

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****Food and Drug Administration**

[Docket No. 98N-0048]

RIN 0910-AA59

**Dietary Supplements; Comments on Report of the Commission on Dietary Supplement Labels**

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing its views on recommendations and guidance of the Commission on Dietary Supplement Labels, as presented in the Commission's Final Report. The document also responds to recommendations and guidance directed to FDA. Elsewhere in this issue of the **Federal Register**, FDA is issuing a proposed rule that responds to guidance in the Commission Report concerning statements about the effect of dietary supplements on the structure or function of the body.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Ilisa B.G. Bernstein, Office of Policy (HF-23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3380, IBernste@oc.fda.gov.

**SUPPLEMENTARY INFORMATION:****I. Background**

Section 12 of the Dietary Supplement Health and Education Act of 1994 (the DSHEA) (Pub. L. 103-417) established an independent agency within the Executive Branch known as the Commission on Dietary Supplement Labels (the Commission). The Commission was charged with conducting a study on, and providing recommendations for regulating label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for evaluating such claims.

The Commission was appointed in October 1995 and convened its first meeting in February 1996. Interested persons presented oral and written testimony at several Commission meetings. A draft report of the Commission was released for public comment on June 24, 1997. On November 24, 1997, the final report of

the Commission (Commission Report) was released.

Under section 12(d)(3) of the DSHEA, within 90 days of issuance of the Commission's final report, the Secretary of Health and Human Services is required to publish in the **Federal Register**

a notice of any recommendation of [the] Commission for changes in regulations of the Secretary for the regulation of dietary supplements and shall include in such notice a notice of proposed rulemaking on such changes together with an opportunity to present views on such changes. Such rulemaking shall be completed not later than 2 years after the date of issuance of such report.

The Commission divided its conclusions into three categories: Findings, guidance, and recommendations. The Commission Report did not contain any recommendations for changes to FDA's "regulations \* \* \* for the regulation of dietary supplements." The Commission made only two recommendations directed to FDA. These recommendations pertain to botanicals and are discussed in section VIII of this document. Neither of the two recommendations suggests changes in regulations governing dietary supplements. Therefore, there are no recommendations subject to the deadlines imposed under section 12 of the DSHEA. In this document the agency is announcing its views on the Commission's recommendation and guidance, as well as a description of the actions the agency intends to take because of these recommendations and guidance. In addition, based on guidance set forth in the Commission Report, the agency is issuing a proposed rule elsewhere in this issue of the **Federal Register** concerning statements about the effects of dietary supplements on the structure or function of the body.

This document addresses only guidance and recommendations made in the Commission Report that are addressed to FDA or relevant to its responsibilities.

**II. Safety of Dietary Supplements**

The Commission Report states that existing postmarket surveillance systems for dietary supplements could be improved. The Commission Report notes that there is no mandatory requirement for industry, consumers, or health care professionals to report adverse events resulting from consumption of foods and dietary supplements, and specifically states that the Commission is not recommending such a requirement. However, the Commission Report does urge FDA, industry, the scientific community, and

consumer groups to work together voluntarily to improve passive postmarketing surveillance systems.

The agency agrees that greater cooperation among FDA, industry, and other interested parties to enhance the effectiveness of current surveillance systems would improve the ability of these systems to identify potential safety problems and thereby improve their public health utility. FDA currently collects reports of adverse events associated with the use of dietary supplements through its MedWatch system, which accepts voluntary reports of adverse events from health professionals and consumers for serious adverse events related to FDA-regulated products. FDA also receives reports of adverse events associated with the use of dietary supplements through the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Monitoring System. All reports FDA receives concerning adverse events associated with dietary supplements are entered into CFSAN's Special Nutritionals Adverse Event Monitoring System database for evaluation and monitoring.

The agency intends to respond to the Commission Report's guidance by initiating a process to further cooperation among interested parties. The agency has asked the FDA Foods Advisory Committee (composed of outside experts who advise the agency on food issues) to consider the issue of postmarket surveillance and particularly, how best to collect and share surveillance information. The Foods Advisory Committee (FAC) considered these issues at its February 1998 meeting and referred them to a FAC internal working group to develop recommendations for consideration by the full FAC.

