

February 1, 2005 3:02 5 10-2 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2004N-0454

To Whom It May Concern:

The National Nutritional Foods Association ("NNFA") is submitting these comments to the Food and Drug Administration ("FDA") in response to the October 20, 2004 Notice, "Dietary Supplements; Premarket Notification for New Dietary Ingredient Notifications," 69 Fed. Reg. 61680.

NNFA is a trade association representing the interests of more than 8,000 retailers, manufacturers, suppliers, and distributors of foods, dietary supplements, and other natural products throughout the United States. NNFA appreciates the opportunity to comment on the questions posed by FDA and applauds FDA's ongoing efforts to fully implement the Dietary Supplement Health and Education Act of 1994 ("DSHEA").

These comments are intended to supplement previous remarks made by NNFA Executive Director, David Seckman, at FDA's November 15, 2004 Public Meeting. As those comments made clear, NNFA believes that the industry needs clarity specifically with respect to when a New Dietary Ingredient ("NDI") notification is required and the type of information to be included if a premarket notification is filed.

At the same time, NNFA cautions the agency to ensure that it complies with Congress' intent in any interpretations of the NDI section. Specifically, NDI

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notifications should be required – and contain information – only for safety purposes. The NDI section should *not* be reinterpreted to be part of FDA's larger efforts to determine whether ingredients are appropriately marketed as dietary supplements, or to circumscribe the definition of dietary supplement.

I. Changes to Existing Dietary Ingredients or Grandfathered Substances Should Not Trigger the New Dietary Ingredient Notification Requirement

FDA asks for further information on: (1) changes in chemical composition that would cause a grandfathered ingredient to be subject to the NDI requirement; and (2) changes in conditions of use that would trigger the need for an additional NDI notification for an existing dietary ingredient. In presenting these questions, FDA implies that there may be changes that automatically would trigger the need for an NDI notification.

NNFA reminds FDA that the statute contains a measure for when NDIs are required, and no new "test" or clarification is needed. "The NDI section exempts new dietary ingredients from the filing requirement if they "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." 21 U.S.C. §350(b)(a)(1). This provision applies, in the first instance, in determining whether an NDI is subject to – or exempt from – the notification requirement. NNFA takes the position that it continues to apply when evaluating changes to grandfathered ingredients or NDIs that were previously the subject of a notification.

Thus, a change to a grandfathered ingredient would not require an NDI if that altered ingredient had been present in the food supply "in a form in which the food has not been chemically altered." Along the same lines, a change to an NDI that had previously been the subject of a notification would *not* require an additional NDI submission as long the change did not "chemically alter" the ingredient. Changes involving a "chemical alteration" would, by the same reasoning, require the filing of an NDI notification.

Moreover, the agency would face a deluge of notifications if it were to make the NDI notification mandatory following any change to an existing or grandfathered ingredient. Surely, an influx of material to be reviewed would not assist the agency in its goal of ensuring the safety of NDIs. NNFA's Counsel is aware that in the GRAS context, the Office of Food Additive Safety has informally stated that it does not want to receive a GFAS Notification for every variation of a substance because the additional burden on the agency is not commensurate with an increased level of safety and consumer protection.

II. Information About the Intended Dietary Supplement is Not Relevant for an NDI Notification

In the Notice, FDA raises several questions about the eventual dietary supplement that would contain an NDI. Thus, under Section A (Status of a Substance as a "New Dietary Ingredient") FDA asks, "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"? In addition, under Section C (Information about the Dietary Supplement), the agency asks, "What

types of information about the dietary supplement should be included in the NDI notification?"

NNFA takes the position that neither of these issues is relevant for purposes of an NDI notification and should not be pursued. The definition of "dietary supplement" introduced by DSHEA and codified at 21 U.S.C. §321(ff)(1) and the NDI section at 21 U.S.C. §350b are functionally separate. The definitional section was drafted broadly by Congress so that it would encompass the largest possible range of substances that had been available as dietary supplements prior to DSHEA. In order to accommodate substances ranging from CoQ-10 to shark cartilage to bee pollen, the drafters of DSHEA included the catch-all definitions of 21 U.S.C. §321(ff)(1)(E) and (F).

The NDI section, in turn, represents a wholly separate venture by Congress. It was drafted as one of DSHEA's multiple safety provisions and is intended to avail FDA of the opportunity for premarket review of *new* ingredients being used in dietary supplements. There is no requirement in DSHEA, however, that information submitted for this premarket review must specify how the *dietary ingredient* will be utilized in final *dietary supplement* form. Instead, the statute simply directs the notifier to show "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 . . . will be reasonably expected to be safe." 21 U.S.C. §350b(a)(2). Thus, though the exposure level of the intended dietary supplement may be relevant to determine safety, other aspects of the final dietary supplement (e.g., form, other ingredients, labeling) are not.

Moreover, FDA is inconsistent in applying the 21 U.S.C. §321(ff)(1) definition to the NDI section. The definition of dietary supplement added by DSHEA contains not only the list of potential dietary ingredients in 21 U.S.C. §321(ff)(1), but also the form and labeling requirements of 21 U.S.C. §321(ff)(2), and the specifications that a dietary supplement may not be an article approved as a new drug ("NDA"), or authorized as an investigational new drug ("IND"), biological or antibiotic, in 21 U.S.C. §321(ff)(3)(B). If the correct interpretation of 21 U.S.C. §350b truly required a review of the dietary supplement definition, these additional considerations should form a part of that review as well. Thus, for each NDI notification, FDA would assess the formulation and labeling of the product, and would review the ingredient to ensure it was not the subject of a NDA or an IND, biological or antibiotic application.¹ It is clear from the agency's questions and its recent actions, however, that it does not intend to broaden the NDI review to this level.

