients…to be closer to the high end of the range in the next few years and closer to the low end after that."

From these statements it is readily apparent that FDA believed the threshold to trigger an NDI filing requirement would be crossed only rarely – only when a dietary ingredient was substantively new and therefore merited premarket safety review. In contrast, the current draft guidance would trigger the need for vastly higher numbers (at least

[37] 61 FR 50774, 1996 and 62 FR 49891, 1997.

thousands and potentially millions) of NDI notices for reasons with no substantive connection to public health. For example, the current draft guidance will apparently require duplicative NDI notices for the same NDI in many different dietary supplements; NDI notices for changes to manufacturing processes or specifications that have no bearing on safety; NDI notices for spurious "chemical alterations" that are actually physical changes or simple food preparation techniques (e.g., filtration, cooking); NDI notices for ingredients made from more than one raw material; etc.

FDA furthermore stated in its small business analysis, "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)." Thus, FDA itself envisioned that one filing by either the NDI manufacturer or one supplement manufacturer would likely suffice for all other users of the ingredient. This is a far cry from the current draft guidance, which contemplates potential filing not only by one company initially but also by any other company selling the NDI in supplements under any circumstances not specifically described in the first filing.

AHPA believes FDA's 1996 analysis to be the correct one, and that FDA must revise the current draft guidance to conform to the original intent.

10. Changes inherent in traditional food manufacturing processes are not "chemical alteration"

In the draft guidance (Section IV Question B5) FDA states:

> "As set forth in the Congressional Statement of Agreement between the House and Senate sponsors of DSHEA,[38] '[T]he term 'chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyoph[i]lization, milling, tincture or solution in water, slurry, a powder, or solid in suspension.' FDA considers this list to represent examples of manufacturing processes that do not involve chemical alteration, but not necessarily a complete list of such processes."

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

AHPA agrees with the above statements and appreciates that FDA has acknowledged them explicitly in the draft guidance. AHPA is concerned, however, that other sections of the draft guidance are written in a manner that is either confusing or inconsistent with the above.

For example, in the draft guidance (Section IV Question B4) FDA cites the following as an example of a "chemical alteration": "A process that makes or breaks chemical bonds, unless the bonds created by the process are reversed when the ingredient is dissolved in water (e.g., creation of a soluble salt) or during ingestion. Example: hydrolysis." AHPA takes no position as to whether this is accurate when applied to a discrete chemical substance; however, this standard cannot be applied to ingredients prepared by making a tincture or solution in water or ethanol. The processes of extraction in water or ethanol do not constitute "chemical alteration," and these processes inherently cause a certain amount of natural "making or breaking of chemical bonds" through hydrolysis, esterification, and/or transesterification during the extraction process. To avoid confusion, AHPA recommends FDA qualify all statements regarding "making or breaking chemical bonds" to clarify that natural changes caused by extraction (or, as discussed below, by heating) are excluded.

As another example of "chemical alteration" FDA cites (Section IV Question B4): "Removal of some components of a tincture or solution in water, which changes the chemical or molecular composition or structure of the mixture. Examples:…filtration." In Section IV Question B5 FDA goes on to say, "FDA generally regards extraction that includes a filtration step or that involves the use of a solvent other than water or alcohol (aqueous ethanol) as a process that chemically alters the source ingredient and therefore triggers the NDI notification requirement for the resulting dietary ingredient." AHPA does not agree that "filtration" is a chemical alteration. Rather, filtration is a physical process no different from pressing or decanting, all of which form an inherent part of any extract manufacturing process; these steps serve to separate the insoluble botanical residue from the liquid extract. FDA acknowledges this itself in Section IV Question B5 when it says, "In a typical extraction, however, the first step is solution in water or another solvent, followed by filtration to remove undissolved material." Thus whether or not Congress explicitly listed "filtration" as a physical modification that does not constitute "chemical alteration," it implicitly included it when it listed "tincture or solution in water."

As a third example of "chemical alteration" FDA lists (Section IV Question B4): "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 or molecular composition or structure of the ingredient." AHPA finds this description to be scientifically nonsensical. Any application of heat will inevitably cause a wide range of "changes to the chemical or molecular composition or structure of the ingredient"; this is inherent in the process of cooking food. AHPA finds it untenable that Congress would have intended any food to suddenly require premarket safety review simply because it was cooked; to the contrary, cooking typically improves food safety both from a microbiological and chemical point of view (e.g., by detoxifying potatoes, fava beans, etc.). AHPA discussed the effect of various traditional food preparation techniques with respect to the status of a food as an ODI or NDI in greater detail in previous comments submitted to the 2011 draft guidance.

As an example of what is not "chemical alteration" FDA states (Section IV Question B5): "In general, FDA considers a process that does not result in chemical alteration to mean a process that: (1) involves an ingredient composed of one single raw material, or derived from a single raw material…." AHPA disagrees that processing can be deemed "chemical alteration" merely by virtue of using more than one raw material. Food does not become "new" or "unsafe" merely because it is made from multiple ingredients; similarly, a water extract made from a mixture of echinacea root and goldenseal root extracted together is no more "chemically altered" than an ingredient made from echinacea water extract and goldenseal water extract that are blended together after extraction.

In the same example, FDA goes on to say that a process that is not "chemical alteration" "does not involve attempts to selectively increase the concentration of particular active ingredients or cause a chemical reaction (other than esterification) that would modify the covalent bonds of any substance in the original material." AHPA appreciates that FDA has here acknowledged the likelihood that esterification may result from, for example, extraction in ethanol, but requests that this be expanded to include hydrolysis and transesterification. AHPA also requests this be clarified to stipulate that merely measuring the levels of constituents that may exist in a dietary ingredient, as is often done for various crude botanicals, extracts, and other materials, is not by itself inherently "chemical alteration." For example, many water or ethanol extracts are characterized as to the level of various markers. This does not mean any

extraordinary measures have been taken to “selectively increase the concentration” of the markers; it merely done for process and quality control purposes.

11. The draft guidance requires adjustment in its discussion of shelf life dating

In Section VI Question A5 FDA states, “You should describe the controls in place to maintain the strength, composition, and purity of the NDI throughout the shelf life of the product.” This statement erroneously implies that shelf life dating is required, when in fact dietary supplements (like other foods) are not required to bear a shelf life date and dietary ingredients, as with other food ingredients, are likewise not required to bear a shelf life date.

Furthermore, the draft guidance states (Section VI Question A18) that when the dietary supplement containing an NDI will include an expiration or use-by date, “The expiration or ‘use by’ date should be based on appropriate supportive stability data showing that (1) no new degradants will form during the labeled shelf life of the product under the conditions of storage specified in the notification, if any, or under normal storage conditions….” AHPA believes this criterion to be impractical and unreasonable, at least for dietary ingredients that are complex chemical mixtures as opposed to discrete chemical entities. Various chemical reactions inevitably occur in any food during the course of storage, resulting in “new degradants.” A requirement to develop methods to identify and quantify such “degradants” in chemically complex foods is impractical and unnecessary, and a requirement that no such “degradants” are allowed to occur is impossible.

12. The toxicological studies set forth in Section VI may be appropriate only for ingredients that are wholly new without history of human consumption, and the results must not be interpreted to require absolute safety

The toxicological study requirements set forth in Section VI of the guidance are so extensive and stringent that AHPA believes that if they were applied to existing foods as a condition of continued use in the food supply, many existing foods would be proven “unsafe.” For example bacon, wheat, salt, sugar, grapefruit, basil, and even water can cause negative health effects when consumed to excess; when consumed over the course of a lifetime; when consumed in combination with certain drugs; or when consumed by sensitive persons.

AHPA does not dispute that substances which are truly new to the food supply require strict scrutiny. However, AHPA calls attention to the fact that the law establishes a requirement not for absolute safety, but rather "reasonable assurance" that the ingredient "does not present a significant or unreasonable risk of illness or injury." [39] New dietary ingredients should not be held to safety standards stricter than those applied to existing foods and AHPA encourages FDA to clarify in the guidance that it will review safety data accordingly.

13. Comments regarding definitions

AHPA would like to make the following comments regarding various definitions proposed in the draft.

