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BEFORE

THE UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON

FDA's Request for Comments on Development of a List of Pre-Dietary Supplement Health and Education Act Dietary Ingredients

December 4, 2017

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Prefatory remarks

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA members include domestic and foreign companies doing business as growers, processors, manufacturers and marketers of herbs and herbal products, as well as non-herbal products, including many that are marketed as dietary supplements. AHPA serves its members by promoting the responsible commerce of herbs and herbal products.

On September 6, 2017, the Food and Drug Administration (FDA or the Agency) published a Federal Register notice (the September 6 Notice[1]) to announce a public meeting and to request comments on issues related to FDA's future development of a list of dietary ingredients marketed in the United States prior to October 15, 1994, when the Dietary Supplement Health and Education Act (DSHEA) became law (referred to hereinafter as pre-DSHEA dietary ingredients, old dietary ingredients, or ODIs).

Many AHPA members manufacture and market dietary supplements that contain ODIs. These companies and their products and ingredients would potentially be affected by any list of ODIs developed by FDA and positioned as having any kind of official or authoritative status. These comments are therefore submitted on behalf of AHPA and its members to address issues related to FDA's possible development of a list of pre-DSHEA ingredients.

Of relevance to these comments, AHPA notes that FDA issued a Federal Register notice on August 12, 2016 that announced availability of a revised draft guidance for industry titled, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (the 2016 revised draft NDI guidance)[2]. The Agency included in that 2016 draft numerous views, interpretations and opinions relevant to the issue of how the ODI status of a dietary ingredient can be documented.

[1] 82 FR 42098.

[2] This draft was revised to replace draft guidance initially issued by FDA in July 2011 (Guidance for Industry. Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. Draft Guidance. July 2011).

AHPA considers any effort by FDA to create an authoritative list of ODIs or pre-DSHEA ingredients that is based on many of the views, interpretations and opinions the Agency communicated in the 2016 revised draft NDI guidance as unlikely to be successful in actually compiling a list of these ingredients. AHPA identifies in the present comments specific concerns on certain of FDA's previously communicated positions relevant to this matter. AHPA and its members will need to see a significant shift in the Agency's thinking on these matters to be able to embrace the current effort to create such a list.

Absence of a requirement to "document" pre-DSHEA status of ODIs should be clarified

FDA has been consistent in discussing documentation of the ODI status of dietary ingredients as "necessary"[3] or as "need[ed]"[4] or "recommend[ed]"[5] to show that a dietary ingredient was marketed before October 15, 1994. But companies that sell ODIs are not required to obtain or provide any such documentation. They must register their facilities, comply with cGMP rules, label their products in accordance with all relevant regulations, and make sure to meet their requirements under the law if any adverse events are reported to be associated with their products. But they do not need to obtain old records to show that, for example, valerian root or saw palmetto fruit is a "dietary ingredient which was marketed in the United States before October 15, 1994".[6]

AHPA has previously requested that FDA communicate this fact clearly, by including in any guidance on new dietary ingredient (NDI) notifications a statement to clarify that the Food, Drug and Cosmetic Act (FDCA) does not require marketers of pre-DSHEA dietary ingredients to have documentation that these ingredients were marketed in the U.S. before October 15, 1994. AHPA restates this request here, in the context of any eventual authoritative pre-DSHEA dietary ingredient list, and so requests that any such list clearly communicate with a footnote or disclaimer or other statement that there is no

[3] 82 FR 42098 at 42099.

[4] The 2011 draft NDI guidance.

[5] The 2016 revised draft NDI guidance.

[6] 21 USC 350b(d).

requirement for a dietary supplement company to document that pre-DSHEA ingredients used in their dietary supplements are old dietary ingredients.

AHPA notes however that supplement companies that market ODIs are responsible for the safety of their products. The NDI provision of the law only establishes that old dietary ingredients are old; it does not establish that every old dietary ingredient is safe in any quantity for any person. Whether a supplement is made with pre-DSHEA ingredients or new dietary ingredients it is held to the same standard under the adulteration clause of the FDCA and so is adulterated if it "presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use."[7] Marketers of both ODI-based and NDI-based dietary supplements thus have an affirmative responsibility to meet this unreasonable risk threshold.

