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5715 '99 JUN 30 P1:43

June 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Reference: Docket No. 99-1174

Sirs:

This communication is in reference to the Federal Register Notice dated May 13, 1999 (Vol.64, No.92, page 25889-25890) as amended, concerning the opportunity for written comments on the development of strategic planning by the Center for Food and Applied Nutrition in regard to regulation of dietary supplements.

The announcement and the public meeting held June 8, 1999 requested comments on several aspects of efforts of the Food and Drug Administration (FDA) to achieve effective regulation of dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

I attended the June 8, 1999 public meeting and heard testimony by organizations that had previously provided information and testimony to the Presidential Commission on Dietary Supplement Labels in 1996, 1997. Their comments and concerns were reviewed by the Commission and were incorporated in the Report of the Commission published in November 1997.

Each of the issues that FDA identified in the May 13, 1999 Federal Register announcement were discussed in the Report of the Commission on Dietary Supplement Labels, published November 24, 1997 in accordance with Section 12 of DSHEA. While FDA did comment on the conclusions of the Commission's report (Fed. Reg. 63 (82):23633-23637) in early 1998, the FDA comments were less than substantive and appeared to be made only to fulfill the requirement of DSHEA that FDA comment on the Commission's Report.

Little or none of the testimony of the public at the June 8, 1999 public meeting raised new issues.

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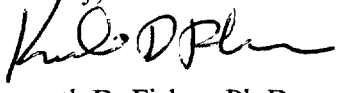
For this reason, I suggest that the November 1997 Final Report of the Commission on Dietary Supplement Labels should be re-examined in the course of the FDA ongoing strategic planning effort. This is particularly pertinent in view of the considerable public input in 1996-97 into the conclusions and recommendations of the Presidentially appointed Commission which in essence were repeated 19 months later at the June 8, 1999 public meeting.

Sincerely,



Kenneth D. Fisher, Ph.D.
Formerly, Executive Director,
Commission on Dietary Supplement Labels

Enclosure: Commission Report

PC: Commission Members

REPORT OF THE COMMISSION ON DIETARY SUPPLEMENT LABELS

COMMISSION ON DIETARY SUPPLEMENT LABELS
November 1997

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Washington, DC 20201

COMMISSION ON DIETARY SUPPLEMENT LABELS

November 24, 1997

The President
The White House
Washington, D.C. 20500

Dear Mr. President:

On behalf of the Commission on Dietary Supplement Labels, I am pleased to transmit the final report of the Commission. The seven-member Commission, which you appointed, examined a number of issues associated with labeling of dietary supplements, as set forth in the Dietary Supplement Health and Education Act of 1994. This report completes the duties of the Commission as assigned in its charter of February 1996.

As requested, the Commission conducted a study on and is providing recommendations for the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims. To accomplish its task, the Commission obtained advice from individuals, consumer organizations, the dietary supplement industry, and scientific organizations through written submissions and a series of public meetings throughout the United States. A preliminary report was released for public comment in June 1997. This final report reflects the consideration of materials, documents, and opinions submitted to the Commission during its deliberations.

The report contains the Commission's recommendations for regulations and provides guidance to government agencies and the dietary supplement industry relative to safety, label statements, health claims, substantiation of claims, and botanical supplements. The report emphasizes the need for public access to the evidence on which label statements are based so that consumers can make informed decisions about the use of dietary supplements.

Although the Commission operated independently from any policy guidance from the Department of Health and Human Services, we are grateful for the logistic and staff support provided by the Department through the Office of Disease Prevention and Health Promotion. We also wish to acknowledge the assistance of dedicated and able staff. We believe our report makes valuable recommendations and provides guidance that will be of benefit to consumers and the supplement industry.

Sincerely,

Malden C. Nesheim, Ph.D.
Chairman

COMMISSION ON DIETARY SUPPLEMENT LABELS

November 24, 1997

The Honorable Albert Gore, Jr.
President of the Senate
Washington, D.C. 20510

Dear Mr. President:

On behalf of the Commission on Dietary Supplement Labels, I am pleased to transmit the final report of the Commission. The seven-member Commission appointed by President Clinton examined a number of issues associated with labeling of dietary supplements, as set forth in the Dietary Supplement Health and Education Act of 1994. This report completes the duties of the Commission as assigned in its charter of February 1996.

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Malden C. Nesheim, Ph.D.
Chairman

COMMISSION ON DIETARY SUPPLEMENT LABELS

November 24, 1997

The Honorable Newt Gingrich
Speaker of the House of
Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

On behalf of the Commission on Dietary Supplement Labels, I am pleased to transmit the final report of the Commission. The seven-member Commission appointed by President Clinton examined a number of issues associated with labeling of dietary supplements, as set forth in the Dietary Supplement Health and Education Act of 1994. This report completes the duties of the Commission as assigned in its charter of February 1996.

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Sincerely,

Malden C. Nesheim, Ph.D.
Chairman

COMMISSION ON DIETARY SUPPLEMENT LABELS

November 24, 1997

The Honorable Donna Shalala
Secretary of Health and Human Services
Washington, D.C. 20201

Dear Madam Secretary:

On behalf of the Commission on Dietary Supplement Labels, I am pleased to transmit the final report of the Commission. The seven-member Commission appointed by President Clinton examined a number of issues associated with labeling of dietary supplements, as set forth in the Dietary Supplement Health and Education Act of 1994. This report completes the duties of the Commission as assigned in its charter of February 1996.

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Sincerely,

Malden C. Nesheim

Malden C. Nesheim, Ph.D.
Chairman

COMMISSION ON DIETARY SUPPLEMENT LABELS
REPORT TO THE PRESIDENT, CONGRESS, AND THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

Prepared by:

Commission on Dietary Supplement Labels

November 1997

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Executive Summary

The Dietary Supplement Health and Education Act (DSHEA or the Act) of 1994 was enacted by Congress following public debate concerning the importance of dietary supplements in leading a healthy life, the need for consumers to have current and accurate information about supplements, and controversy over the Food and Drug Administration's (FDA) regulatory approach to dietary supplements. President Clinton, in signing the legislation into law on October 25, 1994, said:

> After several years of intense efforts, manufacturers, experts in nutrition, and legislators, acting in a conscientious alliance with consumers at the grassroots level, have moved successfully to bring common sense to the treatment of dietary supplements under regulation and law.

This legislation defines dietary supplements, places the responsibility for ensuring their safety on manufacturers, identifies how literature may be used in connection with sales, specifies types of statements of nutritional support that may be made on labels, specifies certain labeling requirements, and provides for the establishment of regulations for good manufacturing practices. The legislation creates an Office of Dietary Supplements (ODS) in the National Institutes of Health (NIH), with a mandate to coordinate scientific research relating to dietary supplements within NIH and to advise Federal agencies on issues relating to dietary supplements.

DSHEA also directs the President to appoint a Commission on Dietary Supplement Labels to consider several issues needing clarification when the Act was passed. The Act indicates that the Commission is to:

> . . . conduct a study on, and provide recommendations for, the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims.

In making its recommendations, the Commission is to:

> . . . evaluate how best to provide truthful, scientifically valid, and not misleading information to consumers so that such consumers may make informed and appropriate health care choices for themselves and their families.

A seven-member Commission was appointed by President Clinton in October 1995, and its charter was approved by the Secretary of the Department of Health and Human Services (HHS) on February 13, 1996. The Commission convened its first meeting in February 1996. In the course of its deliberations, the Commission held public meetings at several sites around the United States and received oral and written testimony from interested organizations and individuals who presented views on issues related to the Commission's charge.

Reflecting the charge to the Commission in DSHEA and in the Commission's charter, this report is addressed to the President, Congress, and the Secretary of HHS. The organization of the report is as follows:

- Chapter I summarizes the major provisions of DSHEA and the charge to the Commission.

- Chapter II reviews the legislative and regulatory context surrounding DSHEA and summarizes information related to consumer use of dietary supplements and the supplement industry.

- Chapters III and IV present findings, guidance, and recommendations related to the key issues identified by the Commission during its deliberations. The conclusions of the Commission are presented in each section of these two chapters in this manner (See Executive Summary Endnote 1):

  - **FINDINGS** are the conclusions reached by the Commission during its deliberations and are based on the information and data received and reviewed by the Commission.

  - **GUIDANCE** represents advice to specific agencies, groups, or individuals. Guidance should be considered by the identified recipients as they develop or implement activities related to the availability of dietary supplements in the marketplace.

  - **RECOMMENDATIONS** are indicated as such and identify the intended recipients. Recommendations that call for consideration of changes in existing regulations, development of new regulations, or legislative action are so indicated.

The Commission on Dietary Supplement Labels was aware of the public interest in its work and desired to have an additional public comment period. Therefore, a draft report was released for public comment on June 24, 1997.

This executive summary highlights the findings, guidance, and recommendations made by the Commission in the areas of safety, health claims, statements of nutritional support, notification letters, substantiation files, publications used in connection with sales, and some special considerations regarding botanical products. The Commission also addressed consumer and health professional information needs; industry expert advice on safety, label statements, and claims; research issues; and the Office of Dietary Supplements.

SAFETY OF DIETARY SUPPLEMENTS

The Commission considers it axiomatic that all marketed dietary supplements should be safe. Congress, in reflecting on the issues associated with safety, concludes in DSHEA that dietary supplements "are safe within a broad range of intake, and safety problems with the supplements are relatively rare." Congress emphasizes in the Act that the government should take swift action when safety problems arise but should not impose unreasonable barriers or limit access to safe products.

GUIDANCE

Manufacturers and the industry as a whole must fully accept the responsibility for assuring the safety of dietary supplements and must take any action necessary to meet the expectation expressed in DSHEA that dietary supplements are and will continue to be safe for use by the consuming public.

- The Commission urges FDA, the industry, the scientific community, and consumer groups to work together

voluntarily to improve passive postmarketing surveillance systems, including adverse reaction reporting systems, to ensure that any safety problems that may arise are identified and corrected promptly.

- Ensuring the safety of supplements includes the need to provide adequate information and warnings to consumers. The Commission strongly suggests that dietary supplement manufacturers include appropriate warnings in product information where necessary, as specifically permitted by DSHEA. In addition, manufacturers should recognize the need to advise women who are pregnant or breast-feeding to consult a health professional about supplement use during the pre- and postnatal periods.

- The Commission urges FDA to use its authority under DSHEA to take swift enforcement action to address potential safety issues such as those posed recently by products containing ephedrine alkaloids. While it is expected that a responsible industry will avoid marketing unsafe products and that the industry will react promptly to remove products shown to be associated with significant or serious adverse reactions, in the final analysis there must be a strong and reliable enforcement system to back up the safety provisions of DSHEA. Failure by FDA to act when strong enforcement is needed undermines public confidence in the ability of not only the Federal government but also the dietary supplement industry to ensure safety and avoid harm to the public.

- FDA and, within many states, certain agencies have the responsibility in enforcement actions to develop, affirmatively, the evidence that shows an unreasonable risk from using existing supplements. FDA and appropriate agencies in some States may need additional resources to develop the necessary evidence, and these agencies need to be given the resources necessary to meet this important responsibility in the context of their overall public health priorities.

NLEA CLAIMS IN DIETARY SUPPLEMENT LABELING

In enacting DSHEA, Congress implicitly intended the Commission to determine whether any changes should be made in the requirements for health claims allowed by the Nutrition Labeling and Education Act of 1990 (NLEA) for dietary supplements. Current FDA rules require the same type of scientific evidence and support and the same process for approval of NLEA health claims on dietary supplements as are required for conventional foods.

GUIDANCE

- The process for approval of health claims as defined by NLEA should remain the same for dietary supplements and conventional foods.

- The standard of significant scientific agreement is appropriate and serves the public interest. The standard of significant agreement should not be so strictly interpreted as to require unanimous or near-unanimous support.

- FDA should ensure that broad input is obtained to ascertain the degree of scientific agreement that exists for a particular health claim. The use of appropriate panels of qualified scientists from outside of the agency is encouraged, and the views of other govern-

ment agencies should be given considerable weight in determining whether significant scientific agreement exists.

SCOPE OF STATEMENTS OF NUTRITIONAL SUPPORT

DSHEA allows dietary supplement labeling to bear statements of nutritional support without preauthorization by FDA. FDA has received notification letters regarding more than 1,000 such statements. Review of the letters and consideration of testimony presented to the Commission indicate that clarification of the scope of a nutritional support statement may be helpful to manufacturers.

GUIDANCE

- While the Commission recognizes that the context of a claim has to be considered on a case-by-case basis, the Commission proposes the following general guidelines:

  1. Statements of nutritional support should provide useful information to consumers about the intended use of a product.

  2. Statements of nutritional support should be supported by scientifically valid evidence substantiating that the statements are truthful and not misleading.

  3. Statements indicating the role of a nutrient or dietary ingredient in affecting the structure or function of humans may be made when the statements do not suggest disease prevention or treatment.

  4. Statements that mention a body system, organ, or function affected by the supplement using terms such as "stimulate," "maintain," "support," "regulate," or "promote" can be appropriate when the statements do not suggest disease prevention or treatment or use for a serious health condition that is beyond the ability of the consumer to evaluate.

  5. Statements should not be made for products to "restore" normal or "correct" abnormal function when the abnormality implies the presence of disease. An example might be a claim to "restore" normal blood pressure when the abnormality implies hypertension.

  6. Health claims are specifically defined under NLEA as statements that characterize the relationship between a nutrient or a food component and a specific disease or health-related condition. Statements of nutritional support should be distinct from NLEA health claims in that they do not state or imply a link between a supplement and prevention of a specific disease or health-related condition.

  7. Statements of nutritional support are not to be drug claims. They should not refer to specific diseases, disorders, or classes of diseases and should not use drug-related terms such as "diagnose," "treat," "prevent," "cure," or "mitigate."

- To the extent resources permit, FDA should continue to provide guidance to manufacturers by responding to letters of notification when the agency deems a proposed statement to be inappropriate as a statement of nutritional support.

NOTIFICATION LETTERS FOR STATEMENTS OF NUTRITIONAL SUPPORT

DSHEA requires that the manufacturer of a dietary supplement bearing a statement of nutritional support notify the Secretary no later than 30 days after the first marketing of the dietary supplement that such a statement is being made. The law also states that the manufacturer must have substantiation that such a statement is truthful and not misleading. The law does not provide that the evidence supporting a statement be reviewed by a regulatory agency prior to marketing of the product. The Commission agreed that guidelines are needed for standardizing the format and content of the notification letters.

GUIDANCE

- Notification letters should continue to be available in the public dockets.
- While the rulemaking process need not be reopened at this time, the Commission suggests that notification letters should include the following information:
  1. A statement that the purpose of the letter is to provide notification of a statement of nutritional support, including the exact wording that appears on the product label.
  2. The name, address, and telephone number of the manufacturer or distributor, and if available, the address and/or toll-free telephone number for consumer inquiries.
  3. The name and description of the product. The name of the product should include the trade name and the common or usual name. A copy of the product label or label copy, if labels are not yet printed, should be included.
  4. The identity of specific individual ingredients or combinations of ingredients for which the statement of nutritional support is made. For botanicals, ingredients should be identified by the common or usual name, the Latin binomial and its scientific authority, and the part(s) of the plant(s) used.
  5. A statement of intended use, including the recommended dosage and appropriate contraindications or warnings.
- In the notification letter or in a separate public notice manufacturers should provide statements of affirmation that they have substantiation for the statement of nutritional support and that the product does not represent a significant or unreasonable risk of illness under conditions of use recommended or suggested in labeling.
- Although some of the information indicated in the above guidelines is not required by FDA, the Commission suggests that manufacturers use these guidelines in preparing their notification letters.