- Botanical raw material. The definition of "botanical raw material" should be deleted, for the following reasons:
  - The term is not used anywhere in the current document.
  - The term does not require definition, since "botanical" is already defined and "raw material" is well understood and needs no clarification.
  - The proposed definition is confusing insofar as it refers to operations such as cleaning and drying that in many cases are not "food processing" but rather are farm activities.
  - The proposed definition is inappropriately narrow and limited. The botanical raw material used for manufacturing may have been subjected to prior chemical or microbiological processing as well as physical processing.
- Component. As discussed in footnote 31 and in AHPA's comments submitted to the 2011 draft guidance, the definition of "component" should be revised to match existing usage of the term in food regulations.
- Constituent. As discussed in footnote 31 and in AHPA's comments submitted to the 2011 draft guidance, "constituent" is commonly used in the natural products industry and related academia to refer to a chemical compound that is found in a botanical or other natural material. AHPA therefore recommends that "constituent" be used in many of the places where the current draft inappropriately uses "component" (as detailed in AHPA's 2011 comments), and

[39] 21 U.S.C. 342 (f)(1)(B).

that the definition of "constituent" should be corrected to read: "A chemical substance that occurs in a botanical or other natural material."

- Concentrate. The first sentence of the proposed definition of "concentrate" is accurate, but the second sentence should be deleted since it is confusing, inconsistent with established usage within the industry, and inaccurately limited. It is true that the type of material the second sentence describes ("an extract from which all or most of the solvent has been removed") is one example of a concentrate, and *within the context of a given manufacturing process* this material may be referred to as the "concentrate" (or as the "native extract"), but once such a material is offered for sale it is more likely to be described as an "extract," "powder extract," "liquid extract," etc. In the marketplace the term "concentrate" is more often (though not exclusively) used to refer to any concentrated material that is intended for dilution prior to use or consumption (e.g., juices; flavors; colors; etc.). One the second sentence is omitted, the third sentence is extraneous; and in any case it is unnecessary since the guidance elsewhere discusses the relevance of solvents and manufacturing processes. Thus the definition should be terminated after the first sentence.
- Extract. The definition of extract is erroneously narrow and misleading, particularly in the second sentence. The initial liquid extract (miscella) is commonly further processed (not necessarily concentrated) through a variety of means (not just drying) into a variety of forms (not just dry powder or semi-solid). Therefore the second sentence should be revised to state, "The initial extract can be further processed into the finished extract through processes such as chromatography or other purification steps, sanitization, drying, milling, blending with other dietary ingredients or excipients, etc."

F. INACCURATE AND INAPPROPRIATE STATEMENTS IN THE DRAFT

AHPA has identified several examples of statements made in the 2016 revised draft guidance that are either inaccurate or that make implications that are inaccurate, or that provide strained examples that do not accurately reflect the current regulation of dietary supplements. AHPA therefore requests each of these to be revised as needed.

1. The estimated number of currently marketed dietary supplements is irrelevant

In the 2016 revised draft guidance FDA reports that the Agency "estimated that the number of dietary supplements on the market was 55,600 and that 5,560 new dietary

supplement products come on the market each year." The Agency goes on to say that this data "is in contrast to the approximately 4,000 products that were on the market in 1994," and also notes that FDA "had received and completed our evaluation of just over 750 NDI notifications since the first notification was received in 1995." These statements may be misinterpreted as implying that the number of NDI notifications is deficient, and that the estimated numbers of supplements now in the market compared to 1994 somehow provides some arithmetic evidence or proof of this deficiency; such evidence or proof, however, is completely speculative, and this irrelevant data should be removed from any subsequent draft or final NDI guidance.

In AHPA's view there is at most a limited association between the number of new dietary supplements that enter the U.S. marketplace each year and the number of NDI notifications that are required to be submitted under the law. To begin with, many of the new dietary supplements that enter the market each year consist only of ODIs, and so there should be no expectation of a need for an NDI notification for these. And as stated elsewhere in these comments, [40] AHPA believes FDA should provide guidance that encourages manufacturers and distributors of new dietary ***ingredients*** to submit their required NDI notifications in a manner that covers all, or at least many of the dietary ***supplement*** products that may come to contain the new ingredient. If such a process becomes the norm then the factor most relevant to the expected number of NDI notifications will be the number of actual new ingredients that enter the market.