The types of records that document pre-DSHEA status should be broadly described

In the September 6 Notice FDA described topics that would be discussed at the public meeting announced in that notice, including a discussion to identify the sorts of records that can be used to show that a dietary ingredient is a pre-DSHEA ingredient.

With regard to this topic, AHPA notes that in introducing the idea of an authoritative list of pre-DSHEA ingredients, or ODIs, FDA stated in the 2016 revised NDI guidance that, since the Agency does not generally have access to marketing records for dietary ingredients and dietary supplements, "the documentation of pre-DSHEA marketing would have to be supplied by industry." FDA identified in that 2016 revised draft NDI guidance several examples of such records as including, "…written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994," and provided as examples "…sales records, bills of lading, sales contracts, manufacturing records, commercial invoices, magazine advertisements, mail order catalogs, or sales brochures."

[7] 21 U.S.C. 342(f)(1)(A).

AHPA believes that in identifying these documents as the types of documentation that FDA recommends to show that an ingredient was marketed prior to October 15, 1994 the Agency has identified records that most likely no longer exist or that only marginally exist. FDA could, of course, glean information from any of the above described internal or external records that are, in fact, still accessible, but the Agency should simultaneously recognize that the limited availability of such documents means that those that can still today be "supplied by industry," as FDA has suggested, are unlikely on their own to provide a robust record of the 1994 dietary ingredients marketplace.

On the other hand, some records that have not been lost over time are the various lists submitted by trade associations to FDA in 1996 and 1998 to identify ingredients believed to have been in the U.S. market when DSHEA was passed in 1994.[8] But FDA has stated that it does not accept these records as authoritative, and has cited as rationale for dismissing them out of hand specific problems with each of these;[9] AHPA notes that the imperfections with these lists that FDA now perceives were first brought to the submitting organizations' attention many years after they were presented to FDA, such that contemporary corrections were not solicited and so could not have been provided.

AHPA completely disagrees that these records should be dismissed out of hand, and opposes the wholesale dismissal of these lists as relevant records of ODIs. Rather, FDA should accept these as documentation of pre-DSHEA marketing of the many ingredients included in any of these lists for which no questions as to their use in supplements has arisen in the interim.

In discussing these industry-supplied lists FDA has also stated its unwillingness to consider these as valid records of pre-DSHEA marketing because it is "unable to verify

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

[9] See for example the 2016 revised draft NDI guidance at page 19 in the response presented to Question 11 in Part IV of this draft.

the accuracy of these lists," and because the submitting organizations were truthful in acknowledging that they had not independently verified that the substances on the list were in use before that date.

Again, AHPA encourages FDA to accept the "good" represented by these lists rather than rejecting them for their absence of the "perfect," and so therefore strongly recommends that FDA state its intention to consider exercising its enforcement discretion by recognizing each of the ingredients in these lists as a pre-DSHEA ingredient unless there is some specific reason to determine otherwise on an ingredient-by-ingredient basis.

FDA has also rejected as authoritative AHPA's publications *Herbs of Commerce* 1st edition (1992) and 2nd edition (2000). The former was published before the passage of DSHEA and the introduction to the latter pointedly states that, to the best of AHPA's knowledge at the time, only plants marketed prior to October 15, 1994 were included. Although this introduction also states that AHPA had not expended any effort in independent verification of this assumption, AHPA again believes that FDA should accept this reference as identifying plant species that were very likely to have been marketed in the U.S. when DSHEA was passed into law, and so should state its intention to exercise enforcement discretion to recognize all listed species as pre-DSHEA dietary ingredients.

AHPA acknowledges that there are some plant species included in one or both editions of *Herbs of Commerce* that were lawful dietary ingredients when these references were published but have been removed from commerce under FDA's extensive authority to regulate supplements in the interim. Examples include various species of *Ephedra* that contain ephedrine alkaloids and that became unlawful for use as dietary ingredients in 2004.[10] It would be a simple matter though for FDA to simply exclude these from any eventual authoritative pre-DSHEA list, or to identify these as unallowed through other provisions of the law. Either such approach would be far superior to completely rejecting the usefulness and validity of these documents as accurate records of pre-DSHEA dietary ingredients.

[10] *See* 21 CFR § 119.1.

FDA also noted in the 2016 revised draft NDI guidance that the editions of *Herbs of Commerce* do not identify the plant part and/or extract type for each of the species listed. Rather than simply rejecting these reference as having no relevance, however, FDA should consider any listing in these texts to represent the commonly used plant part – so chamomile flower but not chamomile root; and ginkgo leaf and seed but not ginkgo bark.[11] And as previously communicated to FDA, it is AHPA's view that manufacturing a botanical extract with traditional processing and food-grade solvents does not constitute chemical alteration, so that an extract derived from a pre-DSHEA botanical ingredient should also be acknowledged as a pre-DSHEA ingredient, or possibly as an NDI for with notification is not required as "an article used for food in a form in which the food has not been chemically altered."[12]

Affidavits should be acknowledged as legitimate sources of information

Another perfectly legitimate record to establish that a dietary ingredient was marketed in the U.S. prior to October 15, 1994 would be a sworn affidavit attesting to this status. FDA stated in the 2016 revised draft NDI guidance, however, that it would not accept such affidavits "unless supported by contemporaneous written records." But any such absolute requirement to support an affidavit with an actual contemporary record would make an affidavit in and of itself, without a record already described in these comments as unlikely to still exist or to only marginally exist, to be of no value at all in FDA's view. AHPA finds this position to be remarkable, and to be completely contrary to the manner by which proofs are made in the courts of the United States.

The term "marketed in the United States" is not restricted to only supplements

Another detail in need of resolution arises from FDA's narrow interpretation of the meaning of the term "marketed in the United States before October 15, 1994" with

[11] AHPA notes that personnel in FDA's Office of Dietary Supplements Programs have significant expertise in botanical sciences, such that it is likely that information on the commonly used parts of plants listed in these references is readily available within this Office.

[12] 21 U.S.C. § 350b(a)(1).

regard to determining the ODI versus NDI status of a dietary ingredient. FDA stated in the 2016 revised draft NDI guidance its view that this means selling or offering the dietary ingredient for sale solely (1) as or in a dietary supplement, (2) in bulk as a dietary ingredient for use in dietary supplements, or (3) as an ingredient in a blend or formulation of dietary ingredients for use in dietary supplements. AHPA believes, however, that this limited view of what constitutes "marketing" in the U.S. is unnecessarily narrow and is inconsistent with the actual language of DSHEA and with the intent of Congress when this good law was passed. AHPA believes that "marketed in the United States" simply means "sold or offered for sale" by or to any U.S. company, irrespective of the end use in an oral dose product.

With this in mind, AHPA believes there are other documents than those few types the Agency has previously identified as the type that would document an ingredient's status as "marketed in the United States" pre-DSHEA, and that are therefore ODIs. AHPA believes, for example that any pre-DSHEA dated letter addressed to U.S. firm, whether from a U.S. or foreign supplier, to offer for sale any ingredient described in 21 U.S.C. § 321(ff)(1)[13] is a valid record of pre-DSHEA marketing (though these too may be difficult to locate at this late date), irrespective of whether these records indicated intended use as dietary ingredients or in dietary supplements. More readily available references that at least imply pre-DSHEA marketing include herb books, farmers' almanacs or pharmacopoeial listings of "herbs or other botanicals" (or any of the other categories of ingredients identified in 321(ff)(1)) with copyright dates prior to 1994, each of which must be considered as implicit evidence of pre-DSHEA marketing of the ingredients identified therein, and which AHPA believes a court of law would consider as such evidence should a court's opinion be requested.

A disclaimer as to incompleteness must accompany any ODI list

In discussing the idea of developing an official or authoritative list of pre-DSHEA dietary ingredients in the 2016 revised draft NDI guidance, FDA explicitly stated, "The mere fact that an ingredient is not on the list would not, however, establish that the ingredient is

[13] That is, a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any of the above.

an NDI or that dietary supplements containing that dietary ingredient are adulterated for failure to notify. Rather, the omission of an ingredient from the list would be regarded as neutral and would not affect the ingredient's regulatory status." AHPA believes this clarification is important and should be retained in future communications and documents regarding any such proposed list, and must be clearly and prominently stated in any eventual ODI list.

Summary of points

To summarize, AHPA believes that for FDA to be successful in creating an authoritative list of ODIs in a manner that balances this task with the Agency's highest priorities, the Agency must make some significant changes to its previous positions as presented in the 2016 revised draft NDI guidance. These include:

- The Agency must accept records that are currently widely available, modified as needed to make corrections or to remove a few specific listed ingredients. These include the lists submitted by industry in the years just after DSHEA was passed, the two editions of AHPA's *Herbs of Commerce*, and numerous other publications such as herb books, farmers' almanacs, and pharmacopoeial references.
- FDA should move away from any quest for absolute proof of pre-DSHEA marketing and move toward exercising enforcement discretion for dietary ingredients that are acknowledged as very likely to have been marketed in the U.S. as of October 15, 1994. This suggestion is consistent with FDA's statement in the September 6 Notice that the Agency should "better focus our enforcement efforts in alignment with our strategic priorities of consumer safety, product integrity, and accurate information."
- Any eventual authoritative list should identify as a pre-DSHEA ingredient any traditionally processed ingredient derived from a pre-DSHEA botanical ingredient, since it should be assumed that every botanical raw material that was marketed in the U.S. pre-DSHEA was also marketed in an extract form manufactured through traditional processing (e.g., tinctures, oils, vinegars, etc.). Alternatively, if FDA does not agree that the just-described assumption can be supported, any eventual list of pre-DSHEA dietary ingredients should include a footnote or other statement to clarify that any such traditionally processed

ingredient, even if considered to be an NDI, is not subject to the NDI notification provision as such an ingredient is not chemically altered, and is therefore "an article used for food in a form in which the food has not been chemically altered."

- FDA should reverse its prior stated position that only pre-DSHEA use of an ingredient in a product that would today be identified as a dietary supplement actually demonstrates an ingredient to be a pre-DSHEA ingredient. AHPA believes otherwise, and believes that Congress intended the mere presence in the marketplace of any orally consumed dietary ingredient – whether in a conventional food, a supplement-form product, or an ingredient used in a traditional therapeutic product other than a new drug – to be sufficient to establish the ingredient as an ODI or pre-DSHEA ingredient. As mentioned elsewhere in these comments, the separate adulteration provisions of the law protect against any use of such ingredients if use would constitute a significant or unreasonable risk of illness or injury.
- Any eventual ODI list must include a disclaimer to state that omission of an ingredient from the list does not indicate that FDA considers such ingredient to be an NDI and does not affect the ingredient's regulatory status.

FDA (and ODSP) should consider prioritizing resources

In closing, AHPA recommends that FDA seriously consider whether the significant Agency and industry resources that would be required to create the envisioned authoritative list of pre-DSHEA dietary ingredients is the best use of these resources.

In the narrow context of DSHEA's NDI provision, it is AHPA's view that these resources would be better directed to providing guidance on how to clearly describe an NDI that is the subject of an NDI notification, as this is the single issue that is most commonly identified by FDA as a "serious concern" in responding to submitted NDI notifications.

More broadly though, if FDA and especially the Office of Dietary Supplement Programs has resources to spare, AHPA believes these resources would be better addressed to improving a mutual Agency-industry understanding of FDA's current good manufacturing practice regulation for supplements as codified at 21 CFR Part 111 and to assisting manufacturers, especially small entities, to comply with this complex rule. This cGMP rule affects 100 percent of dietary supplement products, whereas the NDI

provisions and rules apply only to that proportion of supplement products that actually contain an NDI.

Closing

AHPA greatly appreciates the opportunity to present comments on this matter, though AHPA reserves the right to comment further in any rulemaking or other administrative process that FDA may initiate to develop an official or authoritative list of pre-DSHEA dietary ingredients.

AHPA staff and counsel will make themselves available at any mutually convenient time to further discuss any of the topics addressed herein. Please feel free to contact us if clarification or additional discussion is needed on the issues raised in these comments.

Respectfully submitted,

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