

Docket No. 2004N-0454

BEFORE
THE UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE
AMERICAN HERBAL PRODUCTS ASSOCIATION

ON THE FOOD AND DRUG ADMINISTRATION'S REQUEST FOR COMMENT ON

**FDA's PREMARKET NOTIFICATION PROGRAM FOR
NEW DIETARY INGREDIENTS**

February 1, 2005

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The American Herbal Products Association (“AHPA”) is the national trade association and voice of the herbal products industry, comprised of 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.

In a Federal Register notice on October 20, 2004, the Food and Drug Administration (“FDA”, or “the Agency”) solicited comments on FDA’s premarket notification program for new dietary ingredients (“NDIs”), and on the content and format requirements for NDI notifications made under the Federal Food, Drug and Cosmetic Act (“the Act”). In addition, the Agency provided a list of questions intended to focus public comment on specific NDI issues.

AHPA’s membership includes companies that market and sell dietary ingredients and NDIs for use in dietary supplement products, and also includes companies that market and sell dietary supplements that contain dietary ingredients and NDIs. AHPA and its members therefore have an interest in FDA’s premarket notification program for NDIs and on the content and format requirements for NDI notifications made under the Act. AHPA is therefore submitting these comments, and has provided responses to numerous of the questions provided by FDA in the attached *Appendix 1*, to address these interests of AHPA and its members. Both these comments and the attached responses are focused on herbal and botanical ingredients.

In preparing these comments AHPA staff and/or counsel have reviewed all of the notifications for NDIs that have been submitted to FDA to date, consisting of reports numbered up to and including Report Number 259, and the Agency’s responses to these notifications, that are posted on FDA’s website as of January 31, 2005 at <http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s0316.htm>. AHPA has provided occasional comments here to numerous of FDA’s posted responses and related correspondences, and especially to statements made therein for which AHPA has concern about the Agency’s expressed practice or policy. AHPA does not represent these occasional comments as an exhaustive review of FDA’s correspondences to date to these submitted NDI notifications.

I. Background

Statutory definitions of “dietary supplement” and “dietary ingredient”

The Dietary Supplement Health and Education Act (DSHEA) was signed into law on October 25, 1994 (Public Law 103-417). The law amended the Federal Food, Drug, and Cosmetic Act in a number of ways and added a number of definitions to the Act.

DSHEA did not provide a specific definition of the term “dietary ingredient.” It did however, in defining the term “dietary supplement,” provide a list of ingredients that may be included in dietary supplement products, and described such ingredients as “dietary ingredients,” as follows:

“The term ‘dietary supplement’ means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).” 21 U.S.C. 321(ff)(1).

DSHEA also defined the term “dietary supplement” to distinguish between those drug, antibiotic, or biologic articles that are allowed to be present in a dietary supplement, and those that are not. In summary, an article approved as a drug under section 505 of the Act; certified as an antibiotic under section 507 of the Act; or licensed as a biologic under section 351 of the Public Health Service Act *are allowed* to be sold as dietary supplements if they were first marketed as a dietary supplement or food prior to such approval, certification, or license, and *are not allowed* to be sold if they were not so marketed prior to such approval, certification, or license (see 21 U.S.C. 321(ff)(3) for additional details).

In addition, DSHEA specified that the form in which a dietary supplement product is intended for ingestion is limited to one of the following:¹

- “[The term ‘dietary supplement’] means a product that (A)
(i) is intended for ingestion in a form described in section 350(c)(1)(B)(i) of this title; or
(ii) complies with section 350(c)(1)(B)(ii) of this title.” 21 U.S.C. 321(ff)(2)(A).

21 U.S.C. 350(c)(1)(B)(i), describes forms of products intended for ingestion that include “...tablet, capsule, powder, softgel, gelcap, or liquid form.” The next following paragraph, 21 U.S.C. 350(c)(1)(B)(2), describes “liquid form” for purposes of this paragraph by stating, “For purposes of paragraph (1)(B)(i), a food shall be considered as intended for ingestion in liquid form only if it is formulated in a fluid carrier and it is intended for ingestion in daily quantities measured in drops or similar small units of measure.” And 21 U.S.C. 350(c)(1)(B)(ii) clarifies that a dietary supplement may also be in a form that is not intended for ingestion in tablet, capsule, powder, softgel, gelcap, or in the limited liquid form defined above by complying with the requirement that it “is not represented as conventional food and is not represented for use as a sole item of a meal or of the diet.” The practical effect of this last provision is to enlarge the category of dietary supplements to include dietary supplements in conventional food form (e.g., drinks or bars) that are not represented as a conventional food or as sole items of a meal or of the diet.

Finally, DSHEA provided two additional elements to the definition of the term “dietary supplement.” The statute reinforced the restriction against representing any such product as conventional food or as the sole item of a meal or of the diet (21 U.S.C. 321(ff)(2)(B)) and established that any such product must be labeled as a dietary supplement² (21 U.S.C. 321(ff)(2)(C)).

¹ Even as DSHEA referred to these existing sections of the Act, it also amended the specific language of these sections. See section (3)(C) of DSHEA.

² DSHEA stated that the term “dietary supplement... may be modified with the name of [the dietary] ingredient[s].” In implementing the law FDA established by regulation that in the statement of identity for the product, the word “dietary” may be deleted and replaced by the name of the dietary ingredients in the product or an appropriately descriptive term indicating the type of dietary ingredients that are in the product (e.g., “herbal supplement”). 21 CFR 101.3(g).

In summary, the statutory definitions identified above make clear that, in order for a product to be marketed as a dietary supplement, the product must meet all of the five following definitional requirements:

1. It must contain one or more of the ingredients identified in 21 U.S.C. 321(ff)(1);
2. It must not contain any of the drug, antibiotic, or biologic articles that are explicitly disallowed by 21 U.S.C. 321(ff)(3)(B);
3. It must be intended for ingestion in one of the forms described in 21 U.S.C. 350(c)(1)(B)(i) or (ii);
4. It must be labeled as a “dietary supplement” (or, for example, as an “herbal supplement”); and
5. It must not be represented as a conventional food or as the sole item of a meal or of the diet.

In relation to AHPA’s specific interest in herbs, herbal ingredients, and herbal products, an herbal ingredient can meet the description of dietary ingredients provided in 21 U.S.C. 321(ff), as long as it is not a drug, antibiotic or biologic explicitly disallowed by 21 U.S.C. 321(ff)(3)(B), if it is any of the following:

- An herb or other botanical;
- A concentrate of an herb or other botanical;
- A metabolite of an herb or other botanical;
- A constituent of an herb or other botanical;
- An extract of an herb or other botanical;
- A combination of herbs, other botanicals, or concentrates, metabolites, constituents, or extracts of herbs or other botanicals.

Thus, a product that contains any of the herbal or other botanical dietary ingredients delineated above;³ that is in any of the forms described in 21 U.S.C. 350(c)(1)(B)(i) or (ii); that is labeled as a “dietary supplement” (or, for example, as an “herbal supplement”); and that is not represented as a conventional food or as

³ At times throughout this document AHPA will use the term “herbal or other botanical dietary ingredient” to mean any of the herbal-based or botanical-based dietary ingredients that are identified in 321(ff)(1)(C) or (F).

the sole item of a meal or of the diet is in conformity with the statutory definition of a "dietary supplement."

Statutory definition and regulation of "new dietary supplements"

DSHEA defined the term "new dietary ingredient" as follows:

"...the term 'new dietary ingredient' means a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994." 21 U.S.C. 350b(c).

DSHEA also amended the definition of "adulterated food" under the Act. The amendment relevant to these comments is as follows:

"A food shall be deemed to be adulterated...[I]f it is a dietary supplement or contains a dietary ingredient that... is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury." 21 U.S.C. 342(f)(1)(B).

In addition, DSHEA amended the Act to establish that a dietary supplement that contains an NDI may be adulterated unless certain requirements are met, and specifically:

"A dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 342(f) of this title unless it meets one of the following requirements:

- (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.
- (2) There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe." 21 U.S.C. 350b(a).

Thus, there is no restriction in this section of the law on marketing a dietary supplement that contains an NDI that was not marketed in the United States before October 15, 1994 but that has been present in the food supply as an article used for food, so long as that NDI is in a form in which the food has not been chemically altered. Language included in the Statement of Agreement that constitutes the entire legislative history for DSHEA addressed what was meant by “chemically altered,” stating:

“...the term “chemically altered” does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization [sic], milling, tincture or solution in water, slurry, powder, or solid in suspension.”⁴

On the other hand, the inclusion in a dietary supplement of any other NDI sets in motion the requirement articulated in 21 U.S.C. 350b(a), such that the manufacturer or distributor of the ingredient or the supplement containing the new ingredient must provide the required information to the FDA 75 days prior to marketing.

Again, in relation to AHPA’s specific interest in herbs, herbal ingredients, and herbal products, the manufacturer or distributor of an herbal or other botanical dietary ingredient that was not marketed in the United States before October 15, 1994 but that was present in the food supply as an article used for food in a form in which it has not been chemically altered has no obligation to provide notification to FDA prior to bringing such an ingredient to market. On the other hand, the manufacturer or distributor of any other herbal or other botanical dietary ingredient that was not marketed in the United States before October 15, 1994 is obliged to provide notification to FDA prior to introducing such an ingredient. Both of these last two stated facts are relevant to all herbal or other botanical dietary ingredients, including an herb or other botanical; a concentrate of an herb or other botanical; a metabolite of an herb or other botanical; a constituent of an herb or other botanical; an extract of an herb or other botanical; or a combination of herbs, other botanicals, or concentrates, metabolites, constituents, or extracts of herbs or other botanicals.

⁴ *Congressional Record*, Volume 140. October 7, 1994.

II. "New" vs. "old" dietary ingredients

Dietary supplements and ingredients were marketed prior to DSHEA

It is AHPA's belief and position that thousands of herbal ingredients were marketed in the United States prior to October 15, 1994 and are therefore excluded from the statutory definition of a "new dietary ingredient."

In differentiating between a dietary ingredient that is a new dietary ingredient and one that is not new, DSHEA relied entirely on whether the ingredient was already marketed in the United States at the time the law was passed, that is, prior to October 15, 1994. It bears repeating the exact language of the statute in making such differentiation:

"...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." 21 U.S.C. 350b(c).

Importantly, DSHEA did not state that this pre-1994 use of an ingredient needs to meet any requirement other than marketing in the U.S. to establish that it is not included in the definition of a "new dietary ingredient." In order to establish its exclusion from this definition, the pre-1994 marketing of an ingredient did not, therefore, need to have been labeled as a "dietary supplement." There is no other principled conclusion available with respect to this point.

It must be recalled that, prior to the passage of DSHEA, numerous products, including herbal or other botanical products, that contained one or more of the dietary ingredients identified in 21 U.S.C. 321(ff)(1) were marketed in the United States in the form of tablets, capsules, liquid herbal extracts, and other forms of ingestion described in 21 U.S.C. 350(c)(1)(B)(i) or (ii)⁵. To the best of AHPA's knowledge and institutional memory, however, none of these were labeled at that time as "dietary supplements," or as "herbal supplements." Instead these products

⁵ See, for example: Dykstra, G. *et al.* (U.S. Food and Drug Administration). May 1992. *Dietary Supplements Task Force Final Report*, page 1: "The Task Force studied the universe of products in the marketplace, focusing on products sold in capsule, tablet, liquid, and powder form... [and] divided the universe of supplements into three categories: 1) vitamin and mineral products; 2) amino acids; and 3) 'all others,' which include non-essential chemical compounds, herbs without a history of documented food use, plant and animal extracts, and certain other substances." Also, *Ibid.*, page 13: "There are, by some estimates, approximately 3,400 unique nonprescription vitamin and mineral supplements produced by some 600 manufacturers...."

tended to bear statements of identity on the principal display panel, often including the predominant ingredient, that were consistent with food labeling regulations at that time. Such labels may have included such terms as “a vitamin tablet” or “an herbal tincture,” or may have simply referred to the product form in disclosing the contained quantity, for example, “60 capsules.”

Similarly, dietary ingredients that were marketed in the United States prior to the passage of DSHEA were not likely to have been labeled as “dietary ingredients” or “herbal dietary ingredients.” Instead, these tended to be identified simply as “vitamins;” “mineral;” “amino acids;” “herbs;” “herbal extracts;” etc. Even today most marketers of these ingredients do not identify them as, for example, “vitamin dietary ingredients” or “herbal ingredients for dietary supplements,” and in fact AHPA believes that, if any such labeling practice occurred in the past or occurs today, it was and is a significant exception to the norm.