SUBSTANTIATION FILES FOR STATEMENTS OF NUTRITIONAL SUPPORT

The Commission discussed how a statement of nutritional support can be adequately substantiated when it is based solely on historical use without supporting experimental or clinical data. At a minimum, such a statement of nutritional support would have to be carefully qualified to prevent

misleading consumers. Some Commission members believe that, in some circumstances, qualified statements based solely on historical use would be recognized by experts as being adequately substantiated. Other Commissioners believe that experts would want more scientific support for substantiation and especially so in the case of statements that have particular health importance. One Commissioner believes that scientific support for substantiation is needed for all statements with health importance.

DSHEA does not require that substantiation files be made available to FDA, and the majority of the Commission members are not recommending a change in legislation regarding the availability of these files. However, one member believes that FDA needs to be able to obtain access to the relevant files of a manufacturer to enforce effectively the manufacturer's obligation to substantiate statements of nutritional support and the obligation to substantiate safety. That member believes the authority to obtain access to substantiation files should be provided either through a rule similar to that proposed by FDA on nutrient content claims based on new technology for food ingredients or through legislative action.

The Commission provides the following guidance regarding the information a responsible manufacturer should have in a substantiation file for a statement of nutritional support and product safety. While the Commission's guidance on substantiation files is directed to statements of nutritional support and safety, other types of label statements may be made for dietary supplements. The Commission's guidance on substantiation file content may also be helpful in identifying what a responsible manufacturer would do for substantiation of other types of label statements.

GUIDANCE

- Substantiation files for statements of nutritional support and safety should include the following information:

  1. A copy of the notification letter.
  2. The identity and quantity of the dietary ingredient(s) that is (are) the subject of the statement of nutritional support.
  3. The key evidence to substantiate statements of nutritional support, including an interpretive summary of the evidence by an individual(s) or group qualified by training and experience.
  4. Evidence substantiating the safety of the product.
  5. Assurance that good manufacturing practices were followed in the manufacture of the product.
  6. The qualifications of the individual(s) or group who reviewed the evidence for safety and efficacy.

PUBLICATIONS EXEMPT FROM CLASSIFICATION AS LABELING WHEN USED IN CONNECTION WITH SALES

DSHEA directs the Commission to study and make recommendations on the regulation and evaluation of the use of literature in connection with the sale of dietary supplements. DSHEA exempts publications used in connection with the

sale of dietary supplements from being defined as labeling under certain conditions.

The Commission finds that the requirements of Section 5 of DSHEA may be difficult to apply, especially the requirement that an article provide (or be displayed with other publications that provide) a balanced view of the available information. Although this provision of DSHEA seems to have been written with scientific articles in mind, the term publication has a broader meaning. Also, the Commission recognizes that scientific articles may not be consumer friendly. Therefore, it appears likely that the bulk of the literature used in accordance with this provision may be in the form of publications specifically prepared for this purpose and written for the consumer.

GUIDANCE

- Because 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.

BOTANICAL PRODUCTS

Botanical products represent a major category of dietary supplements. The Commission observes that many botanical products sold as dietary supplements are used for prevention or treatment purposes. The scientists on the Commission noted that, in some cases, there is current scientific evidence to support such use. Most Commissioners believe that, in some cases, the consumer would be better served by clear information regarding preventive and therapeutic uses than by the limited statements of nutritional support permitted by DSHEA.

The Commission believes it would be logical and desirable for the U.S. over-the-counter (OTC) drug system to include preventive or therapeutic claims for botanicals, at least for those having a long history of use and general recognition of safety and efficacy based on adequate studies. The Commission also recognizes that there are botanical products used as remedies by some segments of the U.S. population that may not meet standards of evidence needed for OTC approval. In many other industrialized countries in the world, claims for botanical remedies and medicines are permitted, often with specific disclaimers, as a unique category of nonprescription products within the drug regulatory system. The types of disclaimers that are used and that may be needed are described in this report. The appropriate regulation of these products as remedies was considered to be outside of the Commission's charge and expertise but deserving of further study.

GUIDANCE

- More 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. The study should include the types of disclaimers that might apply and the appropriateness of such a system within the U.S. regulatory framework. Such a comprehensive study would go beyond the mandate of this Commission, which is limited to dietary supplement uses of these products.

- The Commission concluded that a comprehensive evaluation of regulatory systems used in other countries for botanical remedies is needed. Such an evaluation should consider the scope of products covered, the means of assuring safety and preventing deception, the effect of such systems on overall medical care, the definition of appropriate drug uses of products, and the appropriateness and applicability of the different types of disclaimers.

RECOMMENDATIONS

- The Commission recognizes that, under DSHEA, botanical products should continue to be marketed as dietary supplements when properly labeled.

- The Commission strongly recommends that FDA promptly establish a review panel for OTC claims for botanical products that are proposed by manufacturers for drug uses. The panel should have appropriate representation of experts on such products.

INFORMATION FOR CONSUMERS AND HEALTH PROFESSIONALS

DSHEA charged the Commission to determine how best to provide truthful, scientifically valid, and not misleading information to consumers so that they may make informed and appropriate health care choices for themselves and their families. The Commission believes additional research is needed on the type of label information that would be most useful to consumers. Other avenues of consumer information, including advice from health professionals, could be critical in assisting consumers in making appropriate decisions relative to supplement use.

GUIDANCE

- The Commission urges that dietary supplement labeling be evaluated in additional consumer research to determine whether consumers actually want and can utilize the information required by existing FDA regulations, by the requirements of DSHEA, and in the recommendations of this Commission. The Commission recognizes that consumer understanding of statements of nutritional support and health claims, as well as consumer perception of dietary supplement use based on literature at the point of sale, are important aspects of the use of information that require additional and continued assessment.

- The Commission believes that it is important for health and nutrition professionals to become more knowledgeable about all types of dietary supplements and to assist the consumer in making appropriate health care choices with respect to use of dietary supplements.

- The Commission urges manufacturers to make available publicly balanced and nonmisleading summaries of the evidence substantiating statements of nutritional support and product safety for the intended use at the stated dosage. The summary should not claim use for prevention or treatment of disease.

NEED FOR INDUSTRY EXPERT ADVICE ON SAFETY, LABEL STATEMENTS, AND CLAIMS

Dietary supplements are eligible for a variety of label statements and claims, each of which has unique regulatory requirements. Despite the diverse regulatory provisions, in a practical sense, the

messages conveyed to consumers by label statements of nutritional support, NLEA health claims, and OTC drug claims may be similar. The Commission believes that the dietary supplement industry and consumers would benefit from an increased level of scientific input into decisions regarding label statements for dietary supplements. An expert advisory panel on dietary supplements could be a valuable source of increased scientific input.

GUIDANCE

- The Commission recommends that the dietary supplement industry consider establishing an expert advisory committee on dietary supplements to provide scientific review of label statements and claims and to provide guidance to the industry regarding the safety, benefit, and appropriate labeling of specific products. Such a committee might be supported by one or more industry trade associations or might be established as an independent entity funded by extramural grants and/or fees for services.

RESEARCH ISSUES

DSHEA recognizes the importance of research in relation to dietary supplements. In establishing ODS within NIH, Congress wished to promote the scientific study of the benefits of dietary supplements. In considering the scientific evidence for the benefits of supplements, the Commission has made a number of observations relative to support of research on dietary supplements, the constraints to such research, and the incentives to the industry to invest in research in this area. The Federal government has been a major supporter of research on the health benefits of dietary supplements in some areas.

GUIDANCE

- The Commission believes that the public interest would be served by more research that assesses the relationships between dietary supplements and maintenance of health and/or prevention of disease.

- Incentive mechanisms should be developed to encourage the dietary supplement industry to invest in research on products offered to the consumer. FDA might consider a mechanism for review of research conducted to validate a statement of nutritional support such that the label disclaimer mandated by DSHEA could be modified or removed. More consideration is needed of ways to provide sufficient resources to FDA to make it possible for the agency to take on such an additional responsibility.

- The Commission recommends that Federal agencies continue to support research on the health benefits and safety of dietary supplements. Research should be expanded beyond the traditionally supported areas associated with vitamin and mineral supplements and include research on some of the more promising botanical products used as dietary supplements.

NIH OFFICE OF DIETARY SUPPLEMENTS

ODS is directed by the Act to conduct and coordinate scientific research relating to dietary supplements within NIH, to coordinate funding for such research, to collect and compile the results of scientific research

on dietary supplements, and to compile a database of such research. In addition, DSHEA directs ODS to ". . . serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director of the National Institutes of Health, the Director of the Centers for Disease Control and Prevention, and the Commissioner of Food and Drugs on issues . . ." relating to safety, benefits, and labeling of dietary supplements.

RECOMMENDATIONS

- ODS should strive to be an effective focal point for research on and understanding of the health effects of dietary supplements.
- ODS should place greater emphasis on its assigned role of advising other government agencies on a broad range of issues relating to dietary supplements.
- Congress should fund ODS at the level authorized by DSHEA.

ENDNOTE

1. The conclusions reported in the Executive Summary are supported by all members of the Commission, but there is a range of views on many of the issues discussed in the course of developing the findings, guidance, and recommendations. Divergent views of members of the Commission are found on pages 22, 25, 34, 36, 37, 39, 41, 43, 44, 47, 52, 55, 57, and 65 of the full report.

Chapter I

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

The Dietary Supplement Health and Education Act of 1994 (DSHEA, or the Act) (Appendix A) was enacted by Congress following public debate concerning the importance of dietary supplements in promoting health, the need for consumers to have access to current and accurate information about supplements, and controversy over the Food and Drug Administration's (FDA) regulatory approach to this product category. Signing DSHEA into law on October 25, 1994, President Clinton said:

> After several years of intense efforts, manufacturers, experts in nutrition, and legislators, acting in a conscientious alliance with consumers at the grassroots level, have moved successfully to bring common sense to the treatment of dietary supplements under regulation and law. (12)

The issues and debates that led to the passage of DSHEA have been discussed by a number of authors (7,88,90,122-125,136). Despite extensive public debate during the consideration of DSHEA, the official legislative history for the Act is limited (134) (see Chapter I Endnote).

DSHEA amends the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) to alter the way dietary supplements are regulated and labeled. This chapter provides an overview of the provisions of DSHEA and discusses the scope of this report.

MAJOR PROVISIONS

The following provisions of DSHEA are contained in the 13 sections of the Act (Appendix A).

1. Short Title, Reference, Table of Contents

Section 1 provides introductory information on the Act.

2. Congressional Findings

In Section 2 of DSHEA, Congress identifies 15 findings that established the rationale for DSHEA and that were meant to establish a conceptual framework for Federal regulatory policy regarding dietary supplements. Integral to the legislative changes was Congress' finding that "improving the health status of United States citizens ranks at the top of the national priorities of the Federal government."

3. Definitions

DSHEA for the first time defines dietary supplements by law. According to Section 3 of the Act, the term "dietary supplement":

> (1) means 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 supplement used 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).

According to DSHEA, a dietary supplement is a product that is labeled as a dietary supplement and is not represented for use as a conventional food or as a sole item of a meal or the diet.

The definition describes the variety of forms—capsule, powder, softgel, gelcap, tablet, liquid, or other form—in which these products can be ingested. This section of DSHEA specifically excludes dietary supplements from the definition of food additives in Section 409 of FDCA.

4. Safety of Dietary Supplements and Burden of Proof on FDA

DSHEA establishes separate standards for the safety of dietary supplements by describing the conditions under which dietary supplements are adulterated (unsafe). DSHEA applies the existing food standards for adulteration to dietary supplements but requires that such a determination be based on conditions of use recommended or suggested on the product label or, in the absence of such recommendations or suggestions, on ordinary conditions of use. For new dietary supplement ingredients (those marketed after October 15, 1994), products may be found to be adulterated if there is inadequate information to provide reasonable assurance that such an ingredient does not present a significant or unreasonable risk of illness or injury. In making such a determination, the burden of proof rests with the Federal government.

5. Dietary Supplement Claims

Under Section 5 of DSHEA, information about a dietary supplement, such as "a publication, including an article, a chapter in a book, or an official abstract of a peer-reviewed scientific publication that appears in an article and was prepared by the author or the editors of the publication, which is reprinted in its entirety, shall not be defined as labeling when used in connection with the sale of a dietary supplement" under certain conditions. Such a publication may be used in connection with the sale as long as it is truthful and not misleading; does not promote a particular manufacturer or brand of dietary supplement; presents a balanced view 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; and does not have appended to it any information by sticker or any other means. DSHEA also requires that when such third-party information is used in an establishment, it may not be displayed next to the supplement product but must be physically separated from the supplement.

6. Statements of Nutritional Support

Section 6 of DSHEA amends the Nutrition Labeling and Education Act of 1990 (NLEA) health claims provisions of FDCA to allow dietary supplement labels to carry

any of four types of statements of nutritional support without obtaining premarketing authorization from FDA. According to DSHEA, an acceptable statement of nutritional support is one that:

> . . . claims a benefit related to a classical nutrient deficiency and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure or function of humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient.

The legislation requires supplement manufacturers to have substantiation of such label claims and to notify FDA within 30 days after first marketing a product with a statement of nutritional support that such a statement is being made. The label must also carry a disclaimer "prominently displayed and in boldface type" that states:

> **This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

7. Dietary Supplement Ingredient Labeling and Nutrition Information Labeling

Section 7 of the Act imposes specific requirements for supplement labels. It specifies some circumstances under which dietary supplements would be misbranded. It provides that supplement labels must list the name and quantity of each ingredient. In the case of a proprietary blend, the "total quantity of all ingredients in the blend" may be provided.

DSHEA requires that, if a dietary supplement purports to conform to the standards of a particular compendium, it must actually do so. Official compendiums identified by FDCA or Federal regulations include the U.S. Pharmacopeia (USP) and the Food Chemicals Codex. Otherwise, the identity and quality of the product must be as stated on the label.

With respect to nutrition labeling, DSHEA permits the inclusion of substances without a Reference Daily Intake (RDI) or Daily Recommended Value (DRV). The nutrition label must include the quantity of each dietary ingredient per serving. The sources of the dietary ingredients may be stated on the nutrition label or in a separate ingredient list. In the case of botanicals, the label must indicate the part of the plant used in the ingredient. Nutrient content claims for dietary supplements can be based on RDIs or DRVs (98), but DSHEA specifically permits percentage level claims for ingredients where a Daily Value (DV) is not established.

8. New Dietary Ingredients

According to Section 8 of DSHEA, the term "new dietary ingredient" means "a dietary ingredient that was not marketed in the United States before October 15, 1994, and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."

This section describes the conditions under which a new dietary ingredient may be used in a dietary supplement. Unless an ingredient has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered," the manufacturer must provide FDA with information, based on a history of use or other evidence of safety, supporting the conclusion that the product "will reasonably be expected to be safe." This information must be provided at least 75 days before introducing a new dietary ingredient into interstate commerce.

9. Good Manufacturing Practices

In addition to laying the foundation for a regulatory framework for dietary supplements and their ingredients, DSHEA, under Section 9, provides FDA with the authority to promulgate good manufacturing practice (GMP) regulations for supplements. The Act stipulates that any new GMP regulations must be modeled after current food GMP regulations and go through the required rulemaking process, allowing for public notice and comment.

10. Conforming Amendments

Section 10 of DSHEA makes changes necessary for conformance in relevant sections of FDCA. It amends Section 201 of FDCA to provide that a food or dietary supplement that bears a statement of nutritional support in accordance with DSHEA is not a drug solely because the label or labeling bears such a statement. Section 301 of FDCA is modified to make the introduction of unsafe dietary supplements into interstate commerce a violation. Section 403 is amended to state that a dietary supplement is not misbranded solely because the label includes directions, conditions of use, or warnings.

11. Withdrawal of the Regulations and Notice

Under Section 11 of DSHEA, the Secretary of the Department of Health and Human Services (HHS) is directed to issue regulations rendering null and void the June 1993 Advance Notice of Proposed Rulemaking (ANPR) concerning dietary supplements (49-52).