NNFA thus recommends that FDA abandon this incomplete attempt to reinvent the NDI section as a "gatekeeper" for evaluating whether products appropriately meet the dietary supplement definition. This is a goal that is legitimately pursued under other provisions of DSHEA.

III. FDA Should Recognize Lists of Grandfathered Ingredients

"Grandfathered" is the terminology FDA uses, apparently to refer to dietary ingredients that were marketed before October 15, 1994 based on the language found in 21 U.S.C. §350b(c). Question A.6. of FDA's October 20, 2004 Notice raises the

¹ Importantly, in the drug context, FDA does not assess whether a substance falls within the definition of "drug," 21 U.S.C. §321(g)(1) when granting an IND to explore safety.

question of whether there is an authoritative list of dietary ingredients marketed prior to October 15, 1994. NNFA acknowledges that there are lists of "grandfathered" ingredients put together by industry organizations, including NNFA. However, NNFA takes the position that such lists, as David Seckman indicated at the meeting, are authoritative, but they are not exhaustive. That is, there may be ingredients that were present on the market prior to DSHEA, but were not included on any of the industry lists.

Moreover, NNFA does not believe that "grandfathered" status is only available to dietary ingredients that were "legally marketed" before October 15, 1994. It is true that FDA sent out numerous Warning Letters to companies marketing dietary supplements prior to the passage of DSHEA. However, many of these letters targeted companies only because of the "structure/function" *claims* that were being made for dietary supplement products being marketed. Prior to DSHEA, such claims were treated by the agency as unapproved drug claims. Other letters related to ingredients that are now widely accepted as legal and safe, such as evening primrose oil, which FDA believed at the time were illegally marketed. Accordingly, for FDA to now take the position that an ingredient that was not "legally marketed" prior to DSHEA can not be grandfathered would seem to run completely counter to the very reason Congress passed DSHEA.

The fact that an ingredient was the subject of such a letter prior to DSHEA does not indicate that it was illegally being marketed as a dietary supplement. Rather, such a letter *confirms* that the dietary ingredient was in fact on the market prior to October 15, 1994 and points to the fact that the available claims for such products were

in flux at that time. Thus, the existence of a Warning Letter targeting a company for marketing a dietary ingredient prior to DSHEA does not *de facto* exclude the ingredient from being considered grandfathered, but should be evidence of use of a product without apparent safety concerns.

IV. Chemical Identification Is Necessary to Evaluate Safety of the NDI

FDA has included a detailed list of questions under the "Chemical Identification of the NDI" section of the October 20, 2004 Notice, inquiring about everything from the chemical characterization of an ingredient, to the conditions of cultivation for a botanical.

NNFA agrees with FDA that specific information about the chemical identity of the NDI should be included in the notification. However, NNFA believes that the amount of information needed to identify the substance will vary in each instance, but must be sufficient: (1) to identify the NDI to FDA; and (2) to ensure that safety data presented is relevant.

NNFA does not believe that there is any reason for FDA to require the level of detail suggested in the Notice for botanical NDIs. Most of the information listed under FDA's Question B.3.² about botanical NDIs is not relevant to an NDI safety evaluation. Botanicals are subject to numerous natural variations, and thus can not be subject to the standardization proposed by FDA. Moreover, botanicals are grown in vastly different locations, and are subject to variations year to year and location to location. It would not add any value either for identification or safety purposes to use

² "What types of information should be included to describe an NDI for purposes of the NDI notification?"

most of FDA's suggested identifying factors. In addition, many of the measurements suggested by FDA reflect information that is subject to natural variation or is proprietary.

Instead, relevant botanical information should be limited to information about genus and species, which can be corroborated through an organoleptic, microscopic or morphologic determination by a botanist.

V. Establishing a Reasonable Expectation of Safety Should Focus On Key Data

FDA raises the question of what "should be included in an NDI notification in order to establish a reasonable expectation of safety." 69 Fed. Reg. 61682. The agency goes on to present an exhaustive list of various forms of safety data that could be presented in an NDI notification.

NNFA reminds FDA that Congress did not intend DSHEA's NDI safety standard to match that required for food additives and "generally recognized as safe" ingredients, or for drugs. According to DSHEA, a demonstration that the NDI may be "reasonably expected to be safe" can be met by (1) evidence of history of use or (2) other evidence of safety.

NNFA takes the position that the party placing the NDI into commerce should determine, in the first instance, what is appropriate to demonstrate safety in an NDI notification. Where history of use data adequately demonstrates that the NDI is "reasonably expected to be safe," this data should satisfy FDA. In cases where such data is not available, or is insufficient to demonstrate safety, the party placing the NDI

into commerce may include studies on substances that are materially identical to the NDI, or may generate their own studies.

VI. No Need for Additional Guidance or Amendment of Current Requirements

NNFA does not believe that there is a need for further definition of terms or guidance on current requirements. Indeed, NNFA is hopeful that by following through on the current rulemaking process, FDA will provide a sufficient amount of clarity on the NDI notification process.

Thank you so much,

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