The fact that none of the herbal or other botanical products that were marketed prior to the passage of DSHEA and that would be recognized today as dietary supplements were labeled prior to 1994 as “dietary supplements” should not be surprising – the term had not been defined as a statement of identity prior to that time. Similarly, there should be nothing surprising about the fact that the ingredients that may be used in dietary supplements but that often have additional uses, were not prior to 1994 and are not today marketed with the term “dietary ingredient.”

Based on the preceding paragraphs it must be concluded that DSHEA did not mean the phrase “marketed in the United States before October 15, 1994” to mean “marketed in the United States *as a dietary ingredient as described herein* before October 15, 1994,” nor did it mean “marketed in the United States *as an ingredient in a dietary supplement* before October 15, 1994.” Rather, the phrase meant exactly what it said and all that needs to be done to ascertain whether an ingredient that fits the definition of 21 U.S.C. 321 (ff)(1) is “new” or “old” is to determine whether that ingredient was “marketed in the United States before October 15, 1994,” and that the context of such marketing was dietary, that is, for ingestion.

It is therefore AHPA's position that a dietary ingredient is specifically excluded from the statutory definition of "new dietary ingredient" if it meets the two following conditions, and that no other conditions need be met:

1. It is described in any of the subparagraphs (A) through (F) inclusive of 21 U.S.C. 321 (ff)(1); and
2. It was available prior to October 15, 1994, either as an ingredient in a product marketed in the United States in a form described in 21 U.S.C. 350(c)(1)(B)(i) or (ii), or as a bulk ingredient marketed in the United States.

The term "marketed" should be broadly interpreted

It is AHPA's position that the term "marketed" must be interpreted broadly. Evidence of marketing of an ingredient prior to October 15, 1994 could include evidence such as proof of purchase or proof of use before that date, but it can also include any other evidence that the ingredient was offered for sale, made available for sale, advertised for sale, or in any other manner marketed prior to that date.

The American Heritage Dictionary of the English Language, 3rd edition⁶ defines the transitive verb form of the English word "market" with two meanings: "1. To offer for sale. 2. To sell." *The Webster's New World Collegiate Dictionary*, 4th edition⁷ provides three definitions of "market" in the transitive verb form, including "to offer for sale" and "to sell," and adds a third related meaning: "to send or take to market." And the *Riverside Webster's II Dictionary*, revised edition,⁸ which does not differentiate between the transitive and intransitive forms, provides two meanings for the verb "market": "To sell or offer for sale," and "To buy food and household supplies."

In summary, every dictionary consulted by AHPA in preparation for these comments provides a definition for the verb "market" that includes not only the actual sale of an article but also the offering for sale of the article. Thus, when DSHEA said "...marketed in the United States before October 15, 1994," it should

⁶ Soukhanov, AH, executive editor. *The American Heritage Dictionary of the English Language*, 3rd edition, page 1101. 1992. Boston: Houghton Mifflin Co.

⁷ Agnes, M., editor in chief. *Webster's New World Collegiate Dictionary*, page 880. 2000. Foster City, CA: IDG Books Worldwide.

⁸ *Riverside Webster's II Dictionary*, page 420. 1996. New York: Berkley Books.

be assumed that this phrase meant “sold or offered for sale in the United States before October 15, 1994.”

AHPA therefore believes that any vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or concentrate, metabolite, constituent, extract, or combination of any of the above that was sold or offered for sale in the United States before October 15, 1994 is specifically excluded from the statutory definition of “new dietary ingredient.”

AHPA is aware that, prior to October 15, 1994, numerous companies were in the business of marketing herbal or other botanical dietary ingredients⁹ in the United States. While many such companies were U.S. domestic firms, numerous companies that were domiciled outside of the United States were also, at that time, marketing herbal or other botanical dietary ingredients in the United States. One of the most prominent means by which marketing occurred was by the herbal marketer, whether foreign or domestic, providing catalogues that listed all of the herbal or other botanical dietary ingredients that were offered for sale by the firm. Another means of marketing by both foreign and domestic firms was by mailing letters that identified marketed ingredients to prospective customers in the United States.

It is AHPA’s firm position that any such catalogue or letter that bears a date prior to October 15, 1994, or any other such dated document that clearly expressed that an herbal or other botanical dietary ingredient (or for that matter, any of the dietary ingredients identified in 21 U.S.C. 321(ff)(1)) was offered for sale in the United States prior to October 15, 1994, constitutes sufficient information to determine with certainty that any ingredient listed in such dated catalogue or other document is specifically excluded from the statutory definition of “new dietary ingredient.” It is AHPA’s position that any such document is *prima facie* evidence that a dietary ingredient was marketed as of the date of such document.

⁹ The term “herbal or other botanical dietary ingredient” is used here and in the following paragraphs with the meaning identified in footnote number 4.

Similarly, and has been discussed above, AHPA is aware that, prior to October 15, 1994, numerous companies were in the business of marketing products in the United States containing herbal or other botanical dietary ingredients and intended for ingestion in a form described in 21 U.S.C. 350(c)(1)(B)(i) or (ii). Again, these included both U.S. domestic and foreign firms. It is AHPA's position that any production record, sales record, catalogue listing, sales literature, advertisement, or other document that provides evidence that such product was offered for sale in the United States before October 15, 1994 constitutes sufficient information to determine that all of the ingredients contained in such marketed product that are described in any subparagraph of 21 U.S.C. 321 (ff)(1) are specifically excluded from the statutory definition of "new dietary ingredient."

Herbs of Commerce, 2nd ed. is a credible list of old herbal dietary ingredients

In early 1995 AHPA informed its members of its intention to compile a list of botanical dietary ingredients marketed in the United States before October 15, 1994, and requested that each of its members identify herbs in trade as of that date. On September 17, 1996 AHPA sent to FDA a list of the botanical ingredients that its members had identified as marketed prior to October 15, 1994. A cover letter that accompanied AHPA's submission of this list to FDA stated as follows:

"The American Herbal Products Association, as a service to its members, has compiled a list of herbs believed to have been marketed in the United States as a dietary supplement or dietary ingredient before October 15, 1994. The list, which includes the scientific name of the herbs, was reviewed by a widely respected and experienced botanical taxonomist. The list represents a compilation of the submissions received from AHPA members, as well as non-members, in response to a written request from AHPA. The request specifically stated that only herbs marketed as dietary supplements or dietary ingredients before October 15, 1994, were to be included in any submissions made to AHPA.

AHPA went to considerable time and expense to compile this list and is pleased to offer a copy to your office to be used for reference purposes. To the best of our knowledge, this list contains only herbs meeting the criteria stated above; however, AHPA has not independently verified the list. Further, AHPA does not represent this list to be conclusive. There may very well be other herbs that were marketed as dietary ingredients prior to 10/15/94 and we assume that any manufacturer claiming such will be able to produce

appropriate evidence should there be any question as to the status of the dietary ingredient.”

The purpose of the first of the two disclaimers in the above paragraph (“...not independently verified...”) was simply to clarify that inclusion of an herb on this list did not provide absolute certainty that the herb was marketed prior to 1994. On the other hand, this disclaimer did not mean that the inclusion of an herb on this list had no meaning whatsoever with regard to prior marketing. On the contrary, the listing of a species in this reference indicated a high probability that the articles of commerce from the listed species were marketed prior to 1994. And the second disclaimer (“[T]here may well be other herbs...”) was meant to indicate AHPA’s concern that there might have been herbs that had been marketed in the United States that were not included on the submitted list, for example, by companies that did not respond to AHPA’s request for information.

The list submitted to FDA in 1996 formed the foundation for AHPA’s *Herbs of Commerce*, 2nd edition with respect to one of the intended purposes of that reference, which was to record the herbs in trade on October 15, 1994. A note in the text’s introduction made it quite clear that the effort was primarily addressed to herbal ingredients in dietary supplements:

“The botanicals that are the subject of *Herbs of Commerce*, 2nd edition... are primarily those that are now sold in this country as ingredients in certain foods defined as dietary supplements.”

Nevertheless, when *Herbs of Commerce*, 2nd edition was published in 2000, disclaimers were also included that were similar to those addressed to FDA in 1996, as follows:

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

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

Similarly, the exclusion of a particular plant should not be seen as proof of or an indication that such plant was not marketed in the United States prior to October 15, 1994. Although every effort was made to broadly distribute the written requests referred to above, no evaluation has been made of the thoroughness of this process in identifying all such botanical ingredients.”

The first of these two disclaimers in the introduction to *Herbs of Commerce*, 2nd edition (“...listing... is not... evidence...”) was again intended to provide a straightforward expression of the fact that the editors did not verify the submitted information. Again, however, and in spite of this disclaimer, AHPA believes that any plant species included in *Herbs of Commerce*, 2nd edition can be presumed to have been in commerce in the United States on October 15, 1994, at least in the form of “an herb or other botanical” in conformity with 21 U.S.C. 321(ff)(1)(C). In other words, this disclaimer should not be interpreted to mean that the listing of a plant in *Herbs of Commerce* has no relationship whatsoever to the presence of the herb in the market. While this text may not be completely authoritative as a list of “old” herbal dietary ingredients, it is an eminently credible reference, and the presence of a plant here does create a presumption of presence in the marketplace prior to October 15, 1994.

Similarly, the second disclaimer here (“...exclusion... should not be seen as proof of or an indication that [a] plant was not marketed in the United States prior to October 15, 1994”) should not be read to indicate proof that the plant was not marketed in the United States prior to the passage of DSHEA. The kinds of dated marketing documents discussed in the prior section of these comments can suffice in such instances to document a history of marketing prior to 1994, even if the species is not listed in *Herbs of Commerce*, 2nd edition.

In summary, AHPA believes that the listing of a species of herb or other botanical in *Herbs of Commerce*, 2nd edition should constitute a presumption that the known articles of commerce from each of the identified herb or other botanical were marketed in the United States before October 15, 1994, and that all such articles should be recognized as exempt from the definition of a “new dietary

ingredient.”^{10,11} In addition, AHPA believes that the absence of any particular species in *Herbs of Commerce*, 2nd edition should not be interpreted as proof that the species was not marketed United States before that date.

Also, if FDA should decide to work to create a more definitive and authoritative list of herbal and other botanical dietary ingredients that were marketed prior to October 15, 1994, AHPA requests that the Agency recognize that AHPA, as the publisher of both editions of *Herbs of Commerce* and as the organization with the broadest reach to vendors, manufacturers, and marketers of botanicals in the United States is uniquely positioned and qualified to undertake such a task.

Extracts of “old” herbs made by long-established extraction processes should be assumed to be “old” dietary ingredients

Herbs and other botanical dietary ingredients are available in the marketplace in various forms. These include plants or parts of plants that have been subjected only to one or more minimal processing steps, such as cleaning; sorting; dehydration; cutting; powdering; etc., and that conform to the description of dietary ingredients in 21 U.S.C. 321(ff)(1)(C), i.e., “herbs or other botanicals.” Other more processed ingredients that have herbs and other botanicals as their starting raw material are also available, and include ingredients described in 21 U.S.C. 321(ff)(1)(F), for example, concentrates, metabolites, constituents and extracts of plants or parts of plants.

The manufacture of extracts from herbs and other botanicals has been practiced and recorded for many centuries, and the form of many of these extracts have been virtually unchanged for many years. AHPA has published two document

¹⁰ A botanical article of commerce is necessary a specific part (or parts) of a plant species. The part of the plant in commerce are explicitly identified for certain of the species listed in *Herbs of Commerce*, 2nd edition, particularly for the approximately 500 species for which *pinyin* names are provided. For many other species, the article of commerce from a species is broadly known, such that there is no confusion that the fruit of the apple (*Malus pumila*) is an article of commerce. In other instances the article of commerce from species listed in *Herbs of Commerce*, 2nd edition are recorded in readily available texts and are well known by persons who are qualified by training, experience, or education in their use.

¹¹ At the same time that AHPA believes that the listing of an herb species in *Herbs of Commerce*, 2nd edition should establish a presumption that the herbs was marketed prior to 1994, the text includes a third disclaimer: “The inclusion of a plant in this reference makes no implication with regard to its appropriate as an ingredient in any product offered for sale to the public... [AHPA] makes no claim, explicit or implied, with regard to the safety of any named herb.”

with relevance to these comments, including *Guidance for Manufacture and Sale of Bulk Botanical Extracts* (“the AHPA Extract Guidance”)¹² and *Standardization of Botanical Products: White Paper* (“the AHPA Standardization White Paper”).¹³ Copies of these documents are included with these comments as “Attachment A” and “Attachment B” respectively. The AHPA Extract Guidance is incorporated by reference into these comments in its entirety, as are sections 4, 5, and 7 of the AHPA Standardization White Paper.

