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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2004N–0454]

Dietary Supplements; Premarket Notification for New Dietary Ingredient Notifications; Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing a meeting and is soliciting comments on FDA's premarket notification program for new dietary ingredients (NDIs). FDA is soliciting comments from industry, consumers, and other interested members of the public concerning the content and format requirements for NDI notifications made under the Federal Food, Drug, and Cosmetic Act (the act). FDA is holding this meeting to give the public an opportunity to provide information and views on the topics outlined in this document. The agency intends to consider all comments received during the meeting and made to the docket in determining whether any future action is necessary or appropriate.

DATES: The public meeting will be held on November 15, 2004, from 9 a.m. to 5 p.m. Attendees must register to attend.

Submit written or electronic comments by December 3, 2004.

For security and space limitation reasons, you are encouraged to register early. You may preregister via phone, fax, or e-mail until close-of-business November 10, 2004, or on site on the day of the meeting, providing space is available. Those wishing to speak should contact Kelly Williams-Randolph (see

FOR FURTHER INFORMATION CONTACT) before close-of-business, 3 business days before the meeting.

ADDRESSES: The meeting will be held at the Center for Food Safety and Applied Nutrition, Harvey W. Wiley Auditorium, 5100 Paint Branch Pkwy., College Park, MD 20740.

Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Kelly Williams-Randolph, Center for Food Safety and Applied Nutrition (HFS–810), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–2506, FAX: 301–436–2639, or e-mail: *Kelly.Williams@cfsan.fda.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

The Dietary Supplement Health and Education Act of 1994 (DSHEA) (Public Law 103–417) amended the act by adding, among other things, provisions that defined the terms "dietary supplement" (section 201(ff) of the act (21 U.S.C. 321(ff))) and "new dietary ingredient" (section 413(c) of the act (21 U.S.C. 350b(c))). DSHEA also provided that a dietary supplement containing an NDI is adulterated unless it meets the requirements set forth in section 413 of the act, which requires premarket notification for certain NDIs.

Under section 413(a) of the act, a dietary supplement that contains an NDI is deemed adulterated unless it meets one of two statutory requirements. One is that the dietary supplement contains only dietary ingredients that "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." (Section 413(a)(1) of the act). The alternative requirement is (section 413(a)(2) of the act) that there be:

[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 * * * provides [FDA] 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.

FDA has issued a regulation § 190.6 (21 CFR 190.6) establishing the procedure by which a manufacturer or distributor of a dietary supplement that contains an NDI must submit the information required by section 413(a)(2) of the act.

II. Why Is FDA Holding This Meeting?

The agency is seeking public comment on several issues that need to be addressed to clarify the requirements of section 413(a)(2) of the act for NDIs that have not been present in the food supply as an article used for food in a form in which the food has not been chemically altered. FDA has identified a number of omissions and other problems in previous notifications that have been submitted by firms to comply with the NDI notification requirements of the act. These omissions include a failure to do the following: (1) Adequately describe the identity and composition of the NDI, (2) provide information that states the basis for a conclusion that the substance is an NDI, (3) provide adequate safety information about the NDI, or (4) provide other necessary information. The problems with NDI notifications described previously suggest that it may be helpful for FDA to consider ways to assist submitters of NDI

notifications to ensure that they contain the information the agency needs to evaluate the notification. There is also recognition by the regulated industry that the quality of NDI notifications could benefit from FDA clarification of the statutory requirements (Ref. 1). Therefore, FDA is seeking comments from industry, consumers, and other interested members of the public concerning the type, quantity, and quality of information that a notifier should provide in notifications under section 413(a)(2) of the act.

III. Registration, Written Questions, and Requests for Oral Presentations

Persons interested in attending the November 15, 2004, meeting may send their registration information (including name, title, business affiliation, address, telephone, and fax number) to the contact person (see **FOR FURTHER INFORMATION CONTACT**) by close-of-business November 10, 2004, or you may register onsite on the day of the meeting, providing space is available. To expedite processing, this registration information also may be sent to the contact person (see **FOR FURTHER INFORMATION CONTACT**) by fax or by e-mail. If, in addition to attending, you wish to make an oral presentation during the meeting, you must inform the contact person 3 days before the meeting when you register and submit the following: (1) A brief written statement of the general nature of the views you wish to present, (2) the names and addresses of all persons who will participate in the presentation, and (3) an indication of the approximate time that you request to make your presentation. Depending upon the number of people who register to make presentations, we may have to limit the time allotted for each presentation. Interested persons are encouraged to submit their presentations and any additional comments to the docket. Any person who wishes to distribute written material at the meeting is responsible for the copy and distribution of such material. If you need

special accommodations due to disability, please notify the contact person at least 7 days in advance. There is no registration fee for this public meeting, but early registration is encouraged because space is limited and it will expedite entry into the building and parking area. Because the meeting will be held in a Federal building, you should also bring photo identification and plan for adequate time to pass through security systems.

IV. Scope of the Meeting

We are holding the public meeting on November 15, 2004, in part, to identify and receive comment on the information a firm should provide in an NDI notification under section 413(a)(2) of the act. As follows, we provide a list of questions intended to focus public comment on specific NDI issues.

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?

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

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?

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?

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?

B. Chemical Identification of the NDI

1. What types of chemistry information should be included to describe an NDI for purposes of the NDI notification? Please consider the following types of information:

a. Chemical name.

b. Chemical Abstract Service (CAS) registry number (if available).

c. Empirical formula.

d. Structural formula.

e. Quantitative composition.

f. Chemical characterization.

g. Chemical specifications.

2. Are there additional types of chemistry information that should be included in the description of an 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:

a. Botanical family name.

b. Part(s) of plant used.

c. Conditions of propagation.

i. Sexual reproduction (propagated from seeds).

ii. Seeds produced through selective breeding—variety and cultivar.

iii. Seeds are bioengineered.

1. Variety, cultivar and seed producer.

2. Asexual reproduction by cloning.

3. Vegetative propagules.

4. tissue culture.

d. Geographical location of cultivated or wild harvested plant.

e. Conditions of cultivation.

i. Time of cultivation—month and year.

ii. Field cultivation—soil pH, fertilizers, pesticides and herbicides.

f. Greenhouse cultivation.

i. Soil pH, fertilizers, pesticides and herbicides.

ii. Hydroponic growth media—nutrients, growth hormones and minerals.

g. Method of drying—air or heat.

h. Processing information—hand or machine sorted, chopped or milled.

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?

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?

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:

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).

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

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

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

b. Documentation of the absence of toxins or other by-products that may affect the safety of the ingredient produced by fermentation or bioengineering.

c. Documentation that the extracts of cultured isolates are neither infectious nor toxic.

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

C. Information About the Dietary Supplement

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

2. Please consider the following types of information:

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

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.

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.

b. The consumption levels (per serving and total exposure).

c. How often and how long the population consumed the food or dietary supplement containing the dietary ingredient.

d. The number of independent references documenting history of safe use.

e. The number of consecutive years of exposure.

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.

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.

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

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?

a. Significantly higher serving level (e.g., twice the serving level historically used).

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).

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).

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).

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

5. What criteria should FDA use to evaluate whether preclinical and clinical studies are of sufficient duration to establish a reasonable expectation of 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?

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:

a. Genetic toxicity 2-3 study battery (e.g., a bacterial gene mutation assay, mammalian cell gene mutation assay, or deoxyribonucleic acid (DNA) repair assay).

b. Short-term feeding studies (<30-day) (rodent).

c. Subchronic feeding studies (90-day) (rodent, nonrodent).

d. Single dose human tolerance studies.

e. Repeat dose human safety studies (30- to 90-day duration).

f. Teratology studies (rodent, nonrodent).

g. Multigeneration reproduction studies (rodent, nonrodent).

h. Special studies (e.g., carcinogenicity, absorption, metabolism and distribution and excretion).

i. Other studies.

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.

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.

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.

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

e. There is no history of use data to establish safe intermittent or chronic daily use.

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

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?

a. Women of child bearing potential.

b. Pregnant women.

c. Lactating women.

d. Children.

e. Geriatric adults.

f. Other.

E. The Role of Definitions in Evaluating NDIs

1. Are there terms that should be defined so that the NDI notification program can be more transparent and consistent?

2. FDA seeks comment on how the following terms should be defined:

a. Amino acid.

b. Botanical.

c. Chemically altered.

d. Concentrate.

e. Constituent.

f. Extract.

g. Ingestion.

h. Metabolite.

i. Mineral.

j. Salts of dietary ingredients.

k. Tincture.

l. Vitamin.

F. Is There a Need for Guidance or Amendment of Current Requirements?

The information presented as follows, could assist FDA in efficiently reviewing NDI notifications. Comment is invited on whether FDA should consider the issuance of draft guidance or amendments to current requirements to include the following:

1. Table of contents and "continuous pagination" in the notification;

2. A discussion that clearly indicates why the notifier has concluded that the "new dietary ingredient" is a dietary ingredient under 21 U.S.C. 321(ff)(1);

3. Detailed requirement for chemical characterization of the NDI;

4. Requirement for composition/formulation of the dietary supplement containing the NDI;

5. A tabular listing of studies, articles and other scientific information provided in the notification to support a conclusion that the NDI, when used under the conditions recommended or suggested in the labeling of the notifier's dietary supplement, will reasonably be expected to be safe, with an indication of whether the test material in these studies is the same substance as is used in the notifier's dietary supplement;

6. A safety document" that clearly describes the scientific reasoning used by the notifier to establish a reasonable expectation of safety, based upon the data provided in the notification; and

7. Option for electronic submission of notifications.

VI. Transcripts

You may request a transcript of the meeting in writing from the Freedom of Information Office (HFI–35), Food and Drug Administration, rm. 12A–16, 5600 Fishers Lane, Rockville, MD 20857, approximately 15 working days after the meeting, at a cost of 10 cents per page. You may also examine the transcript of the meeting at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, as well as on the FDA Internet at *http://www.fda.gov.*

VII. Reference

We have placed the following reference on display in the Division of Dockets Management (see **ADDRESSES**). You may see it at that office between 9 a.m. and 4 p.m., Monday through Friday.

1. M. McGuffin and A. L. Young, Premarket Notifications of New Dietary Ingredients—A Ten-Year Review, *Food and Drug Law Journal*, 59(1): 2004.

VIII. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are

to be identified with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: 10/13/04
October 13, 2004.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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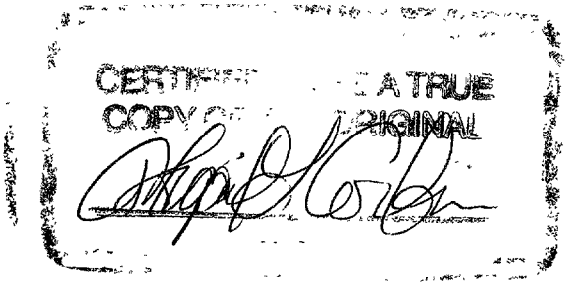
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