The Commission Report strongly suggests that dietary supplement manufacturers include appropriate warning statements in product information where necessary. Although no corresponding guidance or recommendation to the agency was made, the agency intends to work with the FDA Foods Advisory Committee and industry in developing guidance on the use of warning statements on dietary supplement labeling.

Also related to safety of dietary supplements, the Commission Report urges FDA to use its authority under the DSHEA to take swift enforcement action to address potential safety issues. The agency takes seriously its mission to promote and protect the public health. When the agency becomes aware of the presence of harmful dietary supplements in the marketplace, it is

committed to taking timely action, within the legal limits of its authority, to remove unsafe products from the market or to take other steps to protect consumers from adverse health effects that may result from the use of unsafe dietary supplements.

### III. Nutritional Labeling and Education Act (NLEA) Claims in Dietary Supplement Labeling (Health Claims)

A health claim is "any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication \* \* \* characterizes the relationship of any substance to a disease or health-related condition" (21 CFR 101.14(a)(1) (§ 101.14(a)(1)). The Federal Food, Drug, and Cosmetic Act (the act) provides that FDA may authorize a health claim for a conventional food only if the agency determines,

based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

21 U.S.C. 343(r)(3)(B)(i).

Any person may petition FDA to authorize a particular health claim by regulation; however, the health claim may not be made until authorized by regulation. Current regulations at 21 CFR 101.14 and 101.70 set forth general requirements for health claims on the labels or in the labeling of conventional foods and dietary supplements. These regulations apply the same standard (i.e., "significant scientific agreement") and set forth the same process (i.e., petition process) for health claims for dietary supplements as for health claims for conventional foods.

The Commission Report states that the significant scientific agreement standard is appropriate and serves the public interest. The Commission Report also states that the scientific standard and approval process for health claims for dietary supplements should be the same as for conventional foods, which is an endorsement of FDA's current regulations for health claims on dietary supplements. The Commission Report does not recommend any changes in FDA's health claim regulations for dietary supplements.

The Commission Report does suggest, however, that "FDA should ensure that broad input is obtained to ascertain the degree of scientific agreement that exists for a particular health claim." FDA agrees. The agency has considered and will continue to consider the opinions

of scientific experts outside the agency in its deliberations on whether there is significant scientific agreement supporting the validity of a particular disease-substance relationship. For example, FDA considered and relied on data and opinions from several other governmental agencies and professional organizations in deciding to authorize a health claim for folate and neural tube defects. See 58 FR 53254 at 53262-63. The agency is open to input from interested parties as to how to improve its process for considering proposed health claims.

On November 21, 1997, 3 days before the Commission Report was issued, the President signed into law the "Food and Drug Administration Modernization Act of 1997" (FDAMA) (Pub. L. 105-115). FDAMA, among other things, amended the health claims provisions of the act in several respects. The Commission Report does not discuss the provisions of the FDAMA as enacted, although it mentions the predecessor House and Senate bills. The effect of the FDAMA on health claim requirements for dietary supplements is beyond the scope of this document. FDA will address such issues during the rulemaking process to implement the FDAMA.

### IV. Scope of Structure/Function Statements for Dietary Supplements

The DSHEA added section 403(r)(6) (21 U.S.C. 343(r)(6)) to the act. If certain conditions are met, section 403(r)(6) of the act permits several categories of statements to be made for dietary supplements, including statements that "describe[] the role of a nutrient or dietary ingredient intended to affect the structure or function in humans [or] characterize[] the documented mechanism by which a nutrient or dietary ingredient acts to maintain structure or function," also known as "structure/function" claims. The Commission Report contains general guidance for what would constitute an acceptable structure/function claim. Elsewhere in this issue of the **Federal Register** the agency is proposing regulations, consistent with the Commission's guidance, that describe the types of statements that can be made by a manufacturer of a dietary supplement concerning the effect of the dietary supplement on the structure or function of the body in accordance with section 403(r)(6) of the act.

### V. Notification Letters for Statements of Nutritional Support (Statements made under section 403(r)(6) of the act)<sup>1</sup>

The act, as amended by the DSHEA, requires the manufacturer of a dietary supplement bearing a statement made under section 403(r)(6) of the act to notify the Secretary no later than 30 days after the first marketing of the dietary supplement with the statement. In the **Federal Register** of September 27, 1996 (61 FR 50771), the agency proposed procedures for such notifications. A final rule was issued September 23, 1997 (62 FR 49883). The regulations set forth the requirements for when and where such a notification is to be made and what information the notification must contain (see 21 CFR 101.93(a)).

The Commission Report suggests that manufacturers include certain information in the notification letter, including some information not required by FDA's regulations. Specifically, the Commission Report suggests that the notification letter include the following: A statement of the purpose of the notification letter, including the exact wording of the statement that is the subject of the notification; the name, address, and telephone number of the manufacturer or distributor; the trade name of the product, the common or usual name of the product, and a description of the product; a copy of the product label or label mock-up, if labels have not yet been printed; the identity of individual ingredients or combinations of ingredients for which the statement is being made, including, for botanicals, the common or usual name, the Latin binomial and its scientific authority, and the part(s) of the plant(s) used; and a statement of intended use, including the recommended dosage and appropriate contraindications or warnings. The Commission Report also suggests that, either in the notification letter or in a separate public notice, the manufacturer affirm that it has substantiation that the statement made under 403(r)(6) is truthful, not misleading, and scientifically valid and that the product does not present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the

<sup>1</sup> The Commission Report refers to statements under section 403(r)(6) of the act as "statements of nutritional support." As noted in the September 23, 1997, final rule regarding labeling claims for dietary supplements, FDA no longer uses the term "statements of nutritional support" because "many of the substances that can be the subject of this type of claim have no nutritional value. Thus, the term 'statement of nutritional support' is not accurate in all instances." 62 FR 49859 at 49863.

labeling. The Commission Report notes that these are suggestions and expresses the view that the rulemaking process need not be reopened at this time. The agency agrees with the guidance in the Commission Report. The agency also agrees that the rulemaking need not be reopened at this time, but will reconsider the need to do so in the future if experience warrants.

The Commission Report also suggests that the notification letters continue to be made available to the public. The agency will continue making these notification letters publicly available by placing them in Docket No. 97S-0162 at FDA's Docket Management Branch (address above). In addition, the agency will consider other mechanisms to make these submissions available.

#### **VI. Substantiation Files for Statements of Nutritional Support (Statements made under section 403(r)(6) of the act)**

Section 403(r)(6) of the act requires the manufacturer of a dietary supplement making a statement of nutritional support to have substantiation that such statement is truthful and not misleading. Section 403(r)(6) of the act, however, does not specify what constitutes adequate substantiation. The Commission Report includes guidance on what quantity and quality of evidence should be used to substantiate claims made under section 403(r)(6) of the act. The Commission Report also includes guidance on the content of substantiation files for statements made under section 403(r)(6) of the act, including the notification letter, identification of the product's ingredients, evidence to substantiate the statements, evidence to substantiate safety, assurances that good manufacturing practices were followed, and the qualifications of the person(s) who reviewed the data on safety and efficacy. The agency agrees with the guidance.

#### **VII. Publications Exempt From Classification as Labeling When Used in Connection With Sales**

The DSHEA added section 403B of the act (21 U.S.C. 343-2). This provision exempts certain publications used in connection with the sale of dietary supplements from the definition of "labeling" in section 201(m) of the act (21 U.S.C. 321(m)). Under section 403B of the act, a "publication" will be exempt when it:

(1) is not false or misleading; (2) does not promote a particular manufacturer or brand of a dietary supplement; (3) is displayed or presented, or is displayed or presented with other such items on the same subject matter, so as to present a balanced view of the

available scientific information on a dietary supplement; (4) if displayed in an establishment, is physically separate from the dietary supplements; and (5) does not have appended to it any information by sticker or any other method.

21 U.S.C. 343-2.

The Commission Report supports the requirement that information about the uses of dietary supplements be balanced and truthful and advises the dietary supplement industry to strictly observe the five requirements necessary to qualify for the exemption from the labeling definition for publications used in connection with the sale of dietary supplements. The Commission Report states that:

[b]ecause more experience with the implementation of this provision may provide additional information about the use of publications in connection with a sale, the Commission suggests that proactive monitoring of practice in this area be undertaken by FDA as resources permit and that regulatory guidance be developed if necessary.

The agency agrees with the suggestion that it should proactively monitor the use of publications in connection with the sale of dietary supplements and provide guidance, as necessary, to the industry. The agency intends to monitor the use of publications under section 403B of the act. Consistent with FDA's practice with claims made under section 403(r)(6) of the act, the agency intends to continue assisting industry in complying with the requirements of this section. If experience demonstrates a need for regulatory guidance, the agency will develop such guidance in the future.

#### **VIII. Botanical Products**

As previously noted, the DSHEA's charge to the Commission encompassed the regulation of label claims. The Commission interpreted this charge to include the marketing of botanical products as over-the-counter (OTC) drugs when a preventive or therapeutic claim is made.

The Commission Report recommends that botanical products should continue to be available to consumers as dietary supplements when properly labeled as such in compliance with the requirements of the DSHEA. The Commission did not recommend any changes to FDA's regulation of botanical products that are marketed as dietary supplements.

The Commission Report, however, did note that there may be instances in which consumers would be better served by having certain botanical products marketed as OTC drug products, so that statements regarding the prevention or treatment of disease

may accompany the product. As the Commission Report also notes, some botanical ingredients are recognized for specific preventive and therapeutic uses, and botanical pharmacopeias have been established in a number of developed countries. Yet, as the Commission observed, in the United States, many botanicals are being labeled with statements of nutritional support that suggest only indirectly the type of therapeutic use that is traditionally associated with the product.

To address this concern, the Commission Report advises that a study is needed "regarding the establishment of some alternative system for regulating botanical products that are used for purposes other than to supplement the diet but that cannot meet OTC drug requirements." In addition, the Commission Report states that a comprehensive evaluation is needed of the regulatory systems that other countries have adopted to regulate botanicals with preventive or therapeutic uses. While the U.S. drug regulatory system "as it currently exists" may allow some botanical remedies to be marketed OTC, the Commission Report suggests that existing FDA requirements might preclude others from entering the OTC drug market.

Finally, the Commission Report recommends "that FDA promptly establish a review panel for OTC claims for botanical products that are proposed by manufacturers for drug uses," and suggests that FDA "give special attention to the feasibility of approving botanical remedies for OTC uses in which sufficient evidence is available."

For several years, FDA has been engaged in discussions with experts within the Government, academia, and industry, regarding the regulatory status of botanical products. FDA has actively participated in symposia and workshops sponsored by the National Institutes of Health (NIH) and the Drug Information Association (DIA), which focused on topics such as identification and characterization of botanical products, the safety and efficacy evaluation of botanical products, the various regulatory pathways to market that a botanical product could take, and the necessary information that would be required for a particular regulatory route.

Since 1994, FDA has reviewed the relevant laws and regulations, policies and, in some cases, draft policies, from regulatory and advisory authorities around the world. Although the agency agrees that a much more comprehensive evaluation would be helpful, the project

as outlined by the Commission would be costly and resource-intensive. Unfortunately, because resources have not been allocated for such a comprehensive study, FDA is unable to act on its own to implement the Commission's suggestion at this time. Agency personnel, however, are available to work with persons interested in conducting such a study on study design features to provide other technical assistance.

With respect to the Commission Report's points regarding evaluating botanicals under FDA's OTC drug review, under FDA's existing statutory framework, a drug product may avoid "new drug" premarket approval requirements and may be eligible for marketing under an OTC drug monograph if (1) the product is generally recognized as safe and effective under the conditions for use for which it is labeled; and (2) if the product has been used to a material extent and for a material time under those conditions. See section 201(p) of the act. (21 U.S.C. 321(p)). FDA recognizes, however, the need to clarify the criteria for eligibility under the OTC drug review for certain additional OTC drug active ingredients, indications, dosage forms, dosage strengths, routes of administration, and combinations. The agency has interpreted section 201(p)(2) of the act to mean use in the United States (see 61 FR 51625, 51626 (October 3, 1996)).

In the **Federal Register** of October 1996, FDA issued an advance notice of proposed rulemaking (ANPRM) seeking comment on eligibility requirements and, among other matters, whether OTC marketing experience abroad could be used to establish "material time" and "material extent" requirements (61 FR 51625, October 3, 1996). For many botanical products, the history of use is based on marketing experience outside the United States.

Based on the comments received in response to the October 1996 ANPRM, the agency expects to issue a proposed rule setting forth criteria for eligibility in the OTC drug monograph system, including definitions of the terms "material extent" and "material time." Unless and until regulations are in place that would allow FDA to accept foreign marketing experience, it may be difficult for many botanical products to qualify for inclusion in the existing OTC monograph system. Consequently, establishing an OTC advisory panel to evaluate therapeutic and preventive drug claims for botanical products, as the Commission recommends, would be premature at this time. The agency,

however, intends to work expeditiously on rulemaking for this issue.

In the interim, if there were a situation in which the scientific evidence and marketing experience submitted to the agency are sufficient to allow a botanical ingredient to be considered under the existing framework, then the agency would work expeditiously to assess whether the submitted data and experience supports marketing under an OTC drug monograph.

In addition, recognizing the need for guidance for manufacturers seeking to develop botanicals as either OTC or prescription drug products, and recognizing the unique nature of botanical products, the agency currently is developing a draft guidance for industry that discusses the kinds of data necessary to satisfy drug regulatory requirements based on existing statutes and regulations. The draft guidance will be made available for public comment before a final guidance is issued.

#### **IX. Information for Consumers and Health Professionals**

As required by the DSHEA, the Commission considered how best to ensure that consumers receive information that is truthful, scientifically valid, and not misleading so that they may make informed and appropriate health choices. The Commission Report calls for consumer research to determine whether consumers want and can use the information provided to them under the DSHEA, existing FDA regulations, and the recommendations of the Commission. Because advice from health professionals can be critical in helping consumers to make appropriate decisions about dietary supplement use, the Commission Report also states that health care and nutrition professionals should become more knowledgeable about these products. Additionally, the Commission Report urges manufacturers to develop balanced and nonmisleading summaries of the evidence substantiating any statements made under section 403(r)(6) of the act and of the evidence substantiating product safety for the intended use at the recommended dosage. The Commission Report further suggests that manufacturers make these summaries publicly available.

FDA agrees that a better understanding of consumer information needs is desirable. The agency has asked the FDA Foods Advisory Committee (FAC) to consider how best to gather data on how consumers use information on dietary supplement labels to make decisions on whether a dietary

supplement is appropriate for them. FDA has also asked the FAC to consider the development of guidelines or criteria that could be used by the dietary supplement industry and others to conduct consumer research studies or to evaluate the results of consumer research studies. FAC considered these issues at its February 1998 meeting and referred them to a FAC internal working group to develop recommendations for consideration by the full FAC.

#### **X. Research**

The Commission Report addresses various issues related to research about dietary supplements. The Commission Report states that the public interest would be served by more research to assess the relationships between dietary supplements and the maintenance of health and/or prevention of disease. Additionally, the Commission Report states that incentive mechanisms should be developed to encourage the dietary supplement industry to invest in research on these products. To that end, the Commission Report suggests that FDA consider a "mechanism for review of research conducted to validate a statement of nutritional support so that the label disclaimer mandated by DSHEA could be modified or removed." The Commission Report notes that consideration is needed of ways to provide FDA with sufficient resources to make it possible for the agency to take on such an additional responsibility.

FDA agrees that additional research should be undertaken in the public and private sector to assess the relationships between dietary supplements and the maintenance of health and/or prevention of disease. The agency has provided, and will continue to provide, assistance and guidance to industry and other Federal agencies in designing studies for these types of assessments. Additionally, the agency has worked closely, and will continue to work, with NIH's Office of Dietary Supplements.

With regard to the Commission Report suggestion that FDA consider reviewing research to validate structure/function claims and other statements made under section 403(r)(6) of the act so that the currently required disclaimer could be removed, the agency notes that current law prevents it from adopting this suggestion. Because the disclaimer requirement is statutory, FDA cannot permit the disclaimer to be removed unless Congress amends section 403(r)(6)(C) of the act accordingly.

Dated: April 22, 1998.

**Michael A. Friedman,**

*Lead Deputy Commissioner for the Food and  
Drug Administration.*

**Donna E. Shalala,**

*Secretary of Health and Human Services.*

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