The AHPA Extract Guidance, among other things, identifies and defines numerous types of herbal extracts, including decoctions; fluid extracts; glycerites; infusions; powdered extracts; tinctures; and many others.¹⁴ The document also differentiates between “traditional-style extracts,” which are present in both liquid and powdered forms, and “semi-purified extracts,” usually present only in powdered form.¹⁵ In addition, the document identifies numerous solvents used in the manufacture of herb extracts, many of which have a long-established recorded use. Identified food-grade solvents include alcohol; water; glycerin; food oils; steam; gases; and vinegar.¹⁶ Finally, the document describes many of the processes that are followed to make any herbal extract, including maceration or percolation when liquid solvents are used, or supercritical extraction when a gas provides the solvent.¹⁷

Both the AHPA Extract Guidance and the AHPA Standardization White Paper identify “traditional-style extracts,” which are manufactured using common, uncomplicated technologies and typically comprise a broad spectrum of the native plant constituents (“broad-spectrum extracts”); and “semi-purified” or “narrow-spectrum extracts,” in which a relatively narrow spectrum of the native botanical constituents are highly concentrated, often using modern technologies such as selective solvents or preparative chromatography.

¹² Eisner, S., managing editor. 2001. *The American Herbal Products Association’s Guidance for Manufacture and Sale of Bulk Botanical Extracts*. Silver Spring, MD: AHPA.

¹³ AHPA Botanical Extracts Committee. 2003. *The American Herbal Products Association’s Standardization of Botanical Products: White Paper*. Silver Spring, MD: AHPA.

¹⁴ Eisner, 2001, pages 4-5.

¹⁵ *Ibid*, page 12.

¹⁶ *Ibid*, pages 6-7.

¹⁷ *Ibid*, pages 8-9.

As a general rule, broad-spectrum traditional-style extracts are “generic” in the sense that they have existed in the public domain in either verbal or written form for centuries and are all roughly the same in chemical composition.¹⁸ The chemical composition of any broad-spectrum extract of any one plant part and species will be roughly the same across a wide variety of manufacturers, insofar as the native extract will comprise a broad subset of the native constituents in that plant part of that species. Therefore a variety of manufacturers can make the preparation in substantially similar forms, and usually have been doing so for a long time.

In contrast, narrow-spectrum extracts are frequently unique to a particular manufacturer. Even preparations which are nominally the same can vary considerably between manufacturers. Thus, for example, a “*Magnolia officinalis* bark powdered extract containing 50% honokiol” made by one manufacturer may be significantly different than that made by a second manufacturer, because the unique manufacturing process used by each manufacturer can cause significant differences in the unidentified remainder of the extract (i.e. the 50% which is not honokiol). In one manufacturer’s product the remaining 50% may be filler; for another manufacturer it may be a second quantified magnolia-bark constituent such as magnolol; from a third manufacturer it may be a mixture of other magnolia-bark constituents which are not quantified and quite possibly are not even identified. These differences make it necessary to include the manufacturing process and product formula, or at least an overview thereof, an integral part of the definition of the preparation.

It is likely that numerous and diverse traditional-style extracts of many, or most, of the herbs identified in *Herbs of Commerce*, 2nd edition had been marketed

¹⁸ A traditional-style broad spectrum extract of a plant part, when the plant part is exhaustively extracted, comprises virtually the same chemical composition as the source material except that the cellulose has been removed. Since the cellulose has *de minimis* impact on physiologic activity, such a broad-spectrum extract will have virtually the same biologic effect as the source botanical material. Furthermore, the vast majority of botanicals in both food and non-food use worldwide are known to be safe within the range of variability encompassed by normal variations in growing conditions and traditional extraction procedures. Hence the source botanical and most traditional-style extracts of the source botanical can reasonably be expected to exhibit virtually the same safety profile, despite some variation in chemical composition. There is no scientific evidence that the chemical composition must be *identical* in order to provide reasonable assurance of safety; to the contrary, experience and scientific study prove the opposite in most cases.

prior to 1994. In addition, numerous extracts that could be described as “semi-purified” or “narrow spectrum” were also marketed in the United States before 1994.

AHPA believes that any extract of an herb that is (1) listed in *Herbs of Commerce*, 2nd edition; and (2) is a traditional type of extract identified in the AHPA Extract Guidance or the AHPA Standardization White Paper (e.g., a decoction; a fluid extract; an infusion; a glycerite; a tincture; etc.); and (3) is manufactured with any of the common food-grade solvents identified in either of these AHPA documents, is a dietary ingredient under 21 U.S.C. 321(ff)(1)(F) and can be presumed to have been marketed in the United States before October 15, 1994 and therefore is not an NDI. Thus, for example, it can be assumed that a tincture of chamomile flowers (*Matricaria recutita*) or a 4:1 powdered extract of burdock root (*Arctium lappa*), where water and alcohol serve as the solvents and no non-traditional purification steps are used, has been marketed in the United States since at least 1994.

At the same time, AHPA believes that numerous other extracts of herbs or other botanicals were also marketed in the United States before October 15, 1994 that were manufactured with other solvents, or that used processes other than the traditional processes discussed above. Any such ingredient is also excluded from the statutory definition of a “new dietary ingredient.”

Animal ingredients that are not “new dietary ingredients”

Numerous AHPA members that market dietary supplements that contain herbal and other botanical dietary ingredients also market dietary supplements that contain dietary ingredients that consist of various parts of several animal species. Some of these consist of ingredients that are commonly referred to as “glandulars” and that are processed from various animal organs, such as heart, kidney, liver, etc. Others are animal ingredients that have long been associated with, and used along with, traditional Asian herbal ingredients. All of these animal ingredients fit into the broad group of dietary ingredients described in 21 U.S.C. 321(ff)(1)(E), that is, “a dietary substance for use by man to supplement the diet by increasing the total dietary intake.”

The use of animal-source dietary ingredients certainly predates DSHEA and is not unknown to FDA and in fact FDA has specifically recognized the presence of these ingredients in the food supply. Even before DSHEA was passed FDA's Dietary Supplement Task Force acknowledged the use in supplements of "animal extracts."¹⁹ In addition, in implementing the food facility registration requirements established by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 the Agency developed a food facility registration form that requires the registrant to disclose, among other things, the general product categories, including categories for food for human consumption, that are applicable to the facility. One of the human food categories that is identified on the registration form is "dietary supplements," and an "optional selection" that is placed as a subdivision of dietary supplements is "animal by-products and extracts."

It is AHPA's belief and position that quite a number of glandular and traditional Asian animal ingredients were marketed in the United States prior to October 15, 1994 and are therefore excluded from the statutory definition of "new dietary ingredient." In addition, AHPA is aware that there is significant evidence, in the form of dated catalogues and other dated marketing documents, that many of these animal ingredients were offered for sale in the United States prior to October 15, 1994.

It has come to AHPA's attention that FDA has on several occasions detained dietary supplements prior to importation that contain animal ingredients, and particularly traditional Asian animal ingredients that were marketed in the United States before October 15, 1994, and that are therefore not NDIs. In recording these detentions FDA's compliance officers have cited violation of the Federal Food, Drug, and Cosmetic Act section 402(f)(1)(B) (21 U.S.C. 342(f)(1)(B)), and stated that the product "appears to be a dietary supplement or ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury." In other words, the

¹⁹ Dykstra, G. *et al.* (U.S. Food and Drug Administration). May 1992. *Dietary Supplements Task Force Final Report*, page 1.

FDA compliance officers are holding ingredients that are not NDIs accountable to a regulation from which these ingredients are specifically exempt.

As a direct comment to this docket, AHPA believes that any animal ingredient, including glandular ingredients and traditional Asian animal ingredients, that was offered for sale in the United States before October 15, 1994 is exempt from the statutory definition of "new dietary ingredient." In addition, AHPA hereby requests that FDA act promptly to correct the erroneous detentions of animal ingredients described above, at every point of import, by clearly communicating to all compliance officers that the statutory requirements for new dietary ingredients do not apply to ingredients that are not NDIs.

AHPA has provided here, as *Appendix 2*, a list of several of the traditional Asian animal ingredients that were offered for sale in the United States before October 15, 1994. AHPA affirms that each of the ingredients included in this attached *Appendix 2* is listed in at least one of the following identified dated catalogues (copies of which are maintained in the AHPA offices) wherein the ingredients were offered for sale in the United States:

- Nuherbs Co., Oakland, CA. Nuherbs Catalogue, Prices effective July 1, 1988.
- Kwok Shing Import-Export, Inc., San Francisco, CA. Catalogue Fall 1989.
- Mayway USA, San Francisco, CA. 1992 Herbal Catalogue.

AHPA makes no assertion that *Appendix 2* represents a complete list of all of the traditional Asian animal ingredients that were marketed in the United States before 1994, and in fact AHPA believes that additional such ingredients were so marketed at that time. Nevertheless, AHPA requests that the articles listed on *Appendix 2* be identified to all compliance officers as exempt from jurisdiction under 21 U.S.C. 342(f)(1)(B).

Relevance of a dietary ingredient in the non-domestic food supply

As noted above, there is no restriction on marketing a dietary supplement that contains an NDI that was not marketed in the United States before October 15,

1994 so long as that NDI has been present in the food supply as an article used for food and has not been chemically altered. Revisiting the specific language of the statute, 21 U.S.C. 350b(a) exempts from notification those “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.”

AHPA notes that there is nothing in this section that requires that such a dietary ingredient have been present in the food supply in the United States in order to be exempt from the notification requirement that must be met by all other NDIs. That specific geographical limitation applies in DSHEA only where it is sought to establish an ingredient as an old dietary ingredient.

Accordingly, it is AHPA’s position that no premarket notification to FDA is required for NDIs that have been present in the food supply, whether inside or outside the United States, that will be marketed in a form in which the food has not been chemically altered. Thus, an ingredient that is present in the food supply in any country, although it would be an NDI if it had not been marketed in the United States before October 15, 1994, would not need to be the subject of an NDI notification unless it were in a form in which the food has been chemically altered.

III. Review of 21 CFR 190.6

FDA’s implementation of regulations for NDI notification

FDA published a proposed rule to implement DSHEA’s notification requirements for NDIs on September 27, 1996 and published a final rule less than one year later, on September 23, 1997. The current regulations are codified at 21 CFR 190.6.

21 CFR 190.6(b) identifies specific requirements for information that must be included in an NDI notification, which is limited to the following:

- The name and address of the manufacturer or distributor of the NDI, or of the dietary supplement that contains the NDI.
- The name of the NDI, and if it is “any herb or other botanical,” the Latin binomial name, including the author.

- A description of the dietary supplement(s) that contain the NDI, which must include: (1) the level of the NDI in the dietary supplement(s), and (2) the recommended or ordinary conditions of use of the dietary supplement(s).
- The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. This information must include any citations to published articles or other evidence that is the basis on which the manufacturer or distributor of the dietary supplement that contains the NDI has concluded that the new dietary supplement will reasonably be expected to be safe. Notifications must also include copies and, if applicable, English language translations of all references cited in support of the notification.

The regulation also requires that the notification bear a signature of a person designated by the notifier. There are no other requirements identified in 21 CFR 190.6 for any additional specific information to be included in an NDI notification.

Requirements need to be clarified for identification of an NDI

Notably absent from the information that is required by 21 CFR 190.6 to be submitted with an NDI notification is a description of the NDI itself. Yet FDA, in reviewing NDI notifications, has developed a policy of objecting to notifications that do not include a sufficiently precise description of the NDI.

In responding to NDI notifications it is not uncommon for FDA to express concern about a perceived absence of sufficient information about the identity of an NDI. For example, an NDI notification which FDA has identified as Report Number 236 was filed on behalf of the firm Fuji Chemical Industry Co., Ltd. for an NDI identified as "Astaxanthin extracted from *Haematococcus* algae." The notification did provide all of the information currently required to be included in an NDI notification under 21 CFR 190.6, including the name and address of the manufacturer; the name of the NDI, including the Latin binomial name and its

author; a description of the dietary supplement in which the NDI will be contained, including the level of the NDI in the dietary supplement and the recommended conditions of use of the dietary supplement; history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe; and a signature.

