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AMERICAN BOTANICAL COUNCIL
HERBALGRAM

December 2, 2011

**VIA ELECTRONIC SUBMISSION**

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues**
**Docket No. FDA-2011-D-0376**
**[76 *Federal Register* 39111; July 5, 2011]**

Dear Sir or Madam:

The American Botanical Council (ABC) is sending the following comments in response to the FDA's July 5, 2012 release of the Draft Guidance on New Dietary Ingredients.

ABC is an independent nonprofit research and education organization, tax exempt under section 501(c)(3) of the IRS code. ABC was incorporated in Austin, Texas, in 1988 and its primary mission is to educate the public on the scientific and clinical literature supporting the responsible use of herbs, teas, medicinal plants, phytomedicines, essential oils, and other beneficial plants.

The membership of ABC is comprised of the following classes of stakeholders: Researchers in many fields related to the study of medicinal and aromatic plants (e.g., botany and ethnobotany, pharmacognosy, pharmacology and ethnopharmacology, nutrition and ethnonutrition, natural products chemistry, horticulture, and related plant and biomedical sciences); health practitioners (both conventional and nonconventional, including physicians, pharmacists, nurses, dietitians, naturopaths, acupuncturists, herbalists, and others); members of the herb and dietary supplement industries (growers, importers, processors, manufacturers, distributors, marketers, brokers, and others); universities; libraries; hospitals; poison control centers; government agencies; consumers; and others. ABC has members in about 80 countries, with the majority residing in the United States.

Throughout its 23-year history, ABC has always supported a rational, science-based role for the use of dietary herbs and medicinal plants and other plant-related substances in self-care and health care. During this time ABC has published thousands of articles, reviews, and summaries of the scientific and clinical literature, as well as leading reference books for health care professionals and researchers.

As a part of its overall educational mission and its commitment to the safe, responsible use of herbs and botanicals, ABC is actively engaged in producing publications and programs that help educate members of the dietary supplement

and related industries with information that can be used to help ensure the identity and quality of botanical raw materials used in dietary supplements.

Consistent with ABC's educational mission and its long history of educational activities, ABC is supportive of FDA's primary role in ensuring the quality and safety of America's food supply, including the agency's responsibility for the quality and safety of dietary supplements. ABC is aware that the FDA is responsible for the regulation of about 25% of consumer products sold in the United States and that the agency is also facing the prospects of increasingly tight budgetary constraints.

ABC is concerned about a number of areas that were discussed in the FDA's draft NDI guidance document and herewith provides its concerns and comments on the FDA's draft Guidance for Industry on New Dietary Ingredients (NDIs). These comments are consistent with ABC's previous interest in the subject of NDIs.

**1. ABC's Prior Publications Related to NDIs**

ABC has had a keen interest in the issue of NDIs. In 2004, ABC published an extensive article on this subject in its quarterly peer-reviewed journal *HerbalGram* (issue #63). [1] The purpose for such publication was ABC's attempt to inform ABC members, other readers of *HerbalGram*, and, by extension, members of the herb and dietary supplement industry, regarding the very existence of Section 8 of The Dietary Supplement Health and Education Act of 1994 (DSHEA) and its importance and need for understanding among members of industry, both domestic and foreign (i.e., to the extent that a foreign producer of herbal products had interest in exporting to the United States and any of its products might be deemed NDIs). The authors of this article demonstrate that about 70 percent of the notifications for botanical NDIs submitted to the FDA at that time were not accepted by the FDA. This was usually due to the lack of adequate safety data being filed or other problems with the submissions—much of which was believed by some to be related to the lack of any formal guidance from the FDA at that time.

In 2004, ABC also distributed in its HerbClip service a summary and review of another extensive article written on NDIs at that time. [2] This seminal article, written by officials of the American Herbal Products Association, provided a detailed and comprehensive review of the NDI process in the first 10 years after the passage of DSHEA.

In addition, another area of ABC interest in and activity regarding NDIs pertains to solvents used in the production of botanical extracts. Since the FDA has proposed that the use of solvents other than water and/or ethanol may trigger the need for an NDI notification, the issue of solvents used in dietary ingredients has become increasingly important and of heightened concern to various members of the dietary supplement industry employing botanical extracts in their ingredients and products. ABC is aware that solvents other than water and ethanol have been used to produce botanical extracts since prior to October 15, 1994. Also, ABC has been active in educating industry and others regarding the presence of industrial solvents in dietary ingredients. ABC is currently in the process of publishing a White Paper on Solvents that will be made available online and in a published book format. (More on this publication below.)

**2. ABC's Previous Comments on FDA's Regulation of NDIs**

In 2005, ABC filed public comments with the FDA on the issue of the agency's regulation of NDIs. [3] In those comments, ABC noted that the so-called "grandfathered" or "Old Dietary Ingredients" (ODIs, a term not mentioned in DSHEA, but which is used commonly in the supplement industry and beyond) had been compiled by various trade associations. Even though these lists were used as reference points by industry and were not considered "authoritative" by the FDA (i.e., each ingredient on the lists had not been adequately verified to have been sold prior to October 15, 1994, with formal evidence, e.g., an invoice, bill of lading, catalog listing, etc.), ABC's comments suggested that the FDA should officially recognize the lists developed by the American Herbal Products Association (AHPA), Council for Responsible Nutrition (CRN), the National Nutritional Foods Association (now the Natural Products Association, NPA), and the Utah Natural Products Alliance (now known as the United Natural Products Alliance, UNPA), as positive lists of ODIs. ABC emphasized that since ten years had lapsed since the passage of DSHEA, ABC did not believe that it should be necessary to create a new "authoritative" list in which all ingredients are confirmed as ODIs with such confirmatory evidence as the FDA had previously stated the agency would require, a view retained by the FDA in the draft guidance, particularly since some or all of the records needed for such confirmation are probably no longer extant.

ABC also noted that the FDA recently stated in correspondence that an ingredient must have been "lawfully marketed" prior to October 15, 1994, for it to qualify as an ODI. In the comments filed with the FDA, ABC objected to this stipulation, noting that the term "lawfully" does not appear in DSHEA. Under DSHEA, "any dietary ingredient which was marketed in the United States before October 15, 1994," is not a "new dietary ingredient." Thus, the FDA's interpretation is not consistent with express statutory language of DSHEA and is inconsistent with the intent of Congress. ABC noted that in the pre-DSHEA regulatory environment there was considerable confusion about the legal and regulatory status of many botanicals and the FDA tried unsuccessfully to remove some herbs from the market by declaring them "unapproved food additives." The FDA was stopped from doing so by two highly publicized federal court decisions, and these cases, among other issues, became a primary impetus supporting the passage of DSHEA.

**3. Pre-market Approval Process and Intent of Congress**

ABC is well aware of the legal and regulatory issues that characterized the state of the dietary supplement industry prior to the passage of DSHEA in 1994 (although the term "dietary supplement" was not commonly used at that time, the operative term being "food supplement"). One of the biggest areas of contention between members of the industry and the FDA is related to the issue of whether supplements should or should not be regulated as food additives. The FDA obviously took the position that many ingredients in supplement-type products were in fact unapproved food additives. In the high-profile Traco Labs Case of 1991, the Court ruled that black currant seed oil (*Ribes nigrum*) was not a food additive simply because it was encapsulated in a soft-gelatin capsule prior to marketing. [4] DSHEA, passed a few years after the Traco Labs case, specifically exempts "dietary ingredients" intended for use in dietary supplements from the food additive provision of the law. Thus, dietary ingredients are not subject to pre-market approval requirements by the FDA.

It would appear, based on FDA's Draft Guidance for Industry on NDIs, that the Agency is intending to use this guidance as a means to create a non-statutory pre-market approval system vehicle for any dietary ingredient that the agency deems is an NDI, which, based on the guidance, would possibly include a wide variety of dietary supplement ingredients currently sold in the marketplace with no evidence of safety problems, as well as many yet to be introduced, which, by definition, might qualify as NDIs.

**4. Dietary Ingredient vs. Dietary Supplement**

It has been ABC's understanding since the passage of DSHEA that Section 8 of DSHEA refers to the safety of *ingredients* used in dietary supplements, with the presumption that adequate monitoring of ingredients newly introduced into the United States after passage of DSHEA would require documentation of the safety of the new dietary ingredient as the primary way to help ensure the safety of a finished dietary supplement product containing said ingredient(s). DSHEA provides added authority for the FDA to ensure the safety of finished dietary supplements by establishing a distinct dietary supplement safety standard at 21 USC § 402 (f) (in addition to the general food adulteration standard at § 402 (a)). Section 402(f)(1)(C) also provides the FDA (the Secretary of Health and Human Services) with authority to immediately remove from the marketplace any dietary supplement or dietary ingredient that poses an imminent hazard to public health or safety.

The FDA's apparent intent is to interpret the NDI provision of the law to require a separate NDI notification for every dietary supplement that contains a new dietary ingredient. That the presence of an NDI in a dietary supplement would require an NDI notification *for that particular supplement* appears to fall outside of the scope and intent of Section 8. Per the language of Sections IV(C)(1) and IV(C)(2) of the Draft Guidance, it appears to ABC that the FDA is possibly proposing a regulatory situation that may be tantamount to the creation of new legal category—a *New Dietary Supplement.* ABC is not aware of any statutory language or precedent for the creation of such a new legal or regulatory category.

Further, it appears that the FDA is proposing that a *combination* of a new dietary ingredient with different "old" dietary ingredients in a supplement might trigger the need for an NDI notification. This would appear to presume a potential safety concern based on the combination of ingredients whose safety is already either determined or otherwise accepted (e.g., an already notified NDI with an ODI). In ABC's view, such a requirement might be considered tantamount to requiring a restaurateur to have to pretest the safety of a new food ingredient to be added to others in a soup or a salad, based solely on the fact that they are being combined. ABC does not see the logic of this argument and finds the FDA's position untenable. We believe that the agency should appropriately clarify, rewrite, and/or perhaps even withdraw this

proposed provision from any future guidance on NDIs.

**5. Acknowledging an Authoritative List of Old Dietary Ingredients**

As noted above, although the term "Old Dietary Ingredient" (ODI) is not mentioned in DSHEA, it has become a term of art in the herbal and dietary supplement industry. As the FDA is aware, all four leading trade associations have published a list of ODIs, with a compiled list published in 1999 by the UNPA. [5]

ABC believes that it would be in the best interests of the dietary supplement industry if there were an authoritative list of such ODIs made available to producers of dietary ingredients and those who manufacture and market such ingredients in finished dietary supplements. However, ABC also acknowledges that producers, manufacturers, sellers, and marketers of such ODIs are not required by law to affirmatively prove to FDA before marketing that an ingredient is in fact an ODI. Nevertheless, ABC believes that the existence of such a list would provide considerable guidance to industry and reduce ambiguity and confusion in the matter of determining which items might require NDI notifications.

**5.1 ABC Proposes FDA's Acceptance of an Official List of ODIs.**

ABC believes that a significant portion of the problem associated with NDI submissions is confusion as to what constitutes an ODI versus an NDI. (Again, ABC is aware that "Old Dietary Ingredient" is not a term employed in DSHEA, but has become a widely used term within the dietary supplement community in the United States to refer to dietary ingredients sold in the United States prior to October 15, 1994.) Despite the fact that the FDA has previously dismissed attempts by responsible parties in the dietary supplement industry to accept an aggregated list of proposed ODIs, based on the FDA's assertion that the list did not include plant parts for botanical items listed as ODIs, and that the proposed ODIs were not adequately documented as having been sold prior to passage of DSHEA on October 15, 1994 (e.g., with proof in the form of magazine advertising, catalogs, invoices, bills of lading, etc.), ABC believes nevertheless that it is in the general public interest for the FDA to accept the aggregated list of ODIs as compiled by UNPA in 1999, cited above. [5]

The list compiled by UNPA could be used as a baseline list that is reviewed by a special expert advisory committee of representatives from the various herb and dietary supplement trade associations (AHPA, CHPA, CRN, NPA, and UNPA) as well as independent nonprofit research, education, and/or standard-setting organizations with expertise in the area of dietary supplements, particularly those of botanical origin (e.g., ABC, the American Herbal Pharmacopoeia, the United States Pharmacopiea, et al.) to determine, in the case of botanicals, which botanical parts would be acceptable for an officially recognized list of ODIs, i.e., a list of officially recognized "grandfathered" ODIs. This expert committee could review the issue of "chemically altered" to determine if there is adequate data available to support the classification of an herbal extract made with a solvent other than water and/or ethanol, i.e., whether there are pre-DSHEA data supporting the use of a specific solvents in the production of a botanical extract or other dietary ingredient. (Please see Solvents section below.)

ABC's proposal of an expert advisory panel to establish a list of mutually recognized ODIs is made with the understanding that members of industry do not bear any legal burden of proof to document the pre-DSHEA status of an ODI, nor should any attempt to establish such an expert panel be misinterpreted regarding this issue of burden of proof. Nevertheless, ABC believes that the establishment of such an expert advisory panel on ODIs can be of benefit to both the industry as well as to regulatory agencies by providing more clarity in this matter. In addition, any such proposed list of ODIs should be considered dynamic, not static, subject to revision as new data confirming the sale of an ingredient that in the committee's view should qualify as an ODI.

**6. Solvents used in the preparation of dietary ingredients**

ABC has long been interested in the issue of solvents used in the production of botanical extracts for use as dietary ingredients. In 2010, ABC began the compilation, production and editing of an extensive white paper on such solvents. The white paper provides extensive coverage of over 23 solvents used for making botanical extracts used in dietary supplements. Tentatively titled *Solvents Used in the Manufacture of Botanical Extracts, Food Flavors, and Natural Food Ingredients: An Educational Guide for Ingredient Extractors; Manufacturers of Conventional Foods, Dietary*

*Supplements, Botanical Drugs, Natural Cosmetics, and Other Natural Products; and Analytical Laboratories*, this publication is scheduled for release in 2012 as a PDF downloadable from the ABC website and as a printed reference book.

While ABC acknowledges that different solvents can create variable profiles in extracted constituents from plant materials—some resulting chemical profiles being relatively nuanced while others being potentially dramatic—ABC believes that the emphasis for the matter of determining whether an NDI notification should be made should focus on the safety (which implicates chemical profile) of the resulting extract, not the process by which it is made nor the solvent(s) that is/are used in the extraction process. Consequently, if the use of a non-aqueous, non-ethanolic solvent in an extract produces a reasonably similar chemical profile to an "old" water or ethanolic plant extract, it is possible that an NDI notification might be obviated, as the resulting extract might not be "chemically altered." In this case, the NDI provision of the law would not be triggered. ABC does believe, however, that the responsibility for adequately determining the potential degree of chemical alteration should remain with the producer/seller of the extract, and, if there is any reasonable doubt about the potential safety of the ingredient, an NDI notification would be warranted.

Further, ABC notes that the use of various solvents other than water and ethanol to produce botanical extracts most likely precedes the passage of DSHEA on October 15, 1994 and are thus probably ODIs. Various solvents have been documented in the production of foods and food flavorings well before DSHEA. However, ABC realizes that there is limited access to reliable documentation of the use of various non-aqueous and non-ethanolic solvents in the extraction of specific botanical items sold today in the U.S. market as dietary ingredients. However, insofar as a company marketing, or intending to market, a botanical extract in which a specific solvent has been used can adequately document that such solvent has been employed in the production of an extract of a specific botanical item, then such documentation should be adequate basis on which to obviate the requirement to submit an NDI notification.

**7. So-called "Synthetic Botanicals"**

In the draft Guidance document, the FDA asks the question, "Is a Synthetic Copy of a Constituent or Extract an Herb of Other Botanical a Dietary Ingredient?" [IV.D.2]

The FDA then replies as follows:

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

While ABC, in principle, prefers that all isolated constitutes marketed as dietary ingredients to be used in dietary supplements be as natural as is appropriately reasonable, ABC recognizes that in some cases various forms of industrial processes might be warranted to produce compounds that are chemically identical to natural compounds and that have the same level of safety as the natural compound. ABC understands that the issue in such cases is where the ingredient is reasonably expected to be safe under appropriate use.

In the draft guidance, the FDA mentions the issue of synthetic materials sold as dietary ingredients. While the use of synthetically produced dietary ingredients is more prevalent in the non-botanical domain of the dietary supplement market than it is in the botanical arena, there are some examples of botanically related synthesized dietary ingredients about which ABC has interest.

In principle, ABC believes that botanical extracts, fractions of botanical extracts, and/or isolated compounds from plant parts used for the dietary supplement industry should be naturally derived, i.e., derived directly from plants themselves. However, ABC also recognizes that there may be instances where production of such nature-identical materials through natural means other than direct extraction might be useful and/or otherwise appropriate for a variety of processing, quality control, economic, and/or environmental sustainability reasons. For example, the production of the amino acid L-theanine, found in green tea (*Camellia sinensis*), is a case in point. L-theanine can be produced by a fermentation process that results in a compound identical to the L-theanine found in green tea. Again, the focus should be about the safety of the ingredient, with less emphasis given to the process by which it is produced.

**8. Fungi as Dietary Ingredients**

ABC is has received inquiries from members of the supplement community expressing concern that the FDA may not consider fungal materials to be dietary ingredients. Technically, as the FDA is no doubt aware, fungi are not plants, nor are they related to plants; their genetic composition are more akin to animals. However, some mycophiles have expressed concern that since fungi are not specifically named in the statutory definition of dietary ingredient as provided in DSHEA, that the FDA might consider all fungi sold as dietary ingredients to be NDIs, although it is highly likely that the FDA would consider mushroom fruiting bodies and possibly even mycelia to qualify as "a dietary substance for use by man to supplement the diet by increasing the total dietary intake" – section "(E)" under the definition of dietary supplement as published in DSHEA. [6]

ABC believes that fungal-derived raw materials and their extracts are dietary ingredients—many of them ODIs—and should be allowed to be sold in dietary supplement products, even though they are not specifically included in the above-noted definition of dietary ingredients and even though they are not botanicals. Therefore, ABC is gratified that the FDA saw fit to include fungi in at least one of its examples in a question and answer in the draft guidance, which included a reference to yeast (*Saccharomyces cerevisiae*)—yeasts are classed as fungi—as an illustration in the answer to description of production methods [VI.A.13]

**9. Probiotics**

ABC is aware of concern about the proper treatment of priobiotics (beneficial bacteria) but since ABC is focused primarily on botanicals, and since probiotics are not technically botanicals, ABC will not comment extensively on this issue at this time. ABC does, however, generally take the view that probiotics are "dietary substances" under § 321 (ff)(1)(E).

**10. Conclusion**

In conclusion, ABC is concerned that some of the provisions found in the FDA's Draft Guidance Document on New Dietary Ingredients exceed the intent of Congress in passing DSHEA with respect to pre-market approval of dietary supplements and the relatively onerous extension of Section 8 provisions to include dietary supplement notifications. In addition, ABC proposes that the FDA accept the previously produced list of ODIs as officially sanctioned, and recognize recommendations from an expert advisory panel of appropriately qualified experts with respect to clarifying ambiguities in the current list. ABC also proposes that certain botanical extracts made with solvents other than water and/or ethanol be recognized for their appropriate ODI status if such extracts can document their pre-DSHEA status.

ABC is most willing to work with representatives of the FDA as well as members of the dietary supplement industry, and other interested parties to help affect a reasonable resolution of the matters ABC has discussed above, as well as other issues that may be subject to consideration, for the benefit of dietary supplement consumers.

Respectfully submitted,

Mark Blumenthal
Founder & Executive Director
American Botanical Council
Editor, *HerbalGram* & HerbClip

**References and Notes**

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2. Milot B. Review of the Premarketed Notification Procedures for New Dietary Ingredients. American Botanical Council HerbClip #100141-290; Oct. 14, 2005. Review of McGuffin M, Young A. Premarket notifications of new dietary ingredients—a ten-year review. *Food & Drug Law Journal*. 2004;59:229-244.

3. American Botanical Council. Comments to Food and Drug Administration on Premarket Notifications for New Dietary Ingredients [Docket No. 2004N-0454]. Austin, TX: American Botanical Council, February 1, 2005. Available at: http://cms.herbalgram.org/herbalgram/issue66/article2816.html.

4. U.S. v Two Plastic Drums, 761 F. Supp. 70 (1991)

5. Utah Natural Products Assn. Old Dietary Ingredient List. Salt Lake City, UT: 1999.

6. The definition of dietary supplement in DSHEA: A dietary supplement is “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)…” “any other dietary substance”.