2. Drug-spiked products are not dietary supplements

In the 2016 revised draft guidance FDA identifies "recent concern about the presence of undeclared active ingredients in products marketed as dietary supplements" as one factor that "highlight[s] the importance of submitting NDI notifications as a preventive control to ensure that consumers are not exposed to unnecessary public health risks in the form of new ingredients with unknown safety profiles."

FDA and the Office of Dietary Supplement Programs specifically understand, with absolute certainty, that products marketed as dietary supplements that contain undeclared drug ingredients are not, in fact, dietary supplements. This is an issue that has often been discussed by representatives of FDA's Office of Dietary Supplement

[40] See comments # E1 in particular.

Program and AHPA representatives, and in these discussions there is always complete agreement on this matter.

Furthermore, it is disingenuous for FDA to imply that proper NDI guidance will have any impact whatsoever on criminals who are determined to flout the law for their own financial gain by selling products that the makers know are spiked with undeclared or illegal drugs. People who have decided to break the law so flagrantly are not going to concern themselves with finer points of compliance.

Therefore, mention of this factor – "undeclared active ingredients in products marketed as dietary supplements" – should be deleted from any subsequent draft or final NDI guidance. It unnecessarily blurs an issue that has already been resolved in FDA's other communications on this subject and undermines industry's efforts to work cooperatively with FDA to maintain attention on this ongoing and intentional international adulteration issue.

3. The extreme example of possible harm from combining two NDIs should be removed, or identified as an extreme example

In the 2016 revised draft guidance (presented in Section IV Question C5, "Scenario 6") FDA provides an example of NDIs made from *Convallaria majalis* L. and *Nerium oleander* L.,[41] two botanicals that are frankly toxic due to their content of cardiac glycosides, as justification for the need to evaluate NDIs not only alone but also in combination. However, it strains credulity to believe that FDA would not object strenuously to either one of these ingredients by itself as an NDI, or that a company would seek NDI status for any such ingredient, unless it were processed to remove the dangerous cardiac glycosides and render the ingredient safe for general consumption. And in fact, when Ozelle Pharmaceutical, Inc. submitted an NDI notification for an extract of *Nerium oleander* in 1998 the Agency's response called attention to the absence of any information in the submission "that bears on the presence (or absence) of the known toxic substances contained in oleander."

[41] AHPA acknowledges that a few highly toxic plants such as oleander appear on various industry lists of items in commerce prior to 1994. All such items should be removed in preparation of any potential list of FDA-recognized ODIs.

AHPA does not disagree there may be instances in which a separate notification should be submitted for a dietary supplement that contains two NDIs that were previously the subject of an NDI notifications. However, instances in which the combination of two safe NDIs would present a credible risk that requires submission of a separate NDI notification are undoubtedly rare, and FDA should not present such a rare scenario as if it were the rule. The NDI guidance should be predicated on the assumption, as has been established by Congress and by real world experience, that dietary ingredients, like other foods and even food additives, are normally safe in any combination, when used in food of any physical form, and when used with any excipients or processing aids. The possibility that certain NDIs may require consideration of further variables should at most be addressed as a self-contained topic in a separate Question unto itself that cautions companies that submit NDI notifications to identify such rare exceptions.

4. The relevance of an "acknowledgement without objection" to an NDI notification should be accurately stated

In Section IV Question A13 of the 2016 revised draft guidance, FDA discusses actions that may be taken by a manufacturer or distributor of an NDI or supplement that contains an NDI that the Agency asserts could be dependent on factors that include receipt from FDA of an "acknowledgement without objection" to an NDI.

FDA's position that receipt from FDA of an "acknowledgement without objection" to an NDI is a factor in determining any other NDI notification-related action appears to reflect a view that the NDI notification process is actually an approval process. That is not the case, however. To avoid confusion in the future AHPA requests FDA remove any reference to FDA's response to an NDI notification that may be read as implying that FDA's approval or absence of objection to a notification is required before a new dietary ingredient or a dietary supplement containing a new dietary ingredient may go to market.

G. CONCLUSION

AHPA has provided these comments to express the views of the organization and its members on FDA's 2016 revised draft guidance on new dietary ingredients. 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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