Nevertheless, although this notification conformed fully to the existing regulation, FDA's response to the submitting firm stated that the Agency had "significant concerns" about the notification, and noted:

"Your notification does not contain any information about the actual preparation of your Astaxanthin extracted from the algal source. A description of the method of manufacture or process of obtaining your product, Astaxanthin, may have helped FDA clarify the identity of your product" (emphasis added).

As can be seen from the example above, firms that may be conforming exactly to the requirements specified in the relevant regulation at 21 CFR 190.6 have been informed by FDA that their submissions are not sufficient to meet the Agency's expectation.

AHPA recommends that revisions be promptly proposed by FDA to 21 CFR 190.6 through notice and comment rulemaking to square the regulation with the Agency's expectation of performance by industry, and to establish a clear requirement for the accurate and sufficiently complete identification of any NDI that is the subject of an NDI notification.

The part of a plant is relevant to identity of herbal dietary ingredients

In reviewing the NDI notifications that FDA has received to date AHPA has observed several notifications for herb and other botanical dietary ingredients that did not include, as part of the ingredient description, the part of the plant that is intended to be the article of trade. In some such instances FDA has informed the notifying firm, for example, that the absence of identity of the part of the plant made it impossible to know whether the plant part that was the subject of the history of use information submitted with the NDI was the same as the part of the plant that

the submitting firm intended to introduce as an NDI.²⁰ On the other hand, there are numerous notifications in which the part of the plant was not identified but FDA filed the notification without commenting on this fact.²¹

AHPA further notes that 21 CFR 190.6 does not specify that the part of the plant be stated when submitting a notification for a new herb and other botanical dietary ingredient. In contrast, DSHEA established a requirement, in the section that addressed misbranding, that the “part of the plant from which the ingredient is derived” must be provided in identifying a dietary ingredient that is an herb or other botanical.²² To further complicate this issue, the just cited language from DSHEA only placed this burden on ingredients in subparagraph (C) of the basic dietary supplement definition (i.e., “herbs or other botanicals;” 21 U.S.C. 321(ff)(1)(C)), and did not specify that the part of the plant of the source ingredient of a “concentrate, metabolite, constituent, extract, or combination” of an herb or other botanical, as described in 21 U.S.C. 321(ff)(1)(F), must be disclosed.

It is AHPA’s position that an article of commerce that is an herbal or other botanical, whether in an unprocessed form or as a concentrate; metabolite; constituent; extract; or combination, can not be identified without specifying the part or parts of the plant that constitute the article, or that serve as the starting material for the manufacture of the article. AHPA therefore recommends that, if the Agency agrees to the above suggestion to initiate a process to revise 21 CFR 190.6 by notice and comment, a revision also be considered to require that the part of the plant be required as a part of the identity of any NDI that is an herb or other botanical, or a concentrate; metabolite; constituent; extract; or combination thereof.

Information needed to identify a dietary ingredient under 321(ff)(1)(C)

At the same time that AHPA is advocating for additional requirements to be established for identifying any NDI that is the subject of a notification under 21 CFR 190.6, it must be recognized that there are important differences between the kind of information that is needed to identify an herb or other botanical that is in a form

²⁰ See, for example, Report Number 238

²¹ See, for example, Reports Number 2, 7 and 10.

²² 21 U.S.C. 343(s)(1)(C).

that has not been modified after its harvest, except with such basic and necessary processes as cleaning; dehydrating; and cutting or powdering, and one that is concentrated; extracted; or processed to produce a metabolite or a constituent.

Stated another way, there are differences in the specific information that should be generally expected for an NDI that is an herb or other botanical, that is, one that fits the description under 21 U.S.C. 321(ff)(1)(C), as opposed to a new concentrate; metabolite; constituent; or extract of an herb or other botanical as described in 21 U.S.C. 321(ff)(1)(F).

As a general rule, all that should be needed to identify an unprocessed herb or other botanical is the Latin binomial name of the plant from which the ingredient is derived, and the part of the plant.²³ Information related to conditions of propagation and cultivation or of the geographical location where the ingredient is harvested is generally not relevant to the identification of an unprocessed herb or other botanical.

There may be, from time to time, instances when an unprocessed herb needs additional information to identify it. For example, if a grower seeks to deliberately modify agricultural practices or plant varieties, in a manner that is significantly different from common plant propagation and breeding practices, to produce a “super-strain” of a common plant where one or more constituents is forced to a level that greatly exceeds the normal range of the constituents, then there may be need for more specific characterization of the resultant herbal ingredient. But the emphasis in this example is on deliberate manipulation, and it should not be assumed that such details are generally needed for most unprocessed herbs.

AHPA is aware of instances in which FDA has stated that the chemical composition of an NDI that is an herb or other botanical as described in 21 U.S.C. 321(ff)(1)(C) must be adequately described to establish that such ingredient would be reasonably expected to be safe. For example, an NDI notification which FDA has

²³ Herbs are sometimes processed by steps such as washing, aging, heating, or peeling, or by other processes whereby the processed ingredient is still an “herb or other botanical” as defined in 321(ff)(1)(C), and not a concentrate, metabolite, constituent or extract of the herb or other botanical, as described in 321(ff)(1)(F). If such processes are an integral part of the identity of the resulting ingredient such processes need to be disclosed to properly and fully identify the ingredient.

identified as Report Number 239 was filed by the firm Quinta Nutraceuticals, Inc. for an ingredient claimed to be an NDI and identified as “the botanical herb *Hypoestes rosea*.” FDA’s response to the submitting firm stated that the Agency had “significant concerns” about the notification. The Agency went on to identify several specific concerns, including the following:

“...your notification failed to provide adequate information on the chemical composition of the material that is the subject of your notification, No active components are identified and no specifications for your product are provided in your notification. Thus, FDA is not able to evaluate your conclusion that your product containing the substance *Hypoestes rosea* is reasonably expected to be safe.”

AHPA strongly objects to any position by FDA that would establish a requirement for inclusion in an NDI notification of information about the chemical composition or identification of “active components” of an NDI that is an herb or other botanical.

The fact is that the “active constituent” has been unambiguously identified for very few botanicals, as is discussed at length in section 7c of AHPA’s Standardization White Paper. The following citation from that document is instructive:

“A small proportion of the botanicals in the marketplace has been studied to identify the physiologically active constituents [and though]... [I]n some cases, a clear picture of the active compound[s] has emerged... [I]n many cases, the identity of the active compounds remains completely unknown...

In general, constituents can be divided into three main categories... **Active compounds** are compounds or classes of compounds that have been tested... both in isolation and as part of a botanical preparation, and have been proven to exhibit similar therapeutic activity in both cases... **Co-Active compounds** are compounds or classes of compounds which have been shown to be biochemically active... but which have not been scientifically proven to exhibit the same activity both in isolation and as part of a botanical preparation... The composition of the remainder of the preparation remains highly significant, and the native extract in its entirety should properly be considered the ‘active component’... **Marker compounds** are compounds or classes of compounds used for technical purposes in the manufacturing process. Both biochemically active and inactive compounds may be used as markers... [and] the composition of the remainder of the preparation is of

primary importance, and the native extract in its entirety should properly be considered the 'active component'....

The presence or absence of a particular constituent on a label does not necessarily reveal much about the nature, quality, safety, or efficacy of the preparation. Just because a compound is quantified on the label does not mean that compound is essential to the preparation's quality or efficacy; it may be only a marker. Nor does it mean the preparation has been manipulated to elevate or isolate that constituent. In many cases, there is no substantive difference in the composition of one extract that is standardized for particular constituents and another that is not, as long as the raw materials and manufacturing process are similar; the only difference is that one product has been chemically characterized to a greater degree than the other....

Conversely, just because a compound is not quantified on the label does not mean the compound is not in the product; it may only mean the manufacturer did not quantify it, or did not want to list the quantity on the label. Some manufacturers feel there are more important ways to standardize their products than by testing one or a few individual components."²⁴

If the Agency were to establish a requirement that the "active constituent" of any botanical NDI be identified, an unreasonably high barrier to entry would be created. Identification of the "active constituent" can require hundreds of thousands or even millions of dollars, and years or even decades of research; and for many botanicals the mechanism of activity may be so complex that it is impossible to identify one "active constituent" or even a single class of active constituents. Furthermore, knowledge of the "active constituent" may or may not be related a reasonable expectation of safety, which is of course the whole focus of the NDI notification regulation. This information is not known for most of the herbs and other botanicals that are currently marketed, whether as dietary supplements or as food ingredients, yet the vast majority of these botanicals, and preparations of these botanicals, are safe for their recommended and usual uses.

In light of the above discussion AHPA recommends that FDA should not require the "active constituent" of an herb or other botanical to be identified, but should instead establish a standard policy that the Latin name and part of the plant

²⁴ Eisner, S. 2003, page 22-24.

are, in most cases, sufficient to identify an NDI that is an herb or other botanical as described in 21 U.S.C. 321(ff)(1)(C).

Information needed to identify a dietary ingredient under 321(ff)(1)(F)

In order to properly identify an NDI that is a concentrate, metabolite, constituent or extract of one or more herbs or other botanicals, as described in 21 U.S.C. 321(ff)(1)(F), information must be provided to identify both the herbs or other botanicals that served as the starting material for the ingredient and to identify the ingredient itself.

With regard to the herbs or other botanicals that are the starting material of such an ingredient, only the Latin binomial name of each plant ingredient and the part or parts of the plants are generally needed to be disclosed. As expressed in the preceding section, there may be instances in which additional information is needed to identify the starting material if deliberate manipulation that is significantly different from common plant propagation and breeding practices is undertaken in growing the plants that serve as the starting material.

In addition to the information needed to identify the starting material for such an ingredient, additional information is necessary to fully and properly identify an NDI that is a concentrate, metabolite, constituent or extract of an herb(s) or other botanical(s). The AHPA Extract Guidance provides suggestions on labeling of extracts intended for further processing, and delineates these suggestions based on the form of the extract, whether liquid extracts, traditional-style powdered extracts, or semi-purified powdered extracts, as each of those terms is defined in the document. Four of the first five suggestions in each of these extract categories are either of no relevance or limited relevance to ingredient identification for purposes of an NDI notification (part or item number; lot or batch number) or have already been discussed above as necessary for identification (Latin name and/or common name in *Herbs of Commerce*; plant part). Additional information that the document recommends for labeling of extracts includes:

For liquid extracts

- Brand name, if applicable.
- Solvent used for extraction.
- Dilution ratio of the finished extract. If the dilution ratio is based on the weight of fresh rather than dried herb, this fact must be disclosed.
- Description and amount, in percent or range of percents, of all added ingredients, including all solvents remaining in the product.
- Overview of the manufacturing process, including a general description of each process step.

For traditional-style powdered extracts

- Brand name, if applicable.
- Solvent used for extraction.
- Concentration ratio or range of concentration ratios of the finished extract. If the concentration ratio is based on the weight of fresh rather than dried herb, this fact must be disclosed.
- Description and amount, in percent or range of percents, of all added ingredients.
- Content, minimum content, or range of content of any marker substances, in percent.
- Overview of the manufacturing process, including a general description of each process step.

For semi-purified powdered extracts

- Brand name, if applicable.
- Description and amount, in percent or range of percents, of all added ingredients.
- Content, minimum content, or range of content of each group of components quantified in the extract.
- Overview of the manufacturing process, including a general description of each process step.

AHPA requests that FDA recognize that each of the suggestions for labeling of extracts identified above and published in AHPA's Extract Guidance are relevant to the identity of an NDI that is an extract of an herb or other botanical. While this document does not specifically address concentrates, metabolites or constituents of herbs or other botanicals, AHPA also requests that FDA consider whether these suggestions for labeling of extracts may have relevance for these other ingredients.

IV. Procedures for NDI notification

Since the passage of DSHEA in 1994 until the date of these comments, FDA has posted to an internet accessible docket two hundred and sixty (260) numbered reports of NDI notifications.²⁵ There have been a number of submissions for which the notifier has submitted additional information after receiving communication from the Agency that identified one or several concerns with the original notification and in many of these cases a new report number has been assigned upon receipt of the additional information. If these duplicate-numbered (or occasionally triplicate- or quadruplicate-numbered) reports are accounted for, the Agency has, as of this date, posted two hundred and four (204) unique NDI notifications. And these unique notifications have identified two hundred and fifty-five (255) unique ingredients.

AHPA has provided in the previous section of these comments numerous comments and suggestions for amendments to the existing regulations for NDI notifications at 21 CFR 190.6. Additional comments here follow that are relative to some, but not all, policies and practices that the Agency has developed in responding to notifications submitted to date, and that AHPA has arrived at by reviewing these notification.

FDA should refuse to accept notifications for new dietary *supplements*

FDA has received at least sixteen unique "NDI notifications" for new *dietary supplements*.²⁶ There are at least eight additional unique notifications that should

²⁵ These are numbered M2; M3; 1-69 inclusive; and 71-259 inclusive.

²⁶ Report Numbers 51; 64; 126; 168; 174 (2 dietary supplements); 177; 180; 185; 203; 205; 206; 207; 227; 231; and 241. The identification of the subject of these notifications as dietary *supplement* is usually not subtle. For example:

probably be identified as notifications for new dietary supplement, as the submitting firm specifically identified its dietary supplement as the subject of the notification, but also stated that the ingredients, which included such ingredients as clove, cardamom, cumin and Japanese honeysuckle, were NDIs, although none of these ingredients are NDIs.²⁷ Thus, as many as twenty-four of the 204 unique notifications that FDA has posted as of this date, or almost one of every eight, were notifications that should not have been submitted under the law or governing regulations.

In each of these instances FDA has treated these submissions as if they were legitimate NDI notifications. The Agency's normal practice is to treat the notification as a notification for each and every one of the ingredients that is identified as contained in the new dietary supplement.

Not surprisingly, firms that do not understand the NDI regulations sufficiently well to understand that notifications are not required for new dietary supplements are not particularly successful in providing information that satisfies FDA that there is a basis to conclude that the products that are the subject of these (erroneous) notifications are reasonably expected to be safe. In fact, only one of these 24 notifications for dietary supplements have not received communications from FDA expressing the Agency's concern about one or another failing identified in the notification, and this exception was for a dietary supplement containing Vitamin D₃ (see Report No. 241), which is not a new dietary ingredient.

AHPA strongly encourages FDA to establish a practice wherein it refuses to accept NDI notifications for new dietary supplements. If the simple arithmetic above is accurate and one of every eight notifications is simply filed in error, the Agency would do well to reassign the time spent on these unnecessary filings. In addition, the presence of publicly available documents on FDA letterhead that state that a

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- Report No. 177: "In compliance with section 413(a)(2) of the Dietary Health and Education Act of 1994 [sic], Hi-Tech Pharma, Inc., a Florida corporation, makes its official Premarket Notification for *Cumaris*, **a new dietary supplement**" (emphasis added). The notification then identified three ingredients, two of which are herbs that are not NDIs.
 - Report No. 231: "We are enclosing all the required documents for the filing of the pre-market notification on an imported **new upcoming herbal product** – 'Essence of Mulberry 8 & 8' from Seven Tortoise Co. Ltd. of Taiwan" (emphasis added). The notification then identified four different parts of the mulberry tree as the ingredients of the product.

²⁷ Report Numbers 33; 42; 71; 105; 122; 123; 159; and 160.

firm's product "may be adulterated as dietary supplements that contain the new dietary ingredients specified..." which specification includes, for example, cumin seed or clove, are not unlikely to lead to mischief in the hands of some enterprising plaintiffs' attorney.

Numerous NDI notifications have been filed for ingredients that are not "new"

AHPA has identified numerous ingredients, and especially herbal and other botanical dietary ingredients, that were the subject of filed NDI notifications but that were marketed in the United States before the passage of DSHEA and are therefore not NDIs.

Most such ingredients are those that are included in the erroneous filings for dietary supplements described above, and include at least the following: American ginseng root (*Panax quinquefolius*, Report No. 136); Asian ginseng root (*Panax ginseng*, Report Nos. 168 and 227); Chinese salvia root (*Salvia miltiorrhiza*, Report No. 36); cordyceps mycelia (*Cordyceps sinensis*; Report Nos. 39, 121, 136, and 138); and imperata root (*Imperata cylindrica*; Report No. 33). AHPA does not represent this list to be exhaustive of NDI notifications that have been filed to date for dietary ingredients that are not, in fact, NDIs and AHPA believes there to be many additional such notifications.

Contrary to AHPA's above recommendation that the Agency refuse to accept NDI notifications for new dietary supplements, AHPA is not recommending at this time that the Agency refuse to accept NDI notifications for dietary ingredients that are not in fact new. To the best of AHPA's knowledge, FDA does not possess a definitive list of all dietary ingredients that were marketed prior to October 15, 1994 and so does not have ready access to make a decision to refuse to accept notifications for old dietary ingredients. It is probably not a good use of FDA resources for Agency personnel to research whether or not any given ingredient was or was not marketed in the United States prior to 1994.

At the same time, in those instances when the Agency receives a notification for a well-known ingredient, such as common wheat or American ginseng, AHPA encourages FDA to consider whether some communication to the submitting firm

might not be helpful in clarifying the NDI regulation. In addition, AHPA is willing to provide information to the Agency, as appropriate, to assist in determining whether any particular herbal or other botanical dietary ingredient was or was not marketed in the United States prior to October 15, 1994.

Numerous NDI notifications have been filed for ingredients that have been used for food in a form in which the food has not been chemically altered

DSHEA exempted articles used for food in a form in which the food has not been chemically altered from the requirements to file NDI notifications. AHPA is aware, however, of several filings for dietary ingredients that have been used for food and are in a form in which the food has not been chemically altered. AHPA notes that the Agency has on one occasion informed the submitting firm that the identified ingredient “is a conventional food ingredient” and “is not a dietary ingredient within the meaning of 21 U.S.C. 321 (ff).”²⁸

On other occasions the Agency has proceeded to address the NDI notification for a food ingredient as if the notification were, in fact, for an NDI that had not been used for food. For example, a notification was filed in which the NDI was identified as “freeze-dried kimchi” under the brand name NeoKimchi.²⁹ But kimchi, as the notification stated, “has been consumed in Korea for more than 500 years as an ordinary food.” Nor did the firm state that its product would have been chemically altered, as it described its processing as freeze-drying whole fermented kimchi “via conventional means,” and grinding into powder. Both freeze-drying (“lyophilization”) and grinding (“milling”) are specifically exempted from the meaning of chemical alteration. Nevertheless, FDA responded to the notification by informing the submitting firm that it had “significant concerns” about the notification and cited, for example, the absence of Latin binomial names.³⁰

²⁸ Report No. 57, submitted by Nature’s Marvel International for the ingredient identified as “Luo Han Kuo fruit extract” from *Siraitia grosvenorii*.

²⁹ Report No. 216, submitted by Neo Kim Chi, Inc.

³⁰ Contrary to their normal practice, FDA identified the subject of this notification as the dietary supplement (called “NeoKimchi A”) that the firm had identified as containing the NDI (“NeoKimchi”) rather than the NDI itself. This may have been due to some lack of clarity in the notification. For example, the reference line in the submission read, “Premarket Notification for a New Dietary Ingredient – NeoKimchi A.” The first paragraph, however, stated that the firm was notifying FDA “that it will market the NeoKimchi A products as a dietary

There are other examples of NDI notifications for ingredients that have certainly or probably been used as food and that have not been chemically altered, including, for example, several species of mushroom (see Report No. 76, filed for an apparently non-novel extract of *Agaricus blazei*; also see Report No. 247, filed for powdered *sang huang* mushroom, *Phellinus linteus*; also see numerous reports filed for *Ganoderma lucidum*, including Report Numbers 42, 165 and 185); egg lecithin (See Report No. 142); and mulberry fruit (see Report No. 231, filed for a dietary supplement that includes mulberry fruit). AHPA does not represent this list to be exhaustive of NDI notifications that have been filed to date for dietary ingredients that may be an NDI, but for which notifications are not required since the ingredients have been used for food in a form in which the food has not been chemically altered.

As noted above in discussing NDI notifications that have been submitted for ingredients that are not NDIs, AHPA is not recommending at this time that the Agency refuse to accept NDI notifications for dietary ingredients that have been used as foods and are not chemically altered. AHPA again expresses its willingness to provide information to the Agency, as appropriate, to assist in determining whether any particular herbal or other botanical dietary ingredient is used for food in a form in which the food has not been chemically altered.

FDA must allow notifications to be withdrawn

On just four occasions to date the firm submitting an NDI notification has requested that their notification be withdrawn. For example, a notification was received on August 17, 1997 from BioResponse, LLC for an ingredient identified as an NDI and as 3,3'-diindolylmethane.³¹ The firm subsequently informed FDA that it had become aware that the ingredient had actually been marketed prior to October 15, 1994 and FDA, in a letter dated July 9, 1998 began with the phrase, "This letter acknowledges your withdrawal of your August 11, 1997 new dietary ingredient

supplement." The notification subsequently clearly identified the NDI as NeoKimchi, the freeze-dried kimchi ingredient, and the dietary supplement that would contain the NDI as NeoKimchi A, described as a product in capsule form containing the NDI and two other ingredients. This confusion has little bearing on the point that AHPA is making here, however, as neither of the other two ingredients, lactobacillus and ginseng, are NDIs.

³¹ Report No. 18.

submission....” In another instance³² Solgar Vitamin and Herb notified FDA on March 16, 2001 that it “will not market a product containing Resveratrol at this time,” which ingredient had been the subject of an NDI notification from the prior year, and no further communication from the Agency on this matter is available in the public record. Similarly, Tsumura USA informed FDA that it “will refrain from marketing” its tokaku-toki-jo extract (erroneously filed in this instance, as the subject of the filing was a dietary supplement³³) and requested that the notification be withdrawn. No further communication from the Agency on this matter is available in the public record.

AHPA is aware that on one other occasion FDA refused to allow a firm to withdraw its NDI notification. An NDI notification was filed on September 6, 2000 by Van Drunen Farms for a patent pending extract of barley under the brand name of GMM. Subsequently the Agency was informed by counsel for Van Drunen that “the notification was submitted in error,” since “extracts of barley and malted barley were marketed prior to October 15, 1994.” This later communication also stated that the exemption from filing a notification for articles used for food that had not been chemically altered also applied to the GMM product, since its production process “is within the types of physical modifications that would not render the barley to be ‘chemically altered’ within the meaning of... 21 U.S.C.”

Unlike FDA’s earlier responses, the Agency responded by writing that “the Agency cannot grant your request to withdraw the GMM notification,” that “[T]he information you presented is not sufficient to support your contention that GMM was marketed as a dietary supplement [sic] in the United States prior to October 15, 1994,” and that “[T]he information you presented is not sufficient to support your contention that GMM is exempt from FDA premarket notification” as an article used for food that has not been chemically altered.

AHPA notes that in procedures for the food ingredient GRAS notification system that one of the options set forth is for the FDA’s response letter to state “that the Agency has, at the notifier’s request, ceased to evaluate the GRAS notice.”

³² Report No. 85.

³³ Report No. 207.

It is APHA's position that a similar option ought to be available to NDI notifiers as well, and notes that there is no principled basis for this not to be permitted. AHPA requests that the Agency establish a policy for such an option and communicate that policy clearly and openly.

With regard to the response to Van Drunen cited above, AHPA has no position at this time as to the validity of FDA's expressed positions on this specific NDI notification. The response from FDA cited here, however, presented numerous positions that AHPA would find troubling if the stated positions are formal positions of the Agency, at least insofar as such positions might be applied to herbal and other botanical dietary ingredients. Two examples and commentaries to these examples follow:³⁴

1. "To establish that GMM is not a new dietary ingredient, you must present evidence showing that GMM, or a substance chemically identical to GMM, was actually marketed as a dietary ingredient in the United States before October 15, 1994."
 - There is nothing in DSHEA that suggests that a manufacturer or distributor of a dietary ingredient that was marketed before DSHEA has a legal burden to "present evidence" of its prior marketing. It may, however, be reasonable to assume that there must be some basis for an assertion that an ingredient, or one that is sufficiently similar, but not necessarily "chemically identical," was marketed before 1994. Nevertheless, the burden of proof to show that a dietary supplement is adulterated due to the presence of an NDI for which there is inadequate information to provide reasonable assurance of safety is borne by FDA.³⁵

2. "Although reference to a publication listing a substance chemically identical to GMM as having been marketed prior to October 15, 1994, might buttress a claim that GMM is not a new dietary ingredient, the inclusion of such a substance in one or more of these published lists does not, by itself, suffice to show that the substance is not a new dietary ingredient."
 - It may be this stated point in this correspondence with which AHPA most strongly disagrees. A publication that lists a substance as having been marketed prior to October 15, 1994 does much more than "buttress a claim" that any chemically identical dietary ingredient is not an NDI. The inclusion of such information in a published list instead establishes with certainty that the ingredient is not an NDI.

³⁴ Satchell, FB. July 15, 2001. Letter addressed to Holly Bayne, pages 2-3.

³⁵ 21 U.S.C. 342(f)(1).

The standard for an NDI to be “reasonably be expected to be safe” must be reasonable

DSHEA requires that the manufacturer or distributor of an NDI provide information “which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.” Such expectation of safety is necessarily in relation to use of the dietary supplement and the contained dietary ingredient under recommended conditions of use. AHPA notes that the language of the statute does not require that an NDI be *proven* to be safe. The Agency’s requirements must therefore be commensurate with this statutory requirement and must not exceed this statutory requirement.

AHPA believes that the kind and amount of information that can serve as the basis for a conclusion that an herbal or other botanical dietary ingredient that is an NDI will reasonably be expected to be safe varies considerably, depending on such factors as:

- The ingredient’s history of use, if any.
- The degree of similarity between the chemical composition of the NDI to other botanicals or to other known preparations of the same or similar botanical ingredient.
- The degree to which naturally-occurring constituent ratios are modified.
- The presence of toxicities which must be mitigated prior to use to assure that the consumed ingredient will reasonably be expected to be safe.

Furthermore, AHPA notes that in many cultures worldwide, formal or informal training programs exist whereby individuals are trained in the expert preparation and use of the botanicals indigenous to that culture. These experts are extremely knowledgeable about the safe preparation and use of those botanical materials and about any toxicity concerns that may exist, and experts such as these are the most qualified source of reliable information about these matters. By including review of NDI applications by appropriate, qualified experts in the specific botanical that is the

subject of the application, a reasonable assurance of safety will be provided without erecting undue barriers to entry of safe NDIs.

AHPA proposes that the described information provided below for each of the described categories of herbal and other botanical NDIs can form a basis for a conclusion that the described NDI are reasonably expected to be safe.

An NDI that is the same or similar to ingredients that have an established use for human consumption and for which there are no known safety concerns, so long as such NDI is prepared in a manner that is the same or similar to the processes that have been historically used for those ingredients.

The following information can form the basis for a conclusion that these ingredients are reasonably expected to be safe:

- Reliable documentary evidence of the use, safety, and preparation of the plant part of the species or closely related species. The evidence should consist of generally available, published, and corroborated information that is readily available to interested qualified experts.
- Review of the above evidence and the NDI notification by an expert qualified by experience and training.

An NDI that is the same or similar to ingredients that have an established use for human consumption, and for which either (1) there is a known safety concern, or (2) the NDI is prepared in a manner that is NOT the same or similar to the processes that have been historically used for those ingredients.

The following information can form the basis for a conclusion that these ingredients are reasonably expected to be safe:

- Reliable documentary evidence of the use, safety, and preparation (including necessary measures taken to address known safety concerns, if present) of the plant part of the species or closely related species. The evidence may consist of generally available, published, and corroborated

information that is readily available to interested qualified experts, or alternately may consist of proprietary information.

- Review of the above evidence and the NDI notification by an expert qualified by experience and training.
- Scientific studies only if deemed necessary by the qualified expert.

An NDI that has no history of use for human consumption.

Scientific studies can form the basis for a conclusion that these ingredients are reasonably expected to be safe.

The suggestions above are, as stated, specifically related to new herbal and other botanical dietary ingredients. A similar organization may also be useful for other new dietary ingredients.

In providing these comments AHPA has attempted to strike a balance between strong support for the Congressional intention expressed in the language of DSHEA to assure that ingredients that were already marketed prior to 1994 are allowed to continue to be marketed, and the need to give serious consideration to providing good information for new dietary ingredients so that products that contain these will be reasonably expected to be safe. Many of the issues addressed herein are complex and AHPA sincerely hopes that FDA will maintain an openness to a useful dialogue as we work to resolved these matters.

Sincerely,


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APPENDIX 1

Premarket Notification for New Dietary Ingredient Notifications *Federal Register Notice; October 20, 2004*

Answers to Questions Posed by FDA Prepared by the American Herbal Products Association (AHPA) Docket No. 2004N-0454

A. Status of a Substance as a “New Dietary Ingredient”

1. What should FDA consider to determine whether a substance falls within a particular category of the statutory definition of “dietary ingredients” under sections 201(ff)(1)(A) through (F) of the act?

The agency should consider the common definitions for each of the terms in 201(ff)(1)(A) through (F). With regard to herbal and botanical dietary ingredients, the agency should consider all of the following to be dietary ingredients in the particular category of 201(ff)(1)(C): any botanical (other than tobacco), including algae and fungi, or any part of any botanical (other than tobacco); also, the agency should consider all of the following to be dietary ingredients in the particular category of 201(ff)(1)(F): any concentrate, metabolite, constituent, extract, or combination of any botanical (other than tobacco) or any part of any botanical (other than tobacco); except that any substance described herein that is specifically excluded in 201(ff)(3)(B) can not be considered to be a dietary ingredient in either 201(ff)(1)(C) or (F).

2. What changes in chemical composition to a dietary ingredient would cause it to become a substance that is not a dietary ingredient?

With regard to herbal and botanical dietary ingredients defined in either 201(ff)(1)(C) or (F), only those changes in chemical composition to such ingredients that result in the production of a substance that is not either a concentrate, metabolite, constituent, extract or combination of a botanical or a part of any botanical (other than tobacco) should be excluded from the definition of a dietary ingredient.

In this regard, the addition of food additive or GRAS excipients, binders, carriers and other ingredients added for technical purposes to a botanical ingredient should not cause the resultant ingredient to lose its dietary ingredient status. Neither should the presentation in a new chemical form of a botanical ingredient cause the resultant ingredient to lose its dietary ingredient status. Thus, the acetylated form of a dietary ingredient, e.g., for illustration only, hypericine acetate, should be seen as a dietary ingredient.

3. What should FDA consider to determine whether a dietary ingredient was not marketed in the United States before October 15, 1994, and is therefore an NDI?

This question would be better asked by attempting to make affirmative determinations that a dietary ingredient *was* marketed in the United States before October 15, 1994. All other dietary ingredients are NDIs that require notification or do not require notification, depending on their character.

The following response summarizes comments made by AHPA in the comments to which this document is appended, and particularly in the section titled “‘New’ vs. ‘old’ dietary ingredients.”

With regard to herbal and botanical dietary ingredients defined in 201(ff)(1)(C), that is, “an herb or other botanical,” use of the ingredient prior to that date in the manufacture of a product that was used in products to be ingested establishes that such an ingredient was marketed prior to the date. In addition, offering of the ingredient, in any form, prior to that date by any wholesale or retail source, or by any other channel of trade such as direct seller or multilevel marketer, for example, by a listing of the ingredient in a catalogue of products or raw materials or by offering of the ingredient in a retail store, establishes that such an ingredient was marketed prior to the date.

With regard to herbal and botanical dietary ingredients defined in 201(ff)(1)(F), that is, “a concentrate, metabolite, constituent, extract, or combination [of an herb or other botanical],” the same uses that are described in the above paragraph for an herb or other botanical (i.e., use of the ingredient in a product for ingestion; offering of the ingredient for sale for use in such products) establish that such an ingredient was marketed prior to the date.

In addition, it is AHPA’s position that extracts manufactured from any herb or other botanical that meets the definition of 201(ff)(1)(F) by any of the long-established extraction processes with any of the solvents that are normally used in such extraction processes.

4. What changes in chemical composition to a dietary ingredient that was marketed in the United States before October 15, 1994, would lead to the dietary ingredient becoming an NDI subject to the notification requirement in section 413(a)(2) of the act?

AHPA notes that, in posing this question FDA has used the words “changes in chemical composition,” whereas the relevant statutory language is “chemically altered.” With regard to botanical dietary ingredients defined in either 201(ff)(1)(C) or (F) that were marketed in the United States before October 15, 1994, this is a potentially significant difference in meaning between these terms.

The chemical composition of two or more samples of the same botanical ingredient under 201(ff)(1)(C) may differ from one region to another or one season to another, or even within the same region and season. There is nothing in the law that implies that the chemical composition of, for example, chamomile flowers, in the market

today must be exactly the same as the chemical composition of chamomile flowers that were sold prior to 1994. Similarly, the chemical composition of a traditionally produced aqueous-ethanolic tincture of an herb, or other botanical ingredient under 201(ff)(1)(F), very likely has a different chemical composition, at least in some particular, from batch to batch. There is nothing in the law that implies that the chemical composition of, for example, tincture of chamomile flowers, in the market today must be exactly the same as the chemical composition of tincture of chamomile flowers that was sold prior to 1994.

If the agency meant by this question to identify deliberate changes in chemical composition, or what chemical alterations would lead to NDI status, AHPA reminds the agency that none of the following can be considered changes in chemical composition of a botanical ingredient: minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, powder, or solid in suspension.

5. What changes to the conditions of use (e.g., serving size, duration, frequency of use) recommended or suggested in the labeling for a dietary supplement that contains an NDI would trigger the need for a separate NDI notification?

Presently, FDA is evaluating NDIs on the basis of the proposed conditions of use set forth by the manufacturer or distributor submitting the NDI. Those conditions usually related to serving size or dose, frequency of use and duration of use. FDA has asked submitters to change conditions of use to comport with the data submitted in support of some NDIs, i.e., by limiting the recommended use of an ingredient to one or two months, consistent with the data submitted in support of the conclusion that the NDI is reasonably expected to be safe for use.

It is AHPA's view that material changes in daily dose and duration of use that go beyond the conditions submitted to and reviewed by the FDA in a prior NDI notification create a need for a separate NDI notification.

6. Is there an authoritative list of dietary ingredients that were marketed prior to October 15, 1994, and therefore are not NDIs? If not, should there be? Who should compile such a list and what criteria should be considered for placement of the dietary ingredient on such a list?

As discussed at some length in the AHPA comments to which this document is appended, AHPA believes that the listing of a species of herb or other botanical in *Herbs of Commerce*, 2nd edition should constitute a presumption that the article of commerce that is derived from the identified herb or other botanical was marketed in the United States before October 15, 1994, and that all such species should be recognized as exempt from the definition of a "new dietary ingredient." In addition, AHPA believes that the absence of any particular species in *Herbs of Commerce*, 2nd edition should not be interpreted as proof that the species was not marketed United States before that date.

Should FDA decide to work to create a more definitive and authoritative list of herbal and other botanical dietary ingredients that were marketed prior to October 15, 1994, the Agency should recognize that AHPA, as the publisher of both editions of *Herbs of Commerce*, is uniquely positioned and uniquely qualified to undertake such a task. Criteria for listing of botanical ingredients could include any actual record, dated prior to October 15, 1994, that an ingredient was offered for sale in the United States before that date.

B. Chemical Identification of the NDI

3. What types of information should be included to describe a botanical NDI for purposes of the NDI notification? Please consider the following types of information:

As the agency will note below, AHPA's responses to virtually all of the questions posed in this part is a response that the information is not needed to identify a botanical ingredient. The only exceptions are that AHPA does believe that the part of the plant must be identified, and can conceive of a need to identify conditions of propagation, if deliberate manipulation of propagation in a manner that is significantly different than common plant propagation and breeding practices. See additional discussion in the AHPA comments to which this document is appended. Also, section 4a of AHPA's Standardization White Paper, which is incorporated by reference in AHPA's comments, discusses at length parameters that *might* be important but that are *not necessarily* important to most of the specific questions posed in this series of questions by FDA.

Related to AHPA's belief that none of the other information described here is needed to identify a botanical ingredient, AHPA is deeply concerned about the potential costs associated with providing such unneeded information. AHPA has not, as of this date, initiated any actual cost estimates but believes that any cost associated with providing information that is not necessary is an unacceptable cost.

a. Botanical family name.

The agency currently requires that the Latin binomial name, which consists of the plant's genus and specific epithet, and the author of the Latin binomial name, be included in an NDI notification. AHPA does not believe that the botanical family name needs to be identified in an NDI notification, as that information *is already known* by providing the Latin binomial name. In other words and for example, by identifying ginger as *Zingiber officinale* Roscoe it is already known that the plant that is being identified is that species of the genus *Zingiber* that is in the family *Zingiberaceae* since there is no other genus of *Zingiber*. In the interest of efficiency therefore, and with absolutely nothing lost in clarity, AHPA recommends that no requirement for naming of the botanical family be imposed.

- b. Part(s) of plant used.
The part of the plant used is required in dietary supplement labeling by 21 U.S.C. 343(s)(2)(C) and should be required in any NDI botanical filing.
- c. Conditions of propagation.
As a general rule AHPA does not believe that conditions of propagation are relevant to the identity of a botanical ingredient. See AHPA's comments to which this document is appended for further discussion.
- d. Geographical location of cultivated or wild harvested plant.
AHPA does not believe that the geographic location of the cultivated or wild harvested plant is generally necessary to its identification.
- e. Conditions of cultivation.
- i. Time of cultivation—month and year.
AHPA does not believe this information is relevant to the identity of an NDI botanical.
 - ii. Field cultivation—soil pH, fertilizers, pesticides and herbicides.
AHPA does not believe this information is relevant to the identity of an NDI botanical. Any botanical for use in dietary supplements may not bear or contain an adulterant such as an unregistered pesticide or herbicide. There is therefore not any reason to request this information.
- f. Greenhouse cultivation.
- i. Soil pH, fertilizers, pesticides and herbicides.
AHPA does not believe this information is relevant to the identity of an NDI botanical. Any botanical for use in dietary supplements may not bear or contain an adulterant such as an unregistered pesticide or herbicide. There is therefore not any reason to request this information.
 - ii. Hydroponic growth media—nutrients, growth hormones and minerals.
AHPA does not believe this information is relevant to the identity of an NDI botanical. Any botanical for use in dietary supplements may not bear or contain an adulterant. There is therefore not any reason to request this information.
- g. Method of drying—air or heat.
AHPA does not believe this information is relevant to the identification of a botanical NDI.
- h. Processing information—hand or machine sorted, chopped or milled.
AHPA does not believe this information is relevant to the identification of a botanical NDI.

4. Is there other information that should be included in a botanical NDI notification due to unusual production conditions of the botanical? Please consider the following possible situations:

- a. *Saccharomyces cerevisiae* is cultured in medium with unusually large amounts of selenium. Should the notification describe the degree of selenium uptake as well as the levels of selenium compounds in the final dietary supplement product?

AHPA does not believe such information is necessarily required to be included in an NDI under the described conditions.

- b. Traditional or bioengineering methods are used to produce a plant variety with novel properties. What chemistry information is needed to describe the plant variety in sufficient detail to identify the botanical product?

Information should be provided to describe what has been deliberately altered in the chemical composition, and how the new composition compares to the natural composition.

5. Is there processing information that should be included in the description of a botanical extract in order to adequately describe the NDI? Please consider the following types of information:

NOTE: AHPA has addressed most of the below issues in its publications, *Guidance for Manufacture and Sale of Bulk Botanical Extracts* and *Standardization of Botanical Products: White Paper*, attached as *Attachment A* and *Attachment B* respectively, and incorporated by reference in part or in whole in the AHPA comments to which this document is appended. These issues are also discussed in the AHPA comments and both the comments and attachments should be reviewed for more complete discussions of these issues.

- a. Description of the method of preparation (e.g., extraction) in sufficient detail so as to make clear:

- i. The identity of the source material (dietary ingredient).

This information is needed for all botanical extracts.

- ii. How the extract (NDI) is obtained from that source material.

An overview of the manufacturing process, including a general description of each process step and identification of all ingredients used, including amounts, should be provided.

- iii. How the extract is standardized from batch to batch.

AHPA believes that the term “standardized” has come to mean many things in the herbal market, and that some of these meanings are confusing or worse. The AHPA Standardization White Paper that is attached here as *Attachment B*, was produced to address numerous issues related to standardization, and sections 4 and 5 of that document, which are incorporated by reference in AHPA’s, comments are particularly relevant here.

If the above question is meant to ask how the extract will be consistently manufactured from batch to batch, AHPA believes that this differs depending upon the type of extract, and that the information recommended for labeling of different types of extracts, as given in its document, *Guidance for Manufacture and Sale of Bulk Botanical Extracts*, and as discussed in the AHPA comments to which this document is appended, are relevant to this issue. Specifically, for liquid extract the dilution ratio (including information about fresh ingredients) and an overview of the manufacturing process should be disclosed; for traditional-style powdered extracts the concentration ratio (including information about fresh ingredients), the content, minimum content, or range of content of any marker substances, and an overview of the manufacturing process should be disclosed; and for semi-purified powdered extracts the content, minimum content, or range of content of each group of components quantified in the extract and an overview of the manufacturing process should be disclosed.

- iv. How potential adulterants such as nonfood solvents, pesticides, heavy metals and filth are excluded.

These adulterants are not permitted in dietary ingredients in an amount that would cause a product to be adulterated and assurance of their absence is an issue related to a firm's manufacturing practices. This information is not relevant to an NDI notification.

In relation to this question AHPA also wishes to remind the Agency that a food, including a dietary supplement, is adulterated “[I]f it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause *if the quantity of such substance in such food does not ordinarily render it injurious to health*” (emphasis added). 21 U.S.C. 342(a)(1). Thus the Agency's use of the word “excluded” in this question must be tempered by this statutory language.

- b. Documentation of the absence of toxins or other by-products that may affect the safety of the ingredient produced by fermentation or bioengineering.
AHPA is concerned about the FDA's suggestion that NDI submitters be required to prove a negative, in this case a broad undefined negative. Certainly if the FDA has a reasonable scientific basis to believe that toxins could be created in such processes, the question could be asked of an NDI submitter.
- c. Documentation that the extracts of cultured isolates are neither infectious nor toxic.
AHPA is concerned about the FDA's suggestion that NDI submitters be required to prove a negative, in this case a broad undefined negative. Certainly if the FDA has a reasonable scientific basis to believe that toxins could be created in such processes, the question could be asked of an NDI submitter.

6. Are there additional types of information that should be included in the description of a botanical NDI?

See the AHPA comments to which this document is appended for AHPA's additional suggestions for botanical NDIs.

C. Information About the Dietary Supplement

1. What types of information about the dietary supplement product should be included in an NDI notification?

Information about the dietary supplement that will contain an NDI should include:

- **Information about the serving size or dose of the NDI ingredient in the dietary supplement, including the maximum amount of the NDI to be taken per serving and per day.**
- **Restrictions on the length of time that the dietary supplement should be taken should, if any.**
- **Restrictions on use by specific populations, if any.**
- **The form or forms of the dietary supplement.**
- **Information demonstrating a reasonable expectation of safety**

AHPA believes that a manufacturer or distributor can, in a single NDI notification, meet the requirements for showing a reasonable expectation of safety several dietary supplements that will contain the NDI, by providing information to address all of the points above for a range of products. For example, the manufacturer or distributor could file a single NDI notification for an NDI that will be contained in dietary supplements that are in the form tablets or capsules; that the NDI be present in an amount not to exceed 100 mg per dose or serving; that any such dietary supplement be labeled in a manner to recommend that daily consumption not exceed 500 mg, that continuous use not exceed 60 days, and that children not use the dietary supplement. If the information provided by such firm serves as the basis for a conclusion that all such dietary supplements are reasonable expected to be safe, the Agency should not insist on separate notifications for all such dietary supplements.

Information about the dietary supplement that contains the NDI that is usually not relevant, or that may not be relevant, to an NDI notification include:

- **Other ingredients in the dietary supplement.**
- **A label for the dietary supplement.**

2. Please consider the following types of information:

a. Composition/formulation of the dietary supplement product, including any contaminants.

AHPA does not understand the relationship of this question to “any contaminants.” Dietary supplements containing contaminants at unsafe levels

are or may be adulterated. Nothing in DSHEA suggests that an NDI notification for a dietary ingredient needs to address the ultimate formulation of a dietary supplement containing the NDI ingredient, except with respect to the issues identified in the immediate preceding question.

- b. A copy of the proposed product label and of any other labeling that recommends or suggests conditions of use in addition to or different from those recommended or suggested in the product label.

With respect to the proposed product label, this is established by the marketer of the dietary supplement product, who is not necessarily the NDI notifier. As stated above, AHPA does not believe a label of the dietary supplement product that contains the NDI need be submitted with a notification. If, as suggested in this question, a dietary supplement marketer wishes to include the NDI in a dietary supplement and the conditions for use provided on the label are different than the conditions of use identified in the NDI notification, a new NDI notification may be required. It is therefore incumbent upon the manufacturer or distributor of an NDI who filed the NDI notification to communicate to downstream customers any dosage limits or restrictions on use that were included in the notification.

D. Establishing a Reasonable Expectation of Safety

1. What types of information should be included in an NDI notification in order to establish a reasonable expectation of safety based upon history of use? Please consider the following types of information:

- a. A description of the population that consumed the food or dietary supplement containing the NDI.

This information may be relevant to the safety of an NDI, especially if there were historically subpopulations for whom the NDI was proscribed.

- b. The consumption levels (per serving and total exposure).
This information is relevant to the safety of the NDI.

- c. How often and how long the population consumed the food or dietary supplement containing the dietary ingredient.
This information is relevant to the safety of the NDI.

- d. The number of independent references documenting history of safe use.
The number of references is not necessarily relevant to the safety of the NDI, so long as the identified reference or references are sufficiently credible to provide clear and accurate information about the NDIs historical use.

- e. The number of consecutive years of exposure.

This information may be relevant to the safety of the NDI and would need to be considered in combination with other information, such as the intended use of the NDI.

- f. Documentation of the health monitoring system(s) and database(s) associated with the consumption of the NDI during the historical period of safe use.

Information contained in any such system or database is relevant to the safety of the NDI. At the same time, many herbs and other botanicals have not been subject to such monitoring in the countries where they have been historically used. The Agency should not, therefore, establish an explicit or implicit requirement, by regulation or by procedure, that a history of monitoring is a prerequisite to the establishment of a reasonable expectation of safety based on traditional use.

- g. Reliability of historical safety information if no health monitoring system is in place to detect adverse effects that may be associated with the human consumption of the dietary ingredient.

This information is relevant to the safety of the NDI.

2. Are there additional items that should be included to establish a reasonable expectation of safety based upon history of use?

An NDI notification seeking to establish a reasonable expectation of safety based on history of use should refer, where available, to the use of comparable ingredients in foods or dietary supplements and their history of use.

3. What quality and quantity of data and information are needed to establish a reasonable expectation of safety based upon evidence other than history of use?

It is AHPA's view that data and information necessary to establish a reasonable expectation of safety is that data and information upon which experts qualified by training and experience to safely use such ingredients and to evaluate the safety of such ingredients for ingestion would agree is adequate. The NDI notification itself must reach this conclusion and it is up to the NDI notifier to provide the information to support that conclusion in its filing.

In addition, AHPA has provided in its comments to which this document is appended some specific suggestions as to the kinds of information that can be used to form a basis to conclude that herbs or other botanical NDIs in specifically described categories are reasonable expected to be safe. See AHPA's comments on pages 36-38.

4. In considering the data and information necessary to establish reasonable expectation of safety, how would the following differences in the use of the NDI in the dietary supplement from historical use affect safety determinations?

As an overview to the below question, AHPA repeats here its view that data and information necessary to establish a reasonable expectation of safety, including the differences in use of an NDI from historical use, is that data and information upon

which experts qualified by training and experience to safely use such ingredients and to evaluate the safety of such ingredients for ingestion would agree is adequate.

- a. Significantly higher serving level (e.g., twice the serving level historically used).
There are instances in which a two-fold increase in dose of historical levels may be a cause to reevaluate safety. At the same time, using two time the norm of many botanical ingredients does not create a general expectation of increased risk for the population in general (e.g., if one were to consume 500 mg of black pepper one day rather than the average daily use of 250 mg).

With respect to botanical NDIs, it must also be noted that the “serving level” is often expressed as a range rather than as an exact and specific quantity. The relevant question may therefore be related to a level that is significantly above the historical range.

With respect to botanical NDIs, a significant increase in dose over the historically used dosage range may create a need for the safety of the higher dose to be reviewed by an expert qualified to safely use or evaluate the safety of the botanical. Such expert may or may not determine that additional and original scientific studies be undertaken to evaluate safety of the NDI at the higher dose.

- b. Longer duration of consumption than historically used (e.g., instead of recommending that a consumer drink an herbal tea for a few days or occasionally, the label of the dietary supplement containing the NDI label suggests or recommends continuous daily use for improved digestive function).
There are instances in which the described increase in duration of use may be a cause to reevaluate safety. At the same time, such increased use does not necessarily create a general expectation of increased risk for the population in general (e.g., if one were to consume peppermint tea every day for 50 years, rather than the former practice of only using it occasionally).

With respect to botanical NDIs, a significant increase in duration of use over the historically duration of use may create a need for the safety of the longer use to be reviewed by an expert qualified to safely use or evaluate the safety of the botanical. Such expert may or may not determine that additional and original scientific studies be undertaken to evaluate safety of the NDI at the longer use.

- c. Different route of administration (e.g., the dietary ingredient was historically administered by poultice or injection, whereas the dietary supplement containing the dietary ingredient is ingested).
It seems unlikely that information from the described routs of historical administration would be relevant to evaluating the safety of an oral dose products, and an expert qualified to safely use or evaluate the safety of the ingredient is likely to determine that additional information and/or original scientific studies be undertaken to evaluate safety of an NDI for which there is no history of oral use.

- d. Change from historical use that might increase potential toxic effects (e.g., an NDI that will be consumed as ground root in capsules when the historical use was a tea made from the roots).

There are instances in which the described changes in historical use may be a cause to reevaluate safety. At the same time, such changes do not necessarily create a general expectation of increased risk for the population in general, unless the chemical characteristics of the actual consumed product differ significantly from those of the traditionally consumed product.

With respect to botanical NDIs, the described change from historical use from the historical use may create a need for the safety of the new use to be reviewed by an expert qualified to safely use or evaluate the safety of the botanical. Such expert may or may not determine that additional and original scientific studies be undertaken to evaluate safety of the NDI under the new use.

- e. Change in consumer target group (e.g., from general population to young children, pregnant women, lactating women).

AHPA believes that new information may be needed to address the safety of an ingredient that has historically been proscribed for any specific subpopulation and that will be offered for the general population. AHPA does not believe, however, that an ingredient that has been historically been used by the general population without any such prohibition for a subpopulation, and that will now be marketed to a subpopulation who has historically used the product, as a member of the general population, will generally need new and original research to evaluate its safety.

6. When notifications do not provide any information concerning recommendations for length of product usage, should FDA assume chronic use (i.e., daily) and evaluate safety on that basis?

AHPA believes the described assumption to be reasonable.

7. What types of studies, if any, should be included in order to establish a reasonable expectation of safety when the proposed daily serving amount is comparable to or less than the safe historical daily serving amount? What if the proposed daily serving amount is greater than the safe historical daily serving amount? Please consider the following types of studies:

AHPA repeats here that it has addressed this issue, insofar as it applies to botanical NDIs, in its comments to which this document is appended, and specifically on pages 36-38 of those comments which provides some specific suggestions as to the kinds of information that can be used to form a basis to conclude that herbs or other botanical NDIs in specifically described categories are reasonable expected to be safe. AHPA expressed there it's view that new scientific studies are not generally needed to establish a reasonable expectation of safety for an NDI that has an established history of use for human consumption and for which there are no known

safety concerns, so long as such NDI is prepared in a manner that is the same or similar to the processes that have been historically used for those ingredients; that new scientific studies are only needed if deemed necessary by qualified experts for an NDI that is the same or similar to ingredients that have an established use for human consumption, and for which either (1) there is a known safety concern, or (2) the NDI is prepared in a manner that is NOT the same or similar to the processes that have been historically used for those ingredients; and that new scientific studies will establish a reasonable expectation of safety for NDIs with no history of human consumption.

As an overview to this question, including the question regarding a greater serving size or dose, AHPA repeats here its view that data and information necessary to establish a reasonable expectation of safety, including the differences in use of an NDI from historical use, is that data and information upon which experts qualified by training and experience to safely use such ingredients and to evaluate the safety of such ingredients for ingestion would agree is adequate.

8. How would the evaluation of such studies (previously listed) to establish reasonable expectations of safety, differ under varying duration and frequency of use scenarios such as the following:

- a. The labeling of the dietary supplement containing an NDI recommends or suggests daily chronic use, and the documented historical duration and frequency of use support safe daily chronic use.

AHPA is concerned that this question implies that studies, including studies of genetic toxicity; teratology studies; human tolerance studies; etc, are needed for an NDI where “documented historical duration and frequency of use support safe chronic use.” AHPA disagrees that such studies are needed to establish a reasonable expectation of safety.

- b. The labeling of the dietary supplement containing an NDI recommends or suggests intermittent use, and the documented historical duration and frequency of use support safe intermittent use.

AHPA repeats here its concern expressed immediately above.

- c. The labeling of the dietary supplement containing an NDI recommends or suggests intermittent use, and the documented historical duration and frequency of use support safe daily chronic use.

AHPA repeats here its concern expressed immediately above.

9. What are appropriate and authoritative references for notifiers to consider when developing protocols for collecting safety data in support of NDI notifications?

All credible references should be considered, including, for botanical NDIs, references that document historical use as foods or as drugs (e.g., pharmacopoeia, materias medica, various other compendia published by authoritative entities), as

well as primary published literature and secondary references that have established credibility, for example, by involvement by qualified herbal experts.

10. What considerations should apply to FDA's evaluation of the safety of a dietary supplement containing an NDI with respect to the following special populations?

The views and expertise of qualified experts should be considered in evaluating safety for each of the described populations.

AHPA regrets that sufficient time was not available to provide answers to the questions in sections E and F. AHPA notes, however, that several of the issues identified in these questions were addressed in AHPA's comments to which this document is appended.

Appendix 2
AHPA - Docket No. 2004N-0454
February 1, 2005

Some species of animals marketed in the United States before October 15, 1994 (2 pages)

Species	Pinyin Name	Other Names
<i>Agkistrodon acutus</i>	<i>Qi She</i>	Agkistrodon; Long-noded Pit Viper
<i>Arca subcrenata</i> ; <i>Arca granosa</i> ; <i>Arca inflata</i>	<i>Wa Leng Zi</i>	Arca; Clam Shell; Concha Arcae
<i>Aspongopus chinensis</i>	<i>Jiu Xiang Chong</i>	Aspongopus
<i>Bombyx mori</i>	<i>Jiang Can</i>	Bombyx Batryticatus; Silkworm
<i>Bos taurus</i>	<i>Niu Huang</i>	Bezoar; Calculus Bovis
<i>Bubalus bubalis</i>	<i>Shui Niu Jiao</i>	Cornu Bubali; Waterbuffalo horn
<i>Bugarus multicinctus</i>	<i>Bai Hua She</i>	Bungarus Parvus; Coin-like white-banded Snake
<i>Buthus martensi</i>	<i>Quan Xie</i>	Buthus; Scorpio; Scorpion
<i>Cervus elaphus</i> ; <i>C. nippon</i>	<i>Lu Jiao</i> ; <i>Lu Jiao Shuang</i>	Cornu Cervi; Cornu Cervi Degelatinatum; Cornu Cervi Fragnenta; Deer antler; Deer antler fragments
<i>Cervus elaphus</i> ; <i>C. nippon</i>	<i>Lu Jiao Jiao</i>	Deer antler gelatin; Gelatinum Cornu Cervi
<i>Cervus elaphus</i> ; <i>C. nippon</i>	<i>Lu Rong</i>	Deer antler velvet; Cornu Cervi Pantotrichum; Cornu Cervi Parvum
<i>Chinemys reevesii</i>	<i>Gui Ban</i>	Plastrum Testudinis; Tortoise shell
<i>Chinemys reevesii</i>	<i>Gui Ban Jiao</i>	Colla Plastris Testudinis; Tortoise shell glue
<i>Cordyceps sinensis</i>	<i>Chaun Hua</i> ; <i>Dong Chong</i> <i>Cao</i> ; <i>Dong Chong Jing</i> (extract)	Cordyceps
<i>Cryptotympana atrata</i> ; <i>C. pustulata</i>	<i>Chan Tui</i>	Cicada Slough (or Moulting); Periostracum Cicadae
<i>Elaphe taeniuru</i> ; <i>E. carinata</i> ; <i>Zoacys dhumnades</i>	<i>She Tui</i>	Periostracum Serpentis; Snake skin slough
<i>Equus asinus</i>	<i>E Jiao</i>	Colla Corii Asini; Donkey-hide Glue; Gelatina Asini
<i>Eretmochelys imbricata</i>	<i>Dai Mao</i>	Carapax Eretmochelydis; Hawksbill turtle shell
<i>Eupolyphaga sinensis</i> ; <i>Steleophaga plancyi</i>	<i>Di Bie Chong</i> ; <i>Tu Bie</i> <i>Chong</i>	Chinese Ground Beetle; Eupolyphaga; Steleophaga
<i>Gallus gallus</i>	<i>Ji Nei Jin</i>	Chicken gizzard lining; Corium Stomachicum Galli; Endothelium Corneum Gigeriae Galli
<i>Gekko gekko</i>	<i>Ge Jie</i> ; <i>Jia Jie</i>	Gecko; horned toad
<i>Haliotidis diversicolor</i> ; <i>H. discus hannai</i> ; <i>H. ovina</i> ; <i>H. ruber</i> ; <i>H. asinina</i> ; <i>H. laevigata</i>	<i>Shi Jue Ming</i>	Abalone shell; Concha Haliotidis; Haliotis; Sea-ear shell
<i>Hippocampus kelloggi</i> ; <i>H. histrix</i> ; <i>H. kuda</i> ; <i>H. trimaculatus</i> ; <i>H. japonicus</i>	<i>Hai Ma</i>	Hippocampus; Sea horse
<i>Hirudo pigra</i> ; <i>Hirudo nipponica</i> ; <i>Whitmania acranulata</i>	<i>Shui Zhi</i>	Hirudo; Leech
<i>Hyriopsis cumingii</i> ; <i>Cristaria plicate</i> ; <i>Peteria martensii</i>	<i>Zhen Zhu Mu</i>	Concha Margaritafera; Mother of pearl; Nacre
<i>Manis pentadactyla</i>	<i>Chuan Shan Jia</i>	Anteater
<i>Meretrix meretrix</i> ; <i>Cyclina sinensis</i>	<i>Ge Qiao</i>	Clam Shell; Concha Meretricis seu Cyclinae
<i>Moschus berezovskii</i> ; <i>M. sifanicus</i> ; <i>M. moschiferus</i>	<i>She Xiang</i>	Moschus; Musk; Secretio Moschus

Appendix 2
AHPA - Docket No. 2004N-0454
February 1, 2005

Some species of animals marketed in the United States before October 15, 1994 (2 pages)

Species	Pinyin Name	Other Names
<i>Mylabris phalerata</i> ; <i>Mylabris cichorii</i>	Ban Mao	Mylabris
<i>Ostrea gigas</i> ; <i>O. talienwhanensis</i> ; <i>O. rivularis</i>	Mu Li	Concha Ostreae; Oyster Shell
<i>Pheretima aspergillum</i> ; <i>Pheretima vulgaris</i> ; <i>Pheretima guillelmi</i> ; <i>Pheretima pectinifera</i>	Di Long	Earthworm; Lumbricus
<i>Polistes olivaceous</i> ; <i>Polistes japonicus</i> ; <i>Parapolybia varia</i>	Lu Feng Fang; Feng Fang	Hornet Nest; Nidus Vespae
<i>Pteria martensii</i> ; <i>Hyriopsis cumingii</i> ; <i>Cristaria plicata</i>	Zhen Zhu	Margarita; Pearl
<i>Rana temporaria chensinensis</i>	Ha Ma You	Frog oviduct; Oviductus Ranae
<i>Saiga tatarica</i>	Ling Yang Jiao	Antelope horn; Cornu Antelopis; Cornu Saigae Tataricae
<i>Scolopendra subspinipes</i>	Wu Gong	Centipede; Scolopendra
<i>Sepiella maindroni de rochebrune</i> ; <i>Sepia esculenta</i>	Hai Piao Xiao	Cuttlebone; Cuttlefish bone; Endochondra Sepia; Os Sepia
<i>Solenognathus hardwickii</i> ; <i>S. biaculeatus</i> ; <i>S. linnaeus</i>	Hai Long	Pipefish; Sea dragon; Syngnathus
<i>Tenodera sinensis</i> ; <i>Statilia maculata</i> ; <i>Hierodula patellifera</i>	Sang Piao Xiao	Mantis egg-case; Oötheca Mantidis
<i>Trionycis sinensis</i> ; <i>Amyda sinensis</i>	Bie Jia	Carapax Trionycis; Turtle Shell
<i>Zaocys dhumnades</i>	Wu Shao She	Black-tail snake; Zaocys
	Long Chi	Dens Draconis; "Dragon Teeth;" Fossilized Bone
	Long Gu	"Dragon Bone;" Fossilized Bone; Os Draconis