12. Commission on Dietary Supplement Labels

Section 12 of DSHEA mandates the appointment by the President of a commission to study and make recommendations concerning label claims and statements for dietary supplements (pages 5 through 7 of this Chapter).

13. Office of Dietary Supplements

Section 13 of DSHEA establishes an Office of Dietary Supplements (ODS) within the National Institutes of Health (NIH). According to the Act, the purpose of ODS is to explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care and to promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions.

In fulfilling its duties, as specified in DSHEA, ODS is to:

- Conduct and coordinate scientific research within NIH relating to dietary supplements and the extent to which their use can limit or reduce the risk of diseases and conditions such as heart disease, cancer, birth defects, osteoporosis, cataracts, and prostatism;

- Collect and compile the results of scientific research relating to dietary supplements, including data from foreign sources or NIH's Office of Alternative Medicine;

- Serve as the principal advisor to the Secretary and the Assistant Secretary for Health and provide advice to the Directors of NIH and the Centers for Disease Control and Prevention (CDC), and the Commissioner of Food and Drugs on issues relating to dietary supplements;

- Compile a database on scientific research on dietary supplements and individual nutrients; and

- Coordinate NIH funding relating to dietary supplements.

THE COMMISSION ON DIETARY SUPPLEMENT LABELS

1. Charge

Section 12 of DSHEA establishes a Commission on Dietary Supplement Labels to develop recommendations for the regulation of label claims and statements for dietary supplements. Specifically, DSHEA directs the Commission to:

> . . . conduct a study on, and provide recommendations for, the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims.

The Act stipulates that, in making its recommendations, the Commission is to:

> . . . evaluate how best to provide truthful, scientifically valid, and not misleading information to consumers so that such consumers may make informed and appropriate health care choices for themselves and their families.

DSHEA authorizes the Commission to hold public hearings around the country to collect relevant testimony and evidence.

As mandated by DSHEA, the Commission's seven members are presidential appointees with expertise and experience in the manufacture, regulation, distribution, and use of dietary supplements. DSHEA stipulates that three of the members are to be qualified by scientific training and experience to evaluate the benefits to health of the use of dietary supplements and that one of those three is to have experience in pharmacognosy, medical botany, traditional herbal medicine, or other related sciences. The composition of the Commission meets these requirements.

DSHEA directs the Commission to prepare a final report to the President and Congress that includes the results of its study and any

findings or recommendations the Commission may choose to make, including recommendations for additional legislation.

The Act requires that the Secretary of HHS, within 90 days after the Commission issues its report, publish in the *Federal Register* a notice of any Commission recommendations proposing ". . . changes in regulations of the Secretary for the regulation of dietary supplements . . .", along with a notice of proposed rulemaking on such recommendations. DSHEA also stipulates that the rulemaking process must be completed within two years after the release of the report. It adds that, in the event that HHS fails to complete the rulemaking within two years, the regulations published by FDA on January 4, 1994, pertaining to the general requirements covering health claims for dietary supplements shall become null and void.

2. Charter

DSHEA mandates that the Commission be established as an independent agency within the executive branch. Because funds authorized by DSHEA were not appropriated, the Secretary of HHS allocated departmental funds to cover the operating costs of the Commission. Accordingly, the Commission was chartered by HHS under the Federal Advisory Committee Act, rather than formally established as an independent agency. Congressional sponsors of DSHEA were briefed regarding the reasons for this organizational arrangement.

The appointment of the Commission members was announced by the White House on October 2, 1995. Its charter (Appendix B) was approved by the Secretary on February 13, 1996.

In its discussions at the first and later meetings, the Commission agreed that the congressional mandate in Section 12 of DSHEA should be interpreted broadly. This approach is also indicated in its Charter. Thus, the Commission has considered conceptual issues related to the labeling of dietary supplements, including NLEA health claims and DSHEA statements of nutritional support, and the use of literature in connection with sales. Guidance has also been developed on associated issues, including the suggested information needed by manufacturers to substantiate statements of nutritional support. The safety of dietary supplements has been considered by the Commission because of the relevance of safety to the consumer's ability to make "informed and appropriate health care choices." In addition, the safety and labeling of a supplement are interrelated, because the label indications for use and any warning information affect how the supplement can be used appropriately. As mandated, the Commission also considered the procedures for evaluation of label statements and claims, and possible approaches to their implementation. The report also explores alternatives for manufacturers to make claims for botanical products that might otherwise be made only indirectly as statements of nutritional support. The Commission considered the need for consumer research as part of its evaluation of how to provide information to consumers to enable them to make informed and appropriate health care choices. Research issues have been addressed

because of their relevance to the mandate in Section 12 of DSHEA that directs the Commission to study how to provide consumers with information that is scientifically valid. The Commission concludes that the scope of matters covered in this report, as well as the guidance and recommendations meet the Commission's obligation to report to the President, Congress, and the Secretary, as specified in DSHEA and in the Charter.

3. Procedures

Significant events related to activities of the Commission are highlighted in Figure 1. The Commission procedures are described in Appendix C. Individuals and organizations who testified before the Commission at the public hearings or who otherwise provided formal oral or written comments at the request of the Commission through June 24, 1997, are identified in Appendices D and E.

4. Report

Reflecting the charge to the Commission in DSHEA and in the Commission's charter, this report is addressed to the President, Congress, and the Secretary of HHS. Although many aspects of the report will be of interest to other Federal and State agencies, the general public, and the dietary supplement industry, the primary intent is to provide guidance to those who are responsible for the interpretation and the implementation of DSHEA. The organization of the report is as follows:

- Chapter I summarizes the major provisions of DSHEA and the charge to the Commission. A copy of the legislation and Commission charter are Appendices A and B, respectively.

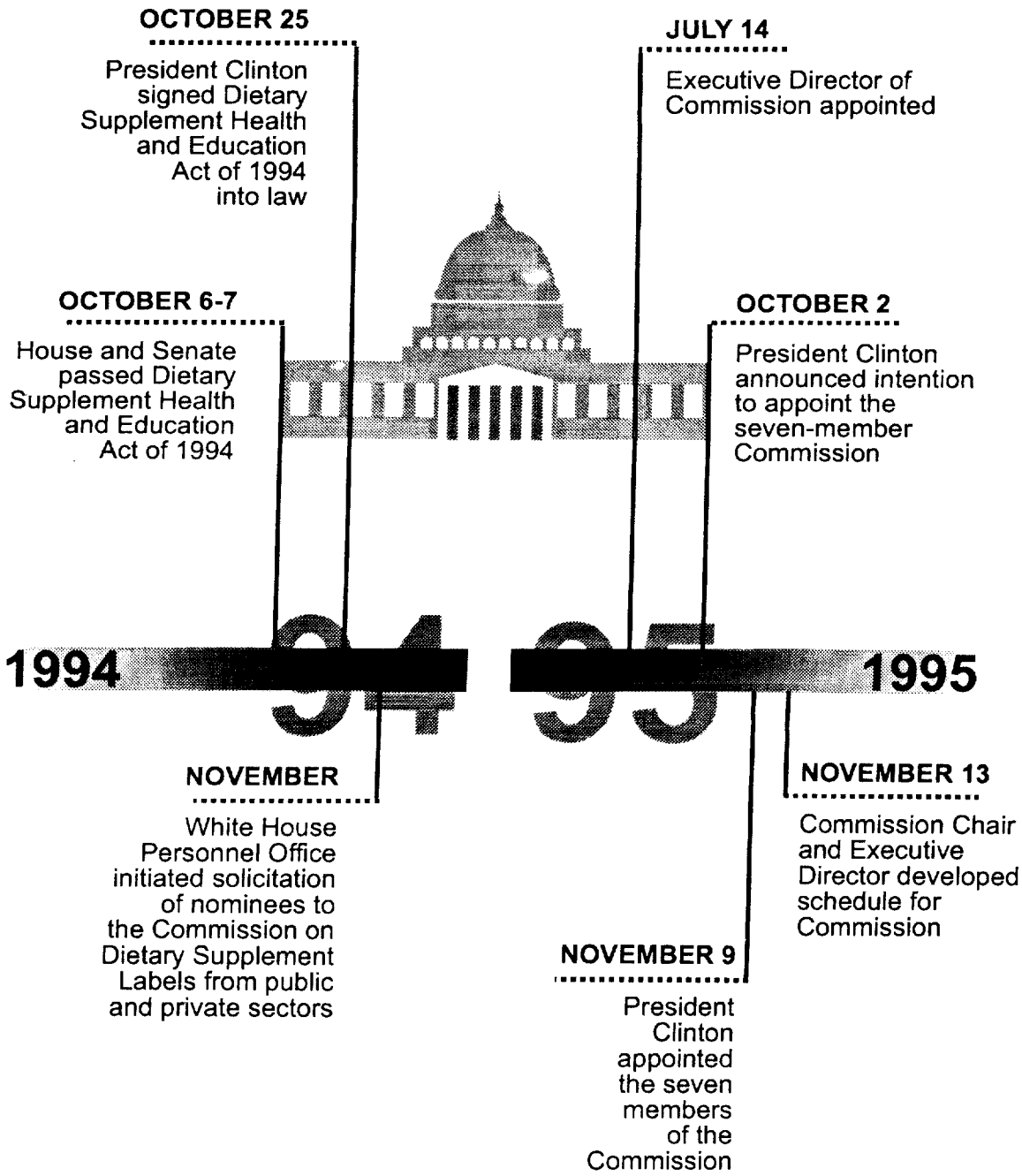
- Chapter II reviews the legislative and regulatory context surrounding DSHEA. It also summarizes key background information related to consumer use of dietary supplements and the supplement industry.

- Chapter III discusses the major findings, guidance, and recommendations developed by the Commission. Topics include the safety of dietary supplements; general information on dietary supplement labels; claims on dietary supplement labels; statements of nutritional support on dietary supplement labels; substantiation of the information and statements on labels; publications used in conjunction with sales that are exempt from classification as labeling; and regulation of botanical products when manufacturers wish to make claims for prevention and treatment of disease.

- Chapter IV presents findings, guidance, and recommendations related to other issues identified by the Commission during its deliberations. Topics include information the public needs to make informed health care choices and how best to make such information available to consumers. The Commission considered mechanisms to improve the ability of manufacturers of dietary supplements and Federal and State regulators to evaluate the safety of products and to support the validity of claims and statements made on the labels of these products. Enforcement issues and research needs related to

Figure 1.

Commission on Dietary Supplement Labels



Chronology: October 1994 to November 1997

FEBRUARY 2

Commission Chair and Executive Director developed schedule of meetings, procedure for activities. Executive Director arranged meetings between Commission Chair and members. Meetings held

MARCH 8

Second meeting: Salt Lake City, Utah

JUNE 6

Fourth meeting: Orlando, Florida

JULY 9

Interested Congressional staff briefed at their request on progress of the Commission through June 30, 1996

MARCH 4

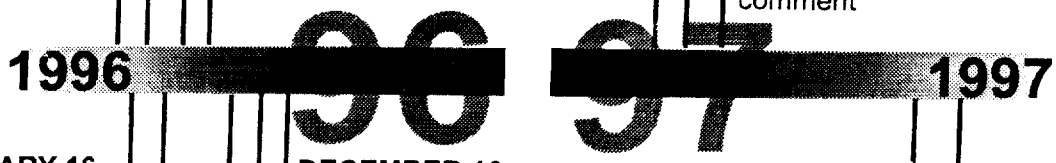
Eighth meeting: Baltimore, Maryland

JUNE 20

Interested Congressional Staff briefed on reasons for release of and contents of Commission's draft report

JUNE 24

Draft report of the Commission released for public comment



FEBRUARY 16

Commission held first information-gathering meeting in Washington, DC

APRIL 26

Third meeting: San Francisco, California

DECEMBER 16

Seventh meeting: Washington, DC

OCTOBER 24-25

Sixth meeting: Washington, DC

SEPTEMBER 19-20

Fifth meeting: Reston, Virginia

AUGUST 14-15

Ninth meeting held to review comments and suggestions received from public on draft report, Washington, DC

NOVEMBER

Final Report of the Commission delivered to the President, Congress, and the Secretary of the Department of Health and Human Services. Final report released to the public

consumer use of dietary supplements are also discussed.

The findings, guidance, and recommendations of the Commission are presented in each section of Chapters III and IV.

- **FINDINGS** are the conclusions reached by the Commission during its deliberations and are based on the information and data received and reviewed by the Commission.

- **GUIDANCE** represents advice to specific agencies, groups, or individuals. Guidance should be considered by the identified recipients as they develop or implement activities related to the availability of dietary supplements in the marketplace.

- **RECOMMENDATIONS** are indicated as such and identify the intended recipients. Recommendations that call for consideration of changes in existing regulations, development of new regulations, or legislative action are so indicated.

The Commission on Dietary Supplement Labels was aware of the public interest in its work and desired to receive public comment on its draft report. Therefore, a draft report was released for public comment on June 24, 1997. While comments were requested by August 4, 1997, the Commission accepted submissions through September 15, 1997. Approximately 400 comments on the draft report were received from the public and evaluated before completion of this final report.

ENDNOTE

1. Statement of Agreement: "This statement comprises the entire legislative history for the Dietary Supplement Health and Education Act of 1994, S.784. It is the intent of the chief sponsors of the bill (Senators Hatch, Harkin and Kennedy, and Congressmen Richardson, Bliley, Moorhead, Gallegly, Dingell, Waxman) that no other reports or statements be considered as legislative history for the bill.

    1. The bill does not affect the Food and Drug Administration's existing authority under the Federal Food, Drug and Cosmetic Actto prohibit the import or sale of any product marketed as a drug in a foreign country.
    2. In section 201(ff)(3)(B)(ii), added by section 3 of the bill, the term 'substantial clinical investigations' does not include compassionate investigational new drug applications or an investigational new drug application submitted by a physician for a single patient.
    3. Section 403B, added by section 5, does not apply to a summary of a publication other than an official abstract of a peer-reviewed scientific publication.
    4. Section 403(r)(6)(A), added by section 6, does not permit premarket approval or require premarket review by the FDA of any statement permitted under that provision.
    5. In section 413(a)(1), added by section 8, the term 'chemically altered' does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, powder, or solid in suspension."

Chapter II

BACKGROUND ON DIETARY SUPPLEMENTS

PERTINENT LEGISLATION AND REGULATIONS

The Federal Food, Drug, and Cosmetic Act of 1938, as amended by DSHEA, is the principal law governing dietary supplements. Under FDCA, FDA has jurisdiction over product safety and labeling issues. This chapter provides background on FDA's regulation of dietary supplements.

Dietary supplements are also subject to other Federal laws. The most relevant of these, the Federal Trade Commission Act (5 U.S.C. 45), provides the Federal Trade Commission (FTC) with the authority to regulate advertisements for all consumer products, including supplements. Relevant FTC policies are discussed in Chapter III.

Currently, Congress is considering changes in some provisions related to dietary supplements, such as health claims under NLEA; however, this report deals with FDCA as amended by DSHEA, as it existed on September 2, 1997.

1. 1906 Through 1994

The legislative and regulatory history concerning dietary supplements since 1906 is extensive. A brief synopsis of events that led up to the passage of NLEA in 1990 and DSHEA in 1994 may be instructive.

The Pure Food and Drug Act of 1906 dealt with unsafe foods, unregulated elixirs, and misbranded products. The 1938 FDCA established a category of foods for special dietary use and required the labels of such foods to provide information on their vitamin, mineral, or other dietary properties.

In 1941, FDA established regulations governing the labeling of vitamin and mineral supplements and other foods for special dietary use containing added vitamins and/or minerals (66). The minimum daily requirement (MDR) was established as the reference standard for expressing the daily need for a vitamin or mineral. The 1941 regulations placed no restriction on the amount or variety of nutrients that could be included in a supplement or a fortified food.

From 1962 to 1976, FDA attempted to revise these regulations to replace the MDR with a new reference standard—the U.S. Recommended Daily Allowance (U.S. RDA)—and to establish a standard of identity restricting the amounts and combinations of vitamins and minerals that could be marketed as dietary supplements. FDA also proposed to require a label disclaimer on vitamin or mineral supplements stating that:

> Vitamins and minerals are supplied in abundant amounts by commonly available foods. Except for persons with special medical needs, there is no scientific basis for recommending routine use of dietary supplements (65).

Two years of hearings, from 1968 to 1970, led FDA to abandon the proposed disclaimer, but the bulk of the proposal remained intact. Quantities of vitamins and minerals were to be limited generally to 150

percent of the U.S. RDA, and only a few combinations of vitamins and minerals were to be allowed. Products with higher levels of nutrients or different combinations of nutrients would be subject to review by an expert advisory committee as part of FDA's over-the-counter (OTC) drug review.

These special dietary use regulations and the dietary supplement standards of identity were finalized in 1973, overturned and remanded to the agency by the courts in 1974, revised and reproposed in 1975, largely invalidated by legislation early in 1976, revised and reissued late in 1976, again overturned by the courts in 1978, and ultimately withdrawn by FDA in 1979 (62,64,93,94). When FDA withdrew those regulations, it withdrew them in their entirety—the basic labeling provisions that had been upheld as well as the provisions that had been overturned by the courts.

In 1976, Congress passed vitamin and mineral legislation (the Rogers/Proxmire amendment) that prohibited FDA from classifying vitamin and mineral supplements as drugs based solely on their combinations or potency (unless drug claims were made), from establishing a standard of identity for these products, and from limiting the quantity or combination of nutrients in them, except for reasons of safety. The 1976 legislation also incorporated FDA's 1941 definition of special dietary use into FDCA.

Since the 1973 regulations were stayed pending judicial review and ultimately withdrawn, no formal labeling regulations for dietary supplements were in effect from 1973 to 1994, but most manufacturers adopted the format set forth in the 1973 regulations. FDA finalized nutrition labeling regulations for dietary supplements in January 1994 (45,46,47), but these labeling provisions were amended by DSHEA in October 1994. Revised nutrition labeling regulations for dietary supplements were proposed in December 1995 (40-43). The final rules were published on September 23, 1997, as this report was being completed (26-31).

In 1990, Congress passed landmark legislation (NLEA) that affected nutrition labeling of food and dietary supplements. NLEA mandated that virtually all food labels not only must contain specific information on nutrient content but also could make claims relating specific nutrients to diseases or disorders. Such "health claims" were to be based on significant scientific agreement on the validity of the claimed relationship between the nutrient and the disease. In developing the process for approval of health claims, FDA established standards for the types and levels of evidence necessary to meet the criteria for approval of health claims.

NLEA directed FDA to consider a different approval procedure and scientific evaluation standard for health claims made about dietary supplements than those used for foods. NLEA also directed FDA to consider a list of 10 potential health claims for specific nutrient/disease relationships.

In the process of establishing mandatory nutrition labeling requirements (55), FDA proposed to replace the U.S. RDAs with new RDIs based on "mean requirements" for vitamins and minerals, which would have had the effect of lowering the daily reference amounts for many nutrients. FDA also proposed some basic requirements for

health claims that appeared to disallow health claims for many dietary supplements.

In 1992, Congress passed the Dietary Supplement Act which essentially prohibited the implementation of NLEA with respect to dietary supplements except for the approved health claims. This legislation, in effect, established a moratorium on the labeling of dietary supplements to permit Congress and FDA time to consider various related issues. It also required that regulations pursuant to NLEA regarding dietary supplements be reproposed.

On June 18, 1993, FDA published a comprehensive ANPR concerning the regulation of dietary supplements (52). This ANPR referenced a number of factors, including increased consumer use of dietary supplements, an internal FDA three-year review of possible regulatory approaches, occurrence of eosinophilia myalgia syndrome as a consequence of L-tryptophan use, and reports of serious illness as a result of using certain botanical supplements.

The 1993 ANPR suggested, among other provisions, that vitamins and minerals be limited to low multiples of the RDIs, that some botanical products were inherently drugs and not dietary supplements, and that many dietary supplements, including amino acids, were unapproved food additives. The ANPR elicited considerable protest from the public and the dietary supplement industry because FDA appeared to be reproposing regulatory provisions withdrawn or struck down by court actions in previous years. The ANPR was a significant motivating factor in industry and congressional efforts to develop and secure passage of DSHEA in 1994.

2. 1994 to the Present

Since the passage of DSHEA, both Congress and FDA have put forth related legislative and regulatory initiatives. In 1995, the Food and Dietary Supplement Consumer Act (HR 1951) was introduced in the U.S. House of Representatives. The bill would have repealed certain provisions of NLEA and DSHEA and would have established a single claims category that would encompass statements that currently fall under the classification of health claims, as well as statements of nutritional support. No action on HR 1951 was taken by either House of Congress. In 1997, the Food and Drug Administration Modernization and Accountability Act (S 830) was introduced into the Senate and the Food and Nutrition Information Reform Act (HR 2469) was introduced into the House of Representatives. Both 1997 bills include changes to procedures for the authorization of health claims by allowing other Federal agencies to determine whether significant scientific agreement exists. Action on both bills is pending. FDA has advanced various regulatory actions resulting from the passage of DSHEA (Table 1).

CONSUMER USE

President Clinton attributed the move toward legislative and regulatory reform for dietary supplements to a growing interest on the part of the American public in the use of dietary supplements. In signing DSHEA into law, he stated:

> . . . in an era of greater consciousness among people about the impact of what they eat on how they live, indeed, how long they live, it is

Table 1

Regulations Related to Dietary Supplements Since Passage of DSHEA

Date	Action	Citation
April 1995	Pursuant to DSHEA's exclusion of dietary ingredients of dietary supplements from food additive regulation, FDA withdrew its relevant "regulatory guidance."	*Federal Register*, Vol. 60, April 19, 1995, p. 19597
December 1995	FDA issued a proposed rule to increase flexibility of label claim language and refine other NLEA provisions in response to citizen petitions.	*Federal Register*, Vol. 60, December 21, 1995, pp. 66206-66227.
December 1995	FDA issued a proposed rule concerning food label requirements for nutrient content claims, health claims and statements of nutritional support for dietary supplements.	*Federal Register*, Vol. 60, December 28, 1995, pp. 67176-67184
December 1995	FDA issued a proposed rule concerning the definition for "high potency" claims for dietary supplements and the definition of "antioxidant" when used in nutrient content claims of dietary supplements.	*Federal Register*, Vol. 60, December 28, 1995, pp. 67184-67194
December 1995	FDA issued proposed rules governing the labeling of dietary supplements with respect to the statement of identity, nutrition labeling and ingredient labeling.	*Federal Register*, Vol. 60, December 28, 1995, pp. 67194-67224
March 1996	FDA issued a final rule on health claims and label statements concerning folate and neural tube defects.	*Federal Register*, Vol. 61, March 5, 1996, pp. 8752-8781
April 1996	FDA declared that DSHEA does not apply to dietary supplements intended for use in animals other than humans.	*Federal Register*, Vol. 61, April 22, 1996, pp. 17706-17708
August 1996	FDA issued a final rule providing for a health claim for sugar alcohols and nonpromotion of dental caries. The health claim may be used with eligible foods and dietary supplements.	*Federal Register*, Vol. 61, August 23, 1996, pp. 43433-43447
September 1996	FDA issued a proposed rule spelling out the procedure by which companies would notify FDA of dietary supple-ment products bearing statements of nutritional support.	*Federal Register*, Vol. 61, September 27, 1996, pp. 50771-50774
September 1996	In response to DSHEA's new dietary ingredient provisions, FDA published a proposed rule that would establish the pro-cedure for premarket notification of a new dietary ingredient.	*Federal Register*, Vol. 61, September 27, 1996, pp. 50774-50778
January 1997	FDA issued a final rule on required warning statements and packaging requirements for iron-containing dietary supplements and drugs.	*Federal Register*, Vol. 62, January 15, 1997, pp. 2218-2250
January 1997 March 1997	FDA issued a final rule providing for a health claim for soluble fiber from whole oats and reduced risk of coronary heart disease. The health claim may be used with eligible foods and dietary supplements. FDA amended the final rule in March 1997 to clarify the regulation.	*Federal Register*, Vol. 62, January 23, 1997, pp. 3584-3601 *Federal Register*, Vol. 62, March 31, 1997, pp. 15343-15344

Table 1 (Continued)

DATE	ACTION	CITATION
February 1997	Acting on DSHEA's provision that HHS may prescribe good manufacturing practices for dietary supplements, FDA issued an advance notice of proposed rulemaking in February 1997 announcing that it was considering whether to institute rule-making to develop current good manufacturing practice regulations for dietary supplements and dietary supplement ingredients.	*Federal Register*, Vol. 62, February 6, 1997, pp. 5700-5709
May 1997	FDA proposed to extend the health claim on the association of soluble fiber and reduced risk of coronary heart disease to include soluble fiber from psyllium husks.	*Federal Register*, Vol. 62, May 22, 1997, pp. 28234-28245
June 1997	FDA proposed rules on dietary supplements containing ephedrine alkaloids.	*Federal Register*, Vol. 62, June 4, 1997, pp. 30678-30724
July 1997	FDA published a final rule in which the agency did not modify the definition of "imminent hazard to the public health" in 21 CFR 2.5.	*Federal Register*, Vol. 62, July 23, 1997, pp. 39439-39440
September 1997	FDA issued a final rule amending food labeling regulations concerning statements of identity and nutrition labeling of dietary supplements. The rule also revokes Compliance Policy Guide 530.400 (CPG 7121.02). Effective date: March 23, 1999.	*Federal Register*, Vol. 62, September 23, 1997, pp. 49826-49858
September 1997	FDA published a final rule amending food labeling requirements for nutrient content claims, health claims, and statements of nutritional support for dietary supplements. Effective date: March 23, 1999.	*Federal Register*, Vol. 62, September 23, 1997, pp. 49859-49868
September 1997	FDA published a final rule amending the definition of "high potency" claims for dietary supplements and amending the definition of "antioxidant" for use in nutrient content claims for dietary supplements. Effective date: March 23, 1999.	*Federal Register*, Vol. 62, September 23, 1997, pp.49868-49881
September 1997	FDA responded to comments on a final rule establishing a uniform date of January 1, 2000, for compliance with food regulations issued between January 1, 1997, and December 31, 1998. Effective date: December 27, 1996.	*Federal Register*, Vol. 62, September 23, 1997, pp. 49881-49883
September 1997	FDA issued a final rule on notification procedures for statements on dietary supplements. Effective date: October 23, 1997.	*Federal Register*, Vol. 62, September 23, 1997, pp. 49883-49886.
September 1997	FDA issued a final rule on premarket notification for new dietary ingredients. Effective date: October 23, 1997.	*Federal Register*, Vol. 62, September 23, 1997, pp. 49886-49892.

> appropriate that we have finally reformed the way the Government treats consumers and these supplements in a way that encourages good health (12).

In enacting DSHEA, Congress estimated that "almost 50 percent of the 260,000,000 Americans regularly consume dietary supplements of vitamins, minerals, or botanicals as a means of improving their nutrition" (Appendix A). In that same year, the United States was expected to spend more than $1 trillion on health care—about 12 percent of the country's gross national product. Congressional findings reported in DSHEA state that "preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures." The Act adds that "consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements."

A variety of sources confirm the congressional finding that a significant portion of the U.S. population uses dietary supplements. Data from a large probability sample of the U.S. population from the third National Health and Nutrition Examination Survey for 1988-94 indicated that a substantial percentage of the U.S. population used dietary supplements (defined as including vitamins, minerals, amino acids, botanicals, and other products) (142). Data from this survey suggest that for the total U.S. population, the prevalence of dietary supplement use by children 3-5 years of age is about 48 percent, while the prevalence of use by adults 20 years of age to over 80 years of age ranges from about 36 percent to 51 percent. Dietary supplement usage appears to differ by age, with increasing use by older adults (35.8 percent for ages 20-29 years, 46.2 percent for ages 50-59 years, and 50.6 percent for ages 80 years and older). In the total sample surveyed, the prevalence of supplement use by women of all ages and ethnicities was higher than that by men (42.9 percent versus 34.5 percent on an age-adjusted basis, respectively).

Similarly, use of dietary supplements by all age groups appears to be greater in non-Hispanic whites (41.6 percent) than in non-Hispanic blacks (30.2 percent) or Mexican-Americans (30.5 percent). In addition, for all groups, the higher the income, the greater the use of dietary supplements. Further, the prevalence of dietary supplement use increases with years of education in all groups.

According to National Health Interview Surveys from 1987 to 1992, regular daily use of certain specified supplements (multivitamins, vitamin A, vitamin C, vitamin E, or calcium) remained at about 24 percent. In both 1987 and 1992, 9 percent of the population reported daily intake of more than one type of the specified supplements, 5 percent took two types of supplements, and 0.3 percent took all five of the types of supplements included in the survey. A comparison of the 1987 and 1992 National Health Interview Survey results indicates a 4.9 percent decline in the total population reporting use of any vitamin or mineral supplement (51.1 percent versus 46.2 percent) (130).

According to data collected by Multi-Sponsor Surveys, Inc., presented during a Commission hearing by Hoffman-La Roche Inc., between 30 and 40 percent of the U.S. population use vitamin and mineral supplements (72). In 1995, 38 percent of adults used vitamin and mineral supplements. This represents approximately 73 million adults, an increase of some 13 million users since 1991. These data suggest that about 33 percent of adults, or 63 million people, take supplements every day or nearly every day. Of these, approximately 49 percent consume one vitamin and mineral supplement per day that supplies the U.S. RDA. Another 27 percent take two or three supplements per day, usually a multivitamin plus calcium, vitamin C, or vitamin E. One adult user in ten takes six or more supplement products of any kind per day (72).

While the usage of vitamin and mineral supplements is well documented, collection of data on the use of other categories of supplements (e.g., botanicals and amino acids) began only recently. A survey of 1,945 individuals conducted by FDA in 1994 indicated that 51 percent of adults 18 years of age and older used some type of supplement (127). Of those supplement users, 73 percent were considered to be "light users" (used one or two supplements) and 27 percent "heavy users" (used three or more supplements), 10 percent were amino acid users, and 16 percent were botanical product users. In 1995, FDA conducted a similar survey and found an increase in the use of some supplements. Of 1,001 adults queried, the survey indicated that 55 percent used some type of supplement. Of those, 72 percent were light users, 28 percent were heavy users, 16 percent used amino acids, and 22 percent used botanical products (127).

According to a telephone survey of 1,000 individuals conducted by Applied Biometrics, some of the reasons reported by consumers as to why they take supplements are to prevent disease or boost immunity, to increase energy, to improve fitness, to increase alertness or mental activity, to reduce stress, and to treat a medical problem (131).

The sources cited above vary in their estimates but are consistent in revealing that a substantial percentage of the U.S. population takes dietary supplements of some kind.

CHARACTERISTICS OF THE U.S. DIETARY SUPPLEMENT INDUSTRY

According to congressional estimates at the time DSHEA was enacted in 1994, some 600 dietary supplement manufacturers in the United States were producing approximately 4,000 products, with total annual sales of such products reaching at least $4 billion (Appendix A).

The supplement industry in the United States is represented, for the most part, by five trade organizations. The American Herbal Products Association represents some 200 companies and individuals who grow, import, process, market, and/or manufacture botanical products (3,87). The Council for Responsible Nutrition represents over 80 companies in the dietary supplement industry (14). The National

Nutritional Foods Association has some 4,000 members representing manufacturers, wholesalers, distributors, and retailers of natural products (75). The Utah Natural Products Alliance represents the interests of dietary supplement companies in Utah, which generate sales in excess of $1 billion per year (77). The Nonprescription Drug Manufacturers Association is composed of manufacturers and distributors of nonprescription drugs and combination or single-ingredient vitamin and mineral products (143).

A number of factors, including rapid growth of the dietary supplement industry, an increase in consumer interest in such products, particularly botanical products, and the variety of avenues through which consumers may obtain supplements, have hampered efforts to collect accurate data on the sale and use of such products.

A review of the global dietary supplement industry (vitamins and minerals, herbs and botanicals, sports nutrition) conducted by the *Nutrition Business Journal* and its affiliate EuroConsult, Inc., indicated that the worldwide dietary supplement industry registered $28.2 billion in consumer sales in 1995 (6). Of that total, Europe accounted for $9.5 billion, the United States $8.2 billion, Japan $5.2 billion, other Asian countries $3.2 billion, and Canada $0.7 billion. In the United States, sales of vitamins and minerals alone were $4.8 billion in 1995, followed by botanical products at $2.5 billion and sports nutrition supplements at $0.8 billion. However, in Europe, consumer sales were highest for botanicals ($6 billion), followed by vitamins and minerals ($3.1 billion) and sports nutrition products ($0.4 billion) (6).

Vitamin and mineral products include single-nutrient supplements as well as a multiplicity of combination products. Within the vitamin and mineral category, the top six product types are multivitamins (with or without minerals), vitamin E, vitamin C, iron, calcium, and B vitamins (15). Multivitamin preparations constitute about 31 percent of all retail sales in the vitamin and mineral category. These data are consistent with information on extent of use by adults presented in testimony to the Commission (72).

Some 1,500 to 1,800 botanicals are sold in the United States as dietary supplements or ethnic traditional medicines (77). According to a survey of the U.S. botanical supplements market, the top 10 botanical products sold at selected U.S. health food stores in 1995 were echinacea, garlic, goldenseal, ginseng, ginkgo, saw palmetto, aloe, ma huang, Siberian ginseng, and cranberry (9).

The dietary supplement industry also represents a major segment of the U.S. import and export trade market. According to 1994 trade data from the Bureau of Census, U.S. Department of Commerce, "medicinal herbs" imported into the United States included licorice roots, oriental ginseng roots (cultivated and wild), mint leaves, plants and plant parts used as herbal teas, ephedra powder, and substances used principally to promote healing. "Medicinal herbs" exported from the United States include American ginseng, echinacea, ginkgo, goldenseal, peppermint, and saw palmetto (9).

Chapter III

MAJOR ISSUES AND RECOMMENDATIONS RELATED TO LABELING OF DIETARY SUPPLEMENTS

The Commission's charge to address major issues relative to the labeling of dietary supplements was reiterated in public testimony presented at meetings held throughout the country and in written submissions to the Commission. DSHEA mandated that the Commission review and make recommendations on label claims, substantiation of claims, and literature available to the public. In addition, the Commission identified issues related to label claims for botanical supplements. This chapter outlines the Commission's deliberations and findings on these issues and provides guidance and recommendations.

SAFETY OF DIETARY SUPPLEMENTS

Because of the concerns relative to safety issues expressed in the public submissions, the Commission included safety as a major topic in its deliberations.

1. DSHEA Provisions on Safety

In reflecting on issues associated with safety, during the creation and passage of DSHEA in 1994, Congress reached the following conclusions:

- Almost 50 percent of the U.S. population consume dietary supplements;
- Dietary supplements are safe within a broad range of intake, and safety problems of supplements are relatively rare; and
- Although the Federal government should take swift action against products that are unsafe or adulterated, it should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers.

FDCA defines the conditions under which a food may be considered "adulterated" (i.e., unsafe) (Section 402(a)). DSHEA subjects dietary supplements to the original adulteration provisions governing food and adds additional conditions (Section 402(f)). Specifically, DSHEA indicates that a dietary supplement is adulterated:

> If it is a dietary supplement or contains a dietary ingredient that—
> A) presents a significant or unreasonable risk of illness or injury under—
> (i) conditions of use recommended or suggested in labeling, or
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;
> B) is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury;
> C) the Secretary declares to pose an imminent hazard to public health or safety, except that the authority to make such declaration shall not be delegated and the Secretary shall promptly after such a

declaration initiate a proceeding in accordance with Sections 554 and 556 of Title 5, United States Code, to affirm or withdraw the declaration; or

D) is or contains a dietary ingredient that renders it adulterated under paragraph (a)(1) under the conditions of use recommended or suggested in the labeling of such dietary supplement.

Under the authority created by DSHEA, FDA can bring enforcement action against an existing supplement if it presents an unreasonable or significant risk of harm. While not yet judicially interpreted, in many respects the test for safety under the new provisions of DSHEA is similar to the test enunciated by the Supreme Court in a landmark 1914 case concerning addition of poisonous and deleterious substances in food (138). Under this case, safety is to be related to the quantity of a substance and the risk when the facts are reasonably considered.

Under DSHEA, the safety of dietary supplements is determined based on the conditions of use recommended or suggested in the labeling (Appendix A). DSHEA exempts dietary supplement ingredients from the food additive provisions of FDCA and establishes conditions for the marketing of new dietary ingredients not marketed in the United States as dietary supplements prior to October 15, 1994. The new provisions have yet to be tested in court.

DSHEA stipulates that a dietary supplement that contains a new dietary ingredient:

. . . shall be deemed adulterated under Section 402(f) unless it meets one of the following requirements:

(1) The dietary supplement contains only dietary ingredients which 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.

(2) There is 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 of the dietary ingredient or dietary supplement provides the Secretary 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 approval is not required with regard to adequacy of substantiation. If FDA objects to marketing of the ingredient, the agency must initiate enforcement action. New uses of an existing supplement, or an increase in the recommended dose, does not make a supplement "new" for purposes of the substantiation requirement.

Under DSHEA, FDA must show affirmatively, in court, that an unreasonable risk is posed by consumption of a dietary supplement. The agency need not show that injury has occurred, only that a reasonable possibility of harm exists. Under provisions in DSHEA, before reporting a violation to the U.S. attorney for civil enforcement action, FDA must provide 10 days' notice to the affected party as well as an opportunity for the affected party to present views relative to the alleged violation, unless an imminent hazard to public health or safety exists.

2. Good Manufacturing Practices

Dietary supplements are considered foods and are subject to requirements of "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food" (108). These regulations provide guidelines with regard to maintenance of buildings and facilities, requirements for food handlers, and cleanliness of equipment, as well as procedural requirements for maintaining safety during the production and processing of foods.

DSHEA specifically authorizes FDA to establish dietary supplement GMPs. Recognizing this perceived need, major industry groups in 1995 jointly prepared extensive revisions to the food GMPs that address aspects of manufacturing practices used by the dietary supplement industry. These proposed GMPs for dietary supplements were submitted to FDA and subsequently published as an ANPR in the *Federal Register* (32). The Commission supports these efforts of FDA and the industry to develop appropriate GMPs for dietary supplements.

3. Safety of Botanicals

The Commission recognizes that most botanical products taken as dietary supplements in the United States are safe when used as directed on labels. There are relatively few reports in the scientific literature that indicate potential or actual toxicity following the use of these products. When such reports are found, they often are single-case reports involving an allergenic reaction or toxicity due to improper labeling, or adulteration, or an idiosyncratic reaction even though the product was taken under proper conditions of use and within reasonable dose limitations (23).

However, there are exceptions in which the use of botanical products has raised concerns about safety. Botanical products such as comfrey root (*Symphytum officinale* L.), which contains hepatotoxic pyrrolizidine alkaloids (86), pose a potential health hazard. There also has been consumer concern and State regulatory response over frequent or protracted use of foods or dietary supplements that contain senna (*Cassia senna* L.) (73). In countries other than the United States, some plants containing known carcinogens or tumor promoters are used medicinally (22,90), even though other well-known toxic plants usually are not consumed (18-20).

4. Federal Enforcement Issues

Section 301 of FDCA provides for broad enforcement powers in regard to adulteration and misbranding of foods, including dietary supplements. The Commission recognizes the importance of having adequate

and timely enforcement procedures for products marketed as dietary supplements that are not safe or have a high potential for abuse while maintaining a regulatory climate that preserves the availability of safe products. The apparent safety of the majority of products now marketed as dietary supplements actually increases the importance of having adequate enforcement mechanisms, because consumers may then assume that a wide margin of safety automatically applies to any product classified as a dietary supplement.

Recent events associated with products containing ephedrine alkaloids illustrate these safety and enforcement concerns. During Commission hearings, some presenters expressed concern about the safety of products containing ephedrine alkaloids. Evidence that such products were implicated in numerous adverse reactions, including fatalities, throughout the country was presented. However, FDA has only recently proposed rules to define the conditions under which products containing ephedrine alkaloids would be considered a "significant or unreasonable" risk to health and safety (33). The Commission is aware of the problems of analytical methodology, identification of the products implicated, and the strength of evidence related to possible causation of several deaths associated with use of products containing ephedrine alkaloids. Despite the difficulty of making clear conclusions based on the reported effects of these products, the Commission questions whether the industry and FDA have responded as promptly to these incidents as would be in the best interest of the public.

Some Commission members hold that the delay in action by FDA has served to undermine public confidence in the agency's commitment to enforce DSHEA. The full Commission urges FDA to take a proactive stance in communicating its position to the public in such cases and in pursuing legal action where justified.

FDA's resources may limit its ability to take effective enforcement action, especially when extensive scientific analysis is required. For example, for many ingredients, there are no well-accepted analytical techniques for qualitative and quantitative analysis of products. Thus, should FDA have reason to initiate action against a product, the agency might have to develop and validate an appropriate analytical methodology to determine composition, presence of toxic substances, or adulteration. Similarly, FDA might need to establish the identity of plant parts in certain products. Such efforts are resource intensive and may be cost prohibitive for an agency with a broad range of regulatory responsibilities. These resource issues arise not only with regard to safety, but also with respect to the appropriateness of label claims.

The Commission observed that under Section 402(f)(2) of FDCA added by DSHEA, FDA must notify a manufacturer, distributor, or other person against whom civil action is pending at least 10 days in advance of the filing of the civil action on the supposed violation. This provision allows the company or individual an opportunity to respond to the alleged violation, both orally and in writing. The

product may continue to be marketed during the 10-day period unless the Secretary declares it an "imminent hazard." DSHEA does not modify the definition of "imminent hazard" (96) but states that the authority to declare an imminent hazard cannot be delegated. Thus, in the case of action against a potentially hazardous dietary supplement ingredient, regulatory approval at several additional levels must be sought and obtained. That is, FDA staff must have sufficient information and data to convince not only the FDA General Counsel and Commissioner, but also the HHS General Counsel and Secretary. These additional requirements are appropriate but increase the time needed, the resources required, and the effort expended. Thus, to invoke this statutory provision may require decisions about administrative and regulatory priorities as well as public health and safety.

5. State Enforcement Issues

Representatives of several States who provided testimony to the Commission noted the absence of uniformity in regulations regarding dietary supplements among the States. They also commented on the demands on enforcement resources and indicated that, at the local level, staff expertise and time as well as fiscal resources for enforcement are limited. These representatives emphasized the need to provide FDA with sufficient resources to fulfill its responsibilities and noted that a cutback in the budget and efforts at the Federal level would increase the regulatory burden of the States. They also expressed concern about the wide and uncontrolled range of information available on the Internet. In discussing specific instances in which States had taken enforcement action, representatives of State health departments and public health organizations directed the Commission's attention to the plethora of locally prepared and marketed products that might not enter interstate commerce with which they had to contend as well as products in ethnic markets that were either not labeled in English or not labeled at all.

6. Postmarketing Surveillance

The safety of foods including dietary supplements is a concern of all responsible governing bodies worldwide. For example, the European Commission continues to work on integrating multinational concerns about the safety of dietary supplements into an acceptable directive that its member states could use to enact conforming laws reflecting their choice of the form and method of implementation (95). The European Commission has raised several issues regarding safety, including the potential excessive intake of dietary supplements and the presence of contaminants and natural toxins. Some countries have approached the safety of dietary supplements by planning or developing lists of ingredients that are permitted or not permitted (95).

In addition, many countries have a mechanism to document adverse health effects. For example, in Australia, the Adverse Drug Reactions Advisory Committee collects data and issues warnings, as necessary, about the side effects of various supplements (81,95). In the United Kingdom, the National Poisons Unit reviewed, retrospectively and prospectively, cases of suspected poisoning from exposure to traditional remedies and food supplements from 1983 until 1991

(120). In France, the Licensing Authority and Pharmacopoeial Authority maintains a pharmacovigilance system to gain an overview of the use and adverse effects of botanicals (70). In addition, the World Health Organization (WHO) maintains a Collaborating Center for International Drug Monitoring in Uppsala, Sweden, which may be expanded to cover botanical remedies (21).

In the United States, there are a number of voluntary systems for reporting adverse reactions to consumer products. The Association of Poison Control Centers maintains records on all adverse events reported to a national network of Poison Control Centers. The USP urges health care practitioners to report adverse effects through its Practitioners' Reporting Network. FDA maintains systems for postmarket reporting of adverse reactions to drugs, biologics, devices, and special nutritional products, including dietary supplements. For example, FDA requires reports of serious adverse reactions for new drugs (114). The Adverse Reaction Monitoring System is a passive surveillance reporting system for complaints of adverse reactions or events associated with foods and dietary supplements (48). MedWatch is an analogous passive surveillance system for notification of adverse events related to medications and devices (78,79). These and other FDA passive surveillance systems, such as the Drug Quality Reporting System and the Office of Regulatory Affairs Consumer Complaint System, are voluntary—there is no legal requirement for individuals, organizations, or facilities to report adverse reactions to these FDA systems. These systems provide a monitoring tool for identifying potentially serious public health issues that may be associated with the use of a particular product or type of product. The strengths of these systems include their large scale surveillance and their cost effectiveness.

However, as with all passive surveillance systems, these systems have certain weaknesses. Reports that are received need critical review to appropriately determine the likely cause. Otherwise, erroneous conclusions might be reached regarding a potential association between products and reported symptoms or conditions. Adverse events associated with product use are thought to be significantly underreported, because many consumers or health professionals may not recognize a link between a particular product use and an injury or illness, or they may not bother to register a complaint. A report may be fragmentary and of uneven quality. In addition, there may be a long lag time between the event and the receipt of the complaint. Difficulties in obtaining comprehensive information on the product used and on the health of the consumer are also often encountered. Despite these limitations, however, the systems serve to alert public health officials about potential problems.

FINDINGS

The Commission considers it axiomatic that all marketed dietary supplements should be safe. The manufacturer bears the primary responsibility for assuring the safety of dietary supplements, both under the terms of FDCA and under the requirements of product liability (4,5). The Commission suggests that when health-related statements are made for dietary supplements in the

form of statements of nutritional support or health claims, the manufacturer or vendor bears an added responsibility for assuring the safety of the product. The Commission concludes that while assurance of safety is primarily the responsibility of the dietary supplement industry, the Federal government shares the responsibility to ensure that there are adequate guidelines on GMPs, procedures for alerting the public when safety problems are detected, and procedures for recalls when necessary.

The Commission believes that existing postmarket surveillance systems could be improved. There is no requirement in the United States for mandatory reporting of adverse reactions to foods, including dietary supplements, and the Commission is not recommending such a requirement. However, better use could be made of the reports that are received under the voluntary systems. The Commission urges FDA, the industry the scientific community, and consumer groups to work together voluntarily to improve passive postmarketing surveillance systems, including adverse reaction reporting systems, to ensure that any safety problems that arise are identified and corrected promptly.

Some members of the Commission hold that FDA has sufficient authority to take action against supplements that are deemed unsafe but has failed to use this authority effectively in the case involving products containing ephedrine alkaloids. They hold that the enactment of DSHEA did not affect the agency's authority to protect the public from unsafe products. Other Commission members believe that FDA's enforcement efforts against dietary supplements are diminished by provisions of DSHEA that place the burden of proving the existence of a significant or unreasonable risk on the agency. One member believes that manufacturers should have a legal obligation, enforceable by FDA, to substantiate the safety not only of new dietary supplements, but also of existing products, particularly when there is a new statement of nutritional support or a new recommendation for increased dosage. This Commission member also believes dietary supplements that have not been adequately tested for safety should bear a warning such as that required for cosmetics (119).

DSHEA limits the determination of safety to the doses recommended on the label, even though harm may occur at higher levels and there may be a risk of use at higher levels. The Commission concludes that consumers should be provided with clear and adequate dosage recommendations on product labels, and labels should direct consumers to use products only as recommended. A label warning should also be utilized by the manufacturers, as specifically authorized by DSHEA, when the need for a warning is indicated for the safe and effective use of the product by consumers. For example, if there is a documented need for a warning relating to consumer abuse of a particular product, and no warning is being provided by the manufacturer, the Commission suggests that FDA use its authority to require warnings about exceeding label doses when there is possible risk of serious harm to consumers who inadvertently or intentionally exceed the recommended dose. Commission members recognize that safety hazards resulting from improper use of physiologically and/or pharmacologically

active products at doses other than those recommended are not limited to dietary supplements. FDA has previously relied on warnings in dealing with issues of safety (102).

GUIDANCE

- Manufacturers and the industry as a whole must fully accept the responsibility for assuring the safety of dietary supplements and must take any action necessary to meet the expectation expressed in DSHEA that dietary supplements are and will continue to be safe for use by the consuming public.

- The Commission urges FDA, the industry, the scientific community, and consumer groups to work together voluntarily to improve passive postmarketing surveillance systems, including adverse reaction reporting systems, to ensure that any safety problems that arise are identified and corrected promptly.

- Ensuring the safety of supplements includes the need to provide adequate information and warnings to consumers. The Commission strongly suggests that dietary supplement manufacturers include appropriate warnings in product information where necessary, as specifically permitted by DSHEA. In addition, manufacturers should recognize the need to advise women who are pregnant or breast-feeding to consult a health professional about supplement use during the pre- and postnatal periods.

- The Commission urges FDA to use its authority under DSHEA to take swift enforcement action to address potential safety issues such as those posed recently by products containing ephedrine alkaloids. While it is expected that a responsible industry will avoid marketing unsafe products and that the industry will react promptly to remove products shown to be associated with significant or serious adverse reactions, in the final analysis there must be a strong and reliable enforcement system to back up the safety provisions of DSHEA. Failure by FDA to act when strong enforcement is needed undermines public confidence in the ability of not only the Federal government but also the dietary supplement industry to ensure safety and avoid harm to the public.

- FDA and, within many States, certain agencies have the responsibility in enforcement actions to develop, affirmatively, evidence that shows an unreasonable risk from using existing supplements. FDA and appropriate agencies in some States may need additional resources to develop the necessary evidence, and these agencies need to be given the resources necessary to meet this important responsibility in the context of their overall public health priorities.

LABEL INFORMATION

The Commission did not address specifically the basic format for ingredient labeling and nutrition labeling. DSHEA mandated some changes in FDA's existing regulations on these topics, and FDA proposed new regulations in December 1995 (40-43). At the time of the Commission's first meeting in February 1996, FDA was already in the process of receiving extensive comments on those proposals from the affected industry

and from other members of the public. It was anticipated that these labeling regulations would be amended based on the public comments and would be finalized before the Commission's report was completed. Further, DSHEA's primary mandate to the Commission in regard to labeling concerned claims-related issues, which have been the focus of the Commission's efforts.

1. Label Format and Statement of Identity

Dietary supplements, like other foods, are subject to certain mandatory labeling requirements. Basic food labeling regulations, which apply equally to conventional foods and dietary supplements, are set forth in the Code of Federal Regulations (CFR) (97). These regulations define the principal display panel (PDP) of a product, which must bear the name of the product and a statement of contents or net weight. The information panel is defined generally as the panel to the right of the PDP. It bears other information required by regulation, such as the ingredient list and nutrition labeling. The name and address of the manufacturer, packer, or distributor of the product must also appear on the label. DSHEA imposed some special requirements for dietary supplement labeling, including the requirement that the term "dietary supplement" appear on the label.

2. Ingredient List

FDCA requires that food labels bear a list of all ingredients, and FDA regulations require that the ingredients be listed in descending order of predominance by weight (103). FDA exempted dietary supplements from this requirement in trade correspondence (66). As a result, dietary supplements historically have provided a table of nutrients, as required by special dietary food regulations, but did not always provide a separate list of all ingredients, including excipients.

DSHEA requires that all ingredients of a dietary supplement be listed on the label, but not necessarily as part of a consolidated ingredient list. Some ingredients may be named in the nutrition label and need not be repeated in a separate ingredient list.

DSHEA also requires that, when a product includes botanicals, the label indicate which part of the plant is used. FDA recently published a final rule on regulations that would require additional information about botanicals, including the Latin binomial and an identification of the scientific authority for the Latin name unless the botanical is listed in *Herbs of Commerce* (68).

3. Special Dietary Use Labeling and Nutrition Labeling

FDCA requires that the label of a food intended for special dietary uses include:

> . . . such information concerning its vitamin, mineral, and other dietary properties as the Secretary determines to be, and by regulations prescribes as, necessary in order fully to inform purchasers as to its value for such uses (Section 403(j)).

To implement this requirement, FDA issued regulations in 1941 (66) regarding the format and content of vitamin and mineral labeling for nutritional supplements and fortified foods. Vitamins and minerals were

to be listed in tabular form, with the name of the nutrient, the quantity in metric units, and a statement of the percentage of the MDR provided. The same regulations established MDRs for several vitamins and minerals. If substances were present in the product for which an MDR had not been established, an asterisk was to be used in the "Percent MDR" column, referring to a footnote that stated: "Requirement in human nutrition not established."

In 1973, after extensive proceedings, FDA revised the special dietary use regulations and initiated nutrition labeling (64). The agency also proposed a restrictive "standard of identity" for vitamin and mineral supplements, which was ultimately overturned by the courts, invalidated in part by legislation passed in 1976, and withdrawn by FDA in 1979. The history of the vitamin and mineral regulations is not discussed here, except to note that the only significant provision remaining was one replacing the MDR with the U.S. RDA as the label reference standard for vitamin and mineral content for conventional foods and dietary supplements.

Nutrition labeling was initiated by FDA as a voluntary program in 1973 (64). Nutrition labeling was not mandatory unless a nutritional claim was made. However, if a conventional food had nutrition labeling, then the label was required to follow the format established by FDA. Dietary supplements were exempt from nutrition labeling because they were intended to be covered by special dietary use regulations.

NLEA required nutrition labeling of all foods and supplements and required FDA to establish an appropriate format (67). NLEA also changed the general emphasis of nutrition labeling to increase the focus on macronutrients believed to have a major positive or negative impact on health. FDA took the opportunity to develop an entirely new and bolder format for nutrition labeling and replaced the U.S. RDA with a new label standard for vitamins and minerals, the RDI.

FDA recognized the need for somewhat different formats for nutrition labeling of conventional foods and nutritional supplements. Final regulations on nutrition labeling for conventional foods were promulgated in January 1993. Final regulations on nutrition labeling for vitamin and mineral supplements were issued in January 1994, prior to the passage of DSHEA. No special provision was made for botanical products, which would have been required to bear conventional nutrition labeling.

DSHEA was passed in October 1994 with provisions that require revision of FDA's regulations on nutrition labeling for dietary supplements. DSHEA specifies that nutrition labeling for dietary supplements be provided "in a manner which is appropriate for the product" and which is specified in FDA regulations. In addition, DSHEA specifically authorizes three departures in dietary supplement labeling from the nutrition labeling format applicable to conventional foods.

- DSHEA specifies that nutrition labeling for dietary supplements shall not require the listing of any substance not present in the product. In contrast, FDA requires conventional foods to list all "mandatory" nutrients, even if the amount present is zero.

- DSHEA specifies that substances without a DV may be listed in dietary supplement nutrition labeling, following the list of nutrients with a DV. In contrast, food labels cannot list any substance in nutrition labeling except those for which a DV has been established or which are specifically permitted by regulation.

- DSHEA permits dietary supplement nutrition labeling to state the source of a nutrient or other substance (e.g., niacin as nicotinic acid). In contrast, food labels may list only the common name of the nutrient (e.g., niacin), without mentioning the source compound within the Nutrition Facts box. DSHEA also provides that, if source compounds are listed in dietary supplement nutrition labeling, they need not be repeated in a separate list of all ingredients.

DSHEA requires implementation of its labeling provisions by December 31, 1996, but the procedures necessary for full implementation were not completed by that date. Final regulations were issued on September 23, 1997, and become effective on March 23, 1999 (26-28).

FINDING

The Commission supports the informative label format mandated by DSHEA and urges orderly implementation of appropriate regulations.

NLEA CLAIMS IN DIETARY SUPPLEMENT LABELING

NLEA not only required mandatory nutrition labeling for all foods including dietary supplements but also defined "nutrient content claims" and established a process for approval of "health claims."

1. NLEA Nutrient Content Claims

NLEA requires that nutrient content claims not be used in food labeling unless the terms used have been defined by FDA and unless the terms are used in accordance with those definitions. This provision came about because terms such as "low fat," "high fiber," and "no cholesterol" were believed to be used in ways that were potentially misleading. FDA issued regulations implementing the requirement that nutrient content claims be defined (98). For the most part, the same nutrient content claims allowed for foods are also allowed for dietary supplements.

Nutrient content claim language allowed for both foods and dietary supplements includes the following:

- The terms "high in," "rich in," and "excellent source of" may be used for nutrients on food and dietary supplement labels provided the product contains 20 percent or more of the DV per serving.

- The terms "good source," "contains," and "provides" may be used on food labels, provided the product contains 10 to 19 percent of the DV of the nutrient per serving.

- Relative terms such as "more" and "added" may be used under specific conditions.

FDA regulations permit nutrient content claims for substances for which a DV has

been established. DSHEA specifically permits percentage nutrient content claims for dietary supplement ingredients for which a DV has not been established. This would allow a statement such as "twice the omega-3 fatty acids per capsule (80 mg) as in 100 mg of menhaden oil (40 mg)" on a dietary supplement label, even though no DV has been established for omega-3 fatty acids (27).

2. NLEA Health Claims

In enacting DSHEA, Congress intended the Commission to address whether changes should be made in the requirements for NLEA health claims for dietary supplements. Current FDA rules require the same type of scientific evidence and support and the same process for approval of NLEA health claims on dietary supplements as are required for conventional foods. DSHEA requires the Secretary to publish any recommendations the Commission makes with respect to changes in the existing FDA regulations concerning NLEA health claims on dietary supplements, along with a notice of proposed rulemaking on such recommendations. In the absence of timely action by the Secretary, dietary supplements will no longer be subject to the requirements applicable to health claims on conventional foods.

Historically, FDA had regarded health claims on foods as impermissible drug claims. In 1987, FDA changed its policy, recognized the appropriateness of health claims on foods, and proposed to develop guidelines or regulations regarding such claims (57). Under this rulemaking initiative, manufacturers would have needed to substantiate their health claims, but prior review by FDA would not have been required. What was sufficient for substantiation became a heated issue in the rulemaking process. As FDA developed its proposed policies, manufacturers were already making health claims for substances such as fiber, and some of these claims provoked public criticism and congressional debate, which led to the enactment of NLEA.

The Commission is aware that challenges have been brought on constitutional grounds to the provisions of NLEA concerning FDA approval of health claims (91,92). A time deadline for FDA action on final rules for health claims has been found necessary (92). The other provisions of NLEA have not been found to be invalid on constitutional grounds in the cases to date. The discussion of NLEA in this report is based on the provisions in their present form.

NLEA defines health claims as statements that characterize a relationship between a nutrient or food component and a specific disease or health-related condition (100). A disease or health-related condition:

> . . . means damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims pertaining to such diseases are thereby not subject to . . . 101.14 or 101.70).

NLEA requires that the standard of evidence for health claims for conventional foods be significant scientific agreement among experts qualified by scientific training and experience to consider whether a claim is supportable. NLEA specified that health claims for dietary supplements would not be subject to that standard but instead would be "subject to a procedure and standard, respecting the validity of such claim, established by regulation of the Secretary" (FDCA 403(r)(5)(D). Numerous suggestions for alternative systems were made in comments on FDA's proposed health claims regulations. In promulgating regulations for health claims, FDA considered this issue and concluded that the same standard and procedure should apply to dietary supplements as to conventional foods (i.e., there should be a "level playing field" for health claims for all foods including supplements).

Significant scientific agreement is to be based on the totality of publicly available scientific evidence, including evidence from well-designed studies conducted in a manner consistent with generally recognized scientific procedures and principles (99, 104,107). FDA regulations for NLEA health claims define the types of substances that are potentially eligible for specific health claims and identify additional requirements for making health claims.

Many of the diet-disease associations of potential relevance for health claims relate to chronic disease processes for which diet is one of many possible causes and which, for both ethical and practical reasons, are often not subject to direct experimentation. Thus, different types of evidence are usually considered in attempting to establish that a causal association actually exists and that dietary change would have preventive value. Where human experimentation is not appropriate, other approaches are useful. For example, an association may be inferred from a combination of epidemiological comparisons or long-term observations of populations exhibiting different dietary patterns, in vitro biochemical studies, and animal studies. Where feasible and appropriate, randomized controlled trials are conducted to establish the effects of dietary manipulations in human populations.

Commission members agree that a high standard of evidence is appropriate for health claims. A valid health claim may promote behaviors that have a beneficial effect on public health and, therefore, be associated with effects on health care costs, quality of life, and productivity.

Evaluating expert agreement is, by definition, a matter of judgment, and must rest on a body of evidence considered adequate to support such agreement (i.e., more than preliminary studies or a few emerging studies, even if the evidence seems convincing). Guidelines for selecting evidence for evaluating a body of scientific evidence are increasingly prominent in the scientific literature (11). The scientific literature also describes many processes for synthesizing and evaluating a body of literature (1,13).

Under NLEA, FDA was initially directed to review the evidence relating to 10 specific nutrient/disease relationships. In evaluating these initial candidates for health claims, FDA contracted with Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology

(FASEB), for expert literature reviews and recommendations and FDA also solicited data from the public. Subsequently FDA approved eight health claims (five of the original 10, plus three modifications of the original 10). Two, omega-3 fatty acids and coronary heart disease as well as zinc and immune function in the elderly, were not approved (Table 2).

Two of the original 10 claims (those relating to calcium and to folic acid) are approved for use in dietary supplement labeling as well as conventional food labeling. In evaluating the health claim for folic acid and neural tube birth defects, FDA convened an advisory committee and was also strongly influenced by the Public Health Service's adoption of a recommendation on this subject. The three modified claims relate to antioxidant vitamins and cancer, fiber and cancer, and fiber and coronary heart disease. FDA disapproved these claims for the substances per se but approved claims for food groups that are good sources of vitamin C, β-carotene, or fiber.

For purposes of considering health claims other than the 10 mentioned in NLEA, FDA developed a petition process, as required by NLEA, whereby a petitioner may request the establishment of regulations authorizing a claim that characterizes the relationship of a nutrient to a disease or health-related condition (104). In considering such petitions, FDA indicated that manufacturers must demonstrate that a product is safe when used at the level needed to support a claim.

In response to petitions, three new health claims have been approved (Table 2), one for sugar alcohols and reduced risk of dental caries (36) and one each for soluble fiber from whole oats and from psyllium husks and reduced risk of coronary heart disease (34,35). FDA did not take action on a petition for a health claim for calcium-rich dairy products and reduced risk of hypertension (129). Health claims currently authorized in 21 CFR are listed in Table 2.

For each of the approved health claims, FDA regulations include "model claims" that may be used by manufacturers to assure that all criteria for a claim are met. However, manufacturers are free to develop their own claims language, provided it meets the criteria set forth by FDA.

Many food and dietary supplement manufacturers complained that the health claims requirements initially established by FDA were too cumbersome and that the model claims were not consumer friendly. In response to petitions filed by the National Food Processors Association and the American Bakers Association, FDA proposed in December 1995 to streamline specific requirements for health claims (44). These regulations are not yet final. The model calcium claims below illustrate the dramatic difference between FDA's original requirements and the streamlined proposal:

> *Original:* "Regular exercise and a healthy diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis later in life. Adequate calcium intake is important, but daily intakes above about 2,000 mg are not likely to provide any additional benefit" (105).

Table 2

STATUS OF HEALTH CLAIMS

Approved Health Claims for Dietary Supplements and Conventional Foods
Calcium and osteoporosis **Folate** and neural tube defects **Soluble fiber** from whole oats and coronary heart disease **Soluble fiber** from psyllium husks and coronary heart disease **Sugar alcohols** and dental caries
Approved Health Claims for Conventional Foods Only
Dietary lipids and cancer **Dietary saturated fat and cholesterol** and coronary heart disease **Fiber-containing grain products, fruits, and vegetables** and cancer **Fruits and vegetables** and cancer (for foods that are naturally a "good source" of vitamin A, vitamin C, or dietary fiber) **Fruits, vegetables, and grain products that contain fiber,** particularly soluble fiber, and coronary heart disease **Sodium** and hypertension
Health Claims Not Authorized
Antioxidant vitamins and cancer **Dietary fiber** and cancer **Dietary fiber** and cardiovascular disease **Omega-3 fatty acids** and coronary heart disease **Zinc** and immune function in the elderly

> *New*: "Especially for teen and young adult women, adequate calcium in a healthful diet may reduce the risk of osteoporosis later in life" (44).

When FDA proposed a health claim relating to folic acid in 1993 (58 *Fed. Reg.* 53254), the original language was:

> *Original*: "Women who consume adequate amounts of folate, a B vitamin, daily throughout their childbearing years may reduce their risk of having a child with neural tube birth defect. Such birth defects, while not widespread, are very serious. They can have many causes. Adequate amounts of folate can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or a supplement. Folate consumption should be limited to 1,000 μg per day from all sources."

In March 1996, FDA finalized a regulation streamlining the model health claim relating to folic acid:

> *New*: "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect" (37,106).

FINDINGS

The Commission recognizes that appropriate NLEA health claims made for dietary supplements and foods may be an important method of public education about dietary practices that may have a positive influence on health. The power of advertising and marketing of products in connection with valid health claims provides a means for public education that is difficult to provide through other channels. For this reason, it is important that health claims be based on results of a body of research that demonstrates that public health benefits can be achieved through this mechanism. A useful consideration of how evidence should be evaluated relative to diet and health relationships has been published by the Committee on Diet and Health (13). Invalid health claims may increase costs to consumers or result in health behaviors that are not helpful or even have negative consequences to health and well-being.

The Commission supports the concept of fairness, in which the requirements for NLEA health claims are the same for foods and for dietary supplements. The Commission believes that different health claim standards for dietary supplements and conventional foods would be confusing to consumers and would be poor public policy. The Commission considered the standards for scientific evidence and the procedures required for health claim approval, including the question as to whether health claims for foods and dietary supplements should be regulated in the same way. The Commission concluded that both the scientific standards and the approval process for health claims for dietary supplements and for conventional foods should be the same. The Commission agrees with the key aspects of the rules that relate to the formal standard for decision making and believes these allow for flexibility in evaluating individual petitions for health claims.

Some Commissioners expressed concern about the current FDA review process for NLEA health claims. The Commission suggests that the process whereby FDA

determines whether significant scientific agreement exists for support of a specific health claim could be improved. For example, there could be greater use of FDA-sponsored conferences or workshops on issues related to health claims of specific substances, such as those held on antioxidants, cancer, and cardiovascular disease (53). In particular, FDA should consider greater involvement of scientists outside of FDA, including scientists in other government agencies, in the review process. The agency should develop criteria for selecting review panels external to FDA that would be considered scientifically qualified, balanced, reliable, and independent. The LSRO/FASEB panels used by FDA provide one example of appropriate outside review.

Recommendations by such outside panels would not have presumptive weight in the approval process, but submission of evidence from such a review by petitioners should strengthen the petition and expedite the review process. The agency would be expected to provide an explanation of any disagreement with such a review panel, given the panel's expertise. Although the views of other governmental agencies should not substitute for the authority of FDA, they should be given serious consideration, and they are important in considering whether significant scientific support for a claim exists. FDA and other agencies need to be continually aware that the public may be confused by disparate recommendations of governmental public health agencies in relation to food or dietary supplements.

GUIDANCE

- The process for approval of health claims as defined by NLEA should remain the same for dietary supplements and conventional foods.

- The standard of significant scientific agreement is appropriate and serves the public interest. The standard of significant agreement should not be so strictly interpreted as to require unanimous or near-unanimous support.

- FDA should ensure that broad input is obtained to ascertain the degree of scientific agreement that exists for a particular health claim. The use of appropriate panels of qualified scientists from outside of the agency is encouraged, and the views of other government agencies should be given considerable weight in determining whether significant scientific agreement exists.

SCOPE OF STATEMENTS OF NUTRITIONAL SUPPORT

DSHEA allows a dietary supplement label to bear a statement of nutritional support when the statement:

(1) Claims a benefit related to a classical nutrient deficiency disease;

(2) Describes the role of a nutrient or dietary ingredient intended to affect structure or function in humans;

(3) Characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain structure or function; or

(4) Describes general well-being from consumption of a nutrient or dietary ingredient.

Statements of nutritional support relating to the structure and function of the body (2 and

3 above) are typically called "structure/function" statements of nutritional support. These are nearest in usage to the types of statements that otherwise might be considered to be health claims or drug claims.

Statements linking foods or nutrients with growth, health, and well-being (that is, with human structure or function but not with a specific disease or dysfunction) historically have been permitted on foods. The FDCA indirectly addresses structure/function statements by defining drugs as "articles (other than food) intended to affect the structure or any function in the body of man or other animals." The statement that "calcium builds strong bones and teeth" is a classic example of an allowable structure/function statement of nutritional support for foods.

DSHEA specifically creates a category of statements of nutritional support, including structure/function statements, to ensure that such information will be permitted for dietary supplements. Nutritional support statements, and especially structure/function statements, have become more visible since the passage of DSHEA and are subject to unique requirements for notification and for special labeling. DSHEA requires that the manufacturer notify FDA within 30 days after the first use of a nutritional support statement, that the manufacturer have substantiation for the statement, and that the label include the following disclaimer:

> **This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

What constitutes an allowable structure/function statement of nutritional support (i.e., a statement that is not a health claim and not a drug claim) has not been specifically outlined in either legislation or regulations. While some members believe statements of nutritional support may imply disease prevention, at least one member believes that statements of nutritional support may neither expressly nor implicitly claim such usage.

Commission members agree that claims for dietary supplements that meet the definition of health claims, as defined under NLEA, should continue to be regulated under the same NLEA provisions that apply to conventional foods. It can be difficult, however, to clearly distinguish an allowable structure/function statement of nutritional support from one that might be considered an unauthorized health or drug claim. The Commission reviewed approximately 1,000 statements of nutritional support referenced in notification letters submitted to FDA. Based on this review, the Commission concluded that the lack of definition of the clear boundaries of these statements leaves many uncertainties as to what actually constitutes a legitimate statement of nutritional support in the context of dietary supplements.

Commission members expressed concern that some statements of nutritional support being made are in fact more akin to drug claims. Commission members who were troubled about the wording of structure/function statements suggested that the most problematic wording is seen in statements ostensibly relating to "normal healthy function" that actually imply the need to

remedy an underlying abnormal or unhealthy state and statements mentioning organs (e.g., heart, liver, and prostate) or systems (e.g., circulatory) associated with major clinical conditions.

The Commission was divided on the distinction between DSHEA-allowable structure/function statements and drug claims for claims referring to organs. Some Commission members believed that such statements were either drug claims or NLEA health claims. It was noted that, for health claims, FDA has defined a disease or health-related condition to include damage to an organ, part, or structure of the body so that it does not function properly (99). Some Commission members believe that the potential for allowing these types of statements for dietary supplements is a fundamental flaw of DSHEA, creating a loophole for quasi-drug claims. Others suggest that the ability to make such statements is implicit in DSHEA and that there is emerging scientific evidence for certain foods and other dietary ingredients having benefit for specific organs or functions of the body. These members of the Commission noted that these provisions of DSHEA were written with the explicit goal of making such information available to the public.

Statements of nutritional support relating to structure or function should not be used to imply effects that are currently considered prescription drug claims. For example, oral contraceptives alter physiological function, but a contraceptive effect is inappropriate as a statement of nutritional support.

Some Commission members noted that prior to DSHEA, FDA took the position that virtually any statement relating to cholesterol would be interpreted as a claim relating to the prevention of heart disease. These Commissioners believe that this position needs reconsideration in light of DSHEA and that it is possible to craft a statement of nutritional support regarding the maintenance of healthy blood cholesterol levels that is a statement of nutritional support and not a health claim or drug claim. In a similar manner, FDA historically has been sensitive to label statements relating to immune function on the grounds that they are implicit or explicit claims relating to acquired immune deficiency syndrome (AIDS). While a statement of nutritional support should not be such that it could be interpreted as a direct or indirect AIDS claim, some Commission members believe it should be possible to make legitimate statements of nutritional support about substantiated effects on immune function or disease resistance.

Statements of nutritional support that mention an acute effect on the structure or function of a major system (e.g., reduces heart rate) raise particular concern for some Commission members. In contrast, effects on stress, mental acuity, or bone or skin health within the normal range seemed to carry less serious connotations. However, some members still have concerns about stress and mental acuity claims and emphasize that these and all statements related to structure and function of the body need to be carefully evaluated on an individual basis. One important concern

relates to safety, that is, the potential seriousness of any effect that might extend beyond the normal range. The consumer's ability to recognize the range of normality is also an issue. One member believes that to be an appropriate statement of nutritional support, a statement would need to identify a dietary relationship for the supplement.

FINDINGS

The Commission has developed guidelines as to what constitutes an acceptable statement of nutritional support of the structure/function type. These guidelines are listed below as Commission policy guidance. The Commission considers that statements of nutritional support should provide information that can help consumers make informed choices about their health. In keeping with DSHEA, the statement should not be false or misleading and should provide scientifically valid information to the consumer. Also, the product should be safe under conditions of intended use.

Analysis by the Commission of FDA's responses to notification letters indicates that the agency has not objected specifically to statements that are consistent with the guidelines the Commission recommends, but FDA has also made it clear that the absence of an objection by the agency does not indicate acceptance of the appropriateness of the claim (128). The provision of early guidance by FDA to manufacturers making statements of nutritional support is appropriate and helpful in clarifying the appropriate scope of these statements.

GUIDANCE

- While the Commission recognizes that the context of a claim has to be considered on a case-by-case basis, the Commission proposes the following general guidelines:

  1. Statements of nutritional support should provide useful information to consumers about the intended use of a product.

  2. Statements of nutritional support should be supported by scientifically valid evidence substantiating that the statements are truthful and not misleading.

  3. Statements indicating the role of a nutrient or dietary ingredient in affecting the structure or function of humans may be made when the statements do not suggest disease prevention or treatment.

  4. Statements that mention a body system, organ, or function affected by the supplement using terms such as "stimulate," "maintain," "support," "regulate," or "promote" can be appropriate when the statements do not suggest disease prevention or treatment or use for a serious health condition that is beyond the ability of the consumer to evaluate.

  5. Statements should not be made that products "restore" normal or "correct" abnormal function when the abnormality implies the presence of disease. An example might be a claim to "restore" normal

blood pressure when the abnormality implies hypertension.

6. Health claims are specifically defined under NLEA as statements that characterize the relationship between a nutrient or a food component and a specific disease or health-related condition. Statements of nutritional support should be distinct from NLEA health claims in that they do not state or imply a link between a supplement and prevention of a specific disease or health-related condition.

7. Statements of nutritional support are not to be drug claims. They should not refer to specific diseases, disorders, or classes of diseases and should not use drug-related terms such as "diagnose," "treat," "prevent," "cure," or "mitigate."

- To the extent resources permit, FDA should continue to provide guidance to manufacturers by responding to letters of notification when the agency deems a proposed statement to be inappropriate as a statement of nutritional support.

NOTIFICATION LETTERS FOR STATEMENTS OF NUTRITIONAL SUPPORT

DSHEA requires that the manufacturer of a dietary supplement bearing a statement of nutritional support notify the Secretary no later than 30 days after the first marketing of the dietary supplement that such a statement is being made. The law also states that the manufacturer must have substantiation that the statement is truthful and not misleading. The law does not provide that the evidence supporting a statement be reviewed by a regulatory agency prior to marketing of the product. Presumably the evidence substantiating a statement would be examined only if a challenge to the labeling or advertising were made.

FINDINGS

The Commission believes that guidelines are needed for standardizing the format and content of the notification letters. In keeping with the intent of DSHEA, which is to provide consumers with truthful, not misleading, and scientifically valid information to make informed health care choices, the Commission suggests that the notification letters and the FDA responses continue to be made available in the public dockets at FDA (Docket Nos. 97S-0162 and 97S-0163).

The Commission considered whether there should be a requirement that a notification letter include a summary of the evidence supporting the statement of nutritional support and the safety of the product. This was an effort by the Commission to fulfill its mandate in DSHEA to "evaluate how best to provide truthful, scientifically valid, and not misleading information to consumers so that such consumers may make informed and appropriate health care choices for themselves and their families." Although DSHEA does not require that a summary of the data supporting statements of nutritional support be submitted to FDA with the notification letters, a majority of the Commission members favored such a requirement. Some members of the

Commission saw major problems with such a recommendation because it would impose a requirement not specified in DSHEA. Further, some Commissioners were concerned that the summary might allow or require public display of information that makes or implies an unintended claim, thereby putting a company at risk of enforcement action for making an impermissible statement of nutritional support because of the nature of the evidence or publications cited. Also, there was some question whether FDA has legal authority to require a summary of the evidence in the notification letter.

The Commission recommended in its June 1997 draft report that the letter of notification include a summary of the evidence supporting both benefit and safety. There was considerable opposition to this recommendation in the public comments on the draft report. Industry representatives objected to a requirement that goes beyond the specific provisions of DSHEA, and some nutrition professionals, public health officials, and consumer groups objected to the public availability of a summary of the evidence because of the potential for confusion when that summary had not been approved by FDA. In response to the comments, the Commission has amended its recommendation to omit the requirement that a summary of evidence supporting both safety and benefit be submitted in the letter of notification.

However, the Commission urges that manufacturers voluntarily include an affirmation in the notification letter or in a separate public notice, indicating that the company has reviewed the evidence supporting the statement of nutritional support and has concluded that it is truthful, not misleading, and scientifically valid. DSHEA requires that manufacturers have evidence that a statement is truthful and not misleading. DSHEA charges the Commission to make recommendations for providing consumers with information that is scientifically valid. Therefore, all three of these criteria need to be reflected in the affirmation.

Also, the Commission suggests that manufacturers include an affirmation in the notification letter or other public notice that they have evaluated the available information relating to safety and have satisfied themselves 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 labeling. This language is consistent with the provisions of DSHEA that state that a product will be considered "adulterated" (unsafe) if it presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling.

Based on the public comments on the draft report, the Commission deleted the recommendation that a consumer summary of the evidence for safety and benefit be submitted as part of the letter of notification. However, the Commission believes consumers need balanced, nonmisleading, and valid information regarding the evidence. These issues are addressed further in Chapter IV of this report.

The Commission recognizes that FDA recently published its final rule outlining

the information that should be contained in a letter of notification (30) (see Endnote 1). The Commission prefers that the notification letter contain more information than FDA has required:

Statement of Purpose: An indication that the purpose of the letter is to provide notification of a statement of nutritional support, including the exact wording that appears on the label.

Vendor Information: The name, address, and telephone number of the manufacturer and, if available, the address and/or toll-free telephone number for consumer inquiries.

Product Identification: The name and description of the product should include the trade name and the common or usual name. A copy of the product label (or label copy, if labels are not yet printed) should be included.

Ingredient Statement: The specific individual ingredients or combination of ingredients for which the statement of nutritional support is made should be identified. For botanicals, ingredients should be identified by the common or usual name, the Latin binomial and its scientific authority, and the part(s) of the plant used. Some Commission members believe that many botanicals are adequately identified by common name, and that scientific nomenclature should be required only when confusion or misidentification might occur.

Intended Use: The statement of intended use should include the recommended dosage, and appropriate contraindications or warnings must be stated.

Statements of Affirmation: The Commission suggests that, in the notification letter or in a separate public notice, manufacturers should affirm that they have evaluated the evidence on safety and benefit. That is, the manufacturer should affirm that there is supporting evidence that the statement of nutritional support is truthful, not misleading, and scientifically valid. The manufacturer should also affirm 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 labeling. Manufacturers also need to comply with the FDA final rule on the contents of notification letters (30).

GUIDANCE

- Notification letters should continue to be available in the public dockets.
- While the rulemaking process need not be reopened at this time, the Commission suggests that notification letters should include the following information:
  1. A statement that the purpose of the letter is to provide notification of a statement of nutritional support, including the exact wording that appears on the product label.
  2. The name, address, and telephone number of the manufacturer or distributor, and if available, the address and/or toll-free telephone number for consumer inquiries.

3. The name and a description of the product. The name of the product should include the trade name and the common or usual name. A copy of the product label or label copy, if labels are not yet printed, should be included.

4. The identity of specific individual ingredients or combinations of ingredients for which the statement of nutritional support is made. For botanicals, ingredients should be identified by the common or usual name, the Latin binomial and its scientific authority, and the part(s) of the plant(s) used.

5. A statement of intended use, including the recommended dosage and appropriate contraindications or warnings.

- In the notification letter or in a separate public notice, manufacturers should provide statements of affirmation that they have substantiation for the statement of nutritional support and that the product does not represent a significant or unreasonable risk of illness under conditions of use recommended or suggested in labeling.

- Although some of the information indicated in the above guidelines is not required by FDA, the Commission suggests that manufacturers use these guidelines in preparing their notification letters.

SUBSTANTIATION FILES FOR STATEMENTS OF NUTRITIONAL SUPPORT

During its public hearings, the Commission was asked by several manufacturers to provide guidance regarding the type of information that a responsible vendor should have to substantiate a statement of nutritional support.

The law does not define "substantiation," and the Commission has considered guidelines as to what constitutes appropriate documentation for a statement of nutritional support. Following appropriate guidelines for substantiation could allow manufacturers to have more confidence that a statement will be sustained if challenged by regulatory agencies. Following the guidelines would increase the likelihood that statements will be appropriately supported and would provide consumers with some basis for judging the soundness of the statements that are made.

Statements of nutritional support as allowed under DSHEA must be substantiated by evidence that the statements are "truthful and not misleading." The evidence needed to substantiate statements of nutritional support will vary depending on the statement made. For example, statements about the relation of a vitamin or mineral to a classic nutrient deficiency disease are generally supported by a significant body of research. DSHEA requires that statements claiming a benefit related to a classic nutrient deficiency

disease disclose the prevalence of the disease in the United States. The Commission concurs that the data on prevalence in the U.S. population should come from recognized sources, such as the several surveys that are components of the National Nutrition Monitoring and Related Research Program, the publications derived from this program, or publications in peer-reviewed journals.

Other types of statements of nutritional support may be substantiated by various types of evidence, including historical usage, animal testing, in vitro studies, epidemiologic data, and human studies. Controlled clinical studies represent important evidence to support a claim, provided the studies have been well designed. While proprietary studies can be important, studies published in peer-reviewed scientific journals have added credibility. Substantiation files should include key data, including evidence from studies showing no benefit or adverse effects. The weight of evidence should substantiate the statement of nutritional support.

The Commission recognizes that the content of the substantiation file may be developed by parties other than the manufacturer or vendor of the finished product, such as an ingredient supplier, a private label manufacturer, a trade association, or an external consultant.

The Commission considered the criteria that FTC has established regarding support of food advertising claims (24). In determining whether a reasonable basis exists for an advertising claim, such as an unqualified health claim, FTC evaluates the competency and the reliability of the scientific evidence and the level of support among scientists that experts would find necessary. Under general principles for substantiation of claims (25), consideration is also given to factors such as the type of claim, the product, the consequences of a false claim, the benefits of a truthful claim, the cost of developing substantiation for the claim, and the amount of substantiation experts in the field believe is reasonable. In addition, expert testimony and consumer surveys are useful in determining what level of substantiation consumers expect to support a particular product claim and the adequacy of the evidence an advertiser possesses. The Commission finds that substantiation for statements of nutritional support will likewise vary depending on the nature of the statement being made, the health importance of the statement, and the difficulty of conducting experimental studies.

The Commission discussed how a statement of nutritional support can be adequately substantiated when it is based solely on historical use without supporting experimental or clinical data. At a minimum, such a statement of nutritional support would have to be carefully qualified to prevent misleading consumers. Some Commission members believe that, in some circumstances, qualified statements based solely on historical use would be recognized by experts as being adequately substantiated. Other Commissioners believe that experts would want more scientific support for substantiation and especially so in the case of statements that have particular health importance.

One Commissioner believes that scientific support for substantiation is needed for all statements with health importance.

DSHEA does not require that substantiation files be made available to FDA, and the majority of the Commission members are not recommending a change in legislation regarding the availability of these files. However, one member believes that FDA needs to be able to obtain access to the relevant files of a manufacturer to enforce effectively the manufacturer's obligation to substantiate statements of nutritional support and the obligation to substantiate safety. That member believes the authority to obtain access to substantiation files should be provided either through a rule similar to that proposed by FDA on nutrient content claims based on new technology for food ingredients (38) or through legislative action.

In the Commission's public hearings, a number of witnesses indicated that guidance regarding the content of the substantiation file is needed. The Commission has developed the following guidelines on the content of substantiation files.

Notification Letter: A copy of the notification letter should be included.

Identification of Dietary Supplement Ingredients: The identity and quantity of the dietary supplement ingredient(s) that is (are) the subject of the statement of nutritional support should be included. If possible, the active component and mechanism of action should also be indicated. In the case of individual chemical compounds, such as vitamins and minerals, the specific components are readily identified; in the case of botanicals or animal products, the active principle(s) in the product responsible for the effect should be identified, where known.

Evidence to Substantiate Statements of Nutritional Support: Such evidence should include copies of key references to experimental or clinical data and/or findings of authoritative bodies and other evidence, where appropriate. References should include relevant information, positive or negative. Research or monographs from appropriate foreign sources may be cited, along with evidence that specific uses or claims are approved in other countries. An interpretive synopsis by an individual(s) or group qualified by training and experience to evaluate the evidence should accompany the literature citations and should assess clearly the evidence supporting the statement. Evidence for efficacy should include the dosage at which effects are observed. Where historical use is cited as the evidence for a statement, the composition of the product should correspond with the material for which such claims of historical use may be made. The complexity of a product may affect the substantiation required.

Evidence to Substantiate Safety: The Commission believes safety is of primary concern in marketing dietary supplements, and the file should indicate the basis of the manufacturer's conclusion that the product can reasonably be expected to be safe at levels of intended use.

Good Manufacturing Practices: Assurance that GMPs were followed in the manufacture of the product should be indicated.

Qualifications of Reviewers: The qualifications of those who reviewed the evidence should be included. Substantiation should be assembled by an individual(s) or group qualified by training and experience to assess the evidence, and the file should list the qualifications of those who reviewed the data on safety and efficacy. If an external advisory body was consulted, it should be identified.

The Commission provides the following guidance regarding the information a responsible manufacturer should have in a substantiation file for a statement of nutritional support and product safety. While the Commission's guidance on substantiation files is directed to statements of nutritional support and safety, other types of label statements may be made for dietary supplements. The Commission's guidance on substantiation file content may be helpful in identifying what a responsible manufacturer would do for substantiation of other types of label statements.

GUIDANCE

- Substantiation files for statements of nutritional support and safety should include the following information:

  1. A copy of the notification letter.

  2. The identity and quantity of the dietary ingredient(s) that is (are) the subject of the statement of nutritional support.

  3. The key evidence to substantiate statements of nutritional support, including an interpretive summary of the evidence by an individual(s) or group qualified by training and experience.

  4. Evidence substantiating the safety of the product.

  5. Assurance that good manufacturing practices were followed in the manufacture of the product.

  6. The qualifications of the individual(s) or group who reviewed the evidence for safety and efficacy.

PUBLICATIONS EXEMPT FROM CLASSIFICATION AS LABELING WHEN USED IN CONNECTION WITH SALES

Historically, FDA has considered literature used directly in connection with the sale of a product to be "labeling" for the product. Section 5 of DSHEA exempts certain publications used in connection with the sale of dietary supplements from being defined as "labeling." The exemption applies to "a publication, including an article, a chapter in a book, or an official abstract of a peer-reviewed scientific publication that appears in an article and was prepared by the author or the editors of the publication, which is reprinted in its entirety . . . ."

DSHEA directs the Commission to study and make recommendations for the regulation and evaluation of label claims and statements for dietary supplements, specifically "including the use of literature in

connection with the sale of dietary supplements."

DSHEA has only a brief official legislative history, and one of the few points it covers reiterates that the labeling exemption "does not apply to a summary of a publication other than an official abstract of a peer-reviewed scientific publication" (see Endnote 2). DSHEA exempts a publication from "labeling" only if 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.

DSHEA specifies that this provision "shall not apply to or restrict a retailer or wholesaler of dietary supplements in any way whatsoever in the sale of books or other publications as a part of the business of such retailer or wholesaler." Further, DSHEA provides that in any proceeding brought under this provision, the government shall bear the burden of proof "to establish that an article or other such matter is false or misleading."

The Commission finds that some of these requirements of Section 5 of DSHEA are difficult to apply. The emphasis on the need to reprint the publication "in its entirety," the care given to describing an official abstract of a scientific publication, and the prohibition against the use of any summary other than the official abstract of a peer-reviewed scientific publication all suggest that Congress was referring primarily to scientific publications in drafting this labeling exemption. However, the term "publication" as used in this section is not restricted to a scientific publication and thus would appear to apply to almost any publication about the available scientific information on a dietary supplement, provided that the five additional requirements noted above are met. This matter also raises a concern about violation of copyright laws applicable to published articles.

The Commission believes the most important of the five requirements outlined in Section 5 of DSHEA is the requirement that the publication itself be balanced or else be displayed with other publications that taken together provide a balanced view of the available information. Determining when a balance exists may be difficult, but the concept itself is straightforward and includes a need to acknowledge negative as well as positive data and to indicate which position is supported by the weight of the evidence.

Well-written scientific review articles generally are balanced, in that they acknowledge both the positive and negative findings on a given topic, but scientific review articles are unlikely to be consumer friendly. The same applies to scientific articles reporting on original research. The

introduction or the discussion section generally will note previous articles that reported findings consistent with or contrary to the new findings. However, scientific articles and perhaps especially the official abstracts of such articles may be difficult for the consumer to understand. Therefore, it appears likely that the bulk of the literature used in accordance with this provision may be in the form of publications specifically prepared for this purpose and written for the consumer. Some Commissioners believe that providing a balanced view of scientific information provided by positive and negative publications used in connection with sales presents particular difficulties. Further study is needed to determine whether there are adequate and reliable means to ensure that a balanced view is provided.

Several organizations are currently publishing materials specifically intended as "third-party literature," the term often used within the industry to refer to literature covered by this section of DSHEA. This literature can provide useful information for consumers, provided it meets all of the requirements of DSHEA, including the requirements that the information be truthful, not misleading, and balanced. The Commission encourages manufacturers, distributors, and others to provide reliable information to help consumers use dietary supplements appropriately, whether that information is in the form of "third-party literature" or in the form of labeling provided by the manufacturer for inclusion on or with the product. One member believes that the publications exempted from labeling should be independent and should not be written, developed, or funded by the manufacturers or sellers of dietary supplements, apart from any support they provide for the underlying scientific research.

There is uncertainty regarding the scope of the circumstances under which literature may be provided to consumers under the labeling exemption. It is clear from DSHEA that such literature may be provided in the retail setting, provided it is displayed in a location separate from the dietary supplement. Apparently it may also be provided in other instances, including direct sales (person-to-person sales), and some suggest it may even apply to mail order sales (7).

DSHEA requires that the literature "not promote a particular manufacturer or brand of a dietary supplement." The Commission has considered what constitutes promotion for purposes of this section. For example, in the case of a scientific article, the "methods" section of the article may identify a product that was used in the study and donated by the manufacturer (69). In the view of the Commission, the practice of donating products for research studies or directly supporting research on dietary supplements should be encouraged, and the mere mention of the identity of a product in a scientific article should not be viewed as "promotion" of that product. If mention of the product in this context were viewed as promotion, then all manufacturers other than the one that provided the material would be free to use the article as "third-party literature." This would not appear to be a reasonable outcome. However, this may be a moot point because, as mentioned above, the full text of a scien-

tific article seems unlikely to be used directly for consumer information.

FINDING

The Commission supports the provision of balanced, truthful information to consumers regarding the uses of dietary supplements. The literature provision of DSHEA should be used with care, strictly observing the five requirements pertaining to such literature.

GUIDANCE

- Because 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.

BOTANICAL PRODUCTS

Botanical products represent a major category of permissible ingredients of dietary supplements, but they also are used as conventional foods, culinary adjuvants, and drugs. In the United States, the highest-volume use of botanicals is undoubtedly as foods. This includes such staples of the U.S. diet as potatoes, tomatoes, corn, wheat, oats, rice, leafy greens, carrots, onions, and garlic. Many plants are also used as spices and flavorings. FDA regulations list approximately 250 botanical ingredients (and their essential oils and extracts) that are generally recognized as safe (GRAS) for use in foods as spices and flavorings, essential oils, and natural extractives (110-113). In addition, more than 100 are listed as approved flavoring agents for use as natural flavorings in foods and beverages (109).

In many countries, botanical remedies are a major component of the pharmacopeia of available medicinals. The Commission is aware that 80 percent of the world's population relies mainly on health care systems that include the use of plant extracts or their active ingredients (2). Further, many developed and developing countries have established regulatory systems covering the recognized preventive and therapeutic uses of botanical remedies (70). The United States is a notable exception.

1. Statements of Nutritional Support

When marketed as dietary supplements, botanical products are permitted to bear statements of nutritional support in the same manner as all dietary supplements. After reviewing letters of notification submitted to FDA, the Commission concluded that in many cases, a statement of nutritional support may be adequate to inform consumers of the appropriate use of a specific botanical product. However, the Commission also concluded that many botanicals now are being labeled with statements of nutritional support that suggest only indirectly the type of therapeutic use that is traditional for the product. In such cases, the Commission questions whether the statement of nutritional support is adequate to convey to consumers the intended use of the product.

For example, Figures 2 and 3 compare statements related to the uses of echinacea and ginger, respectively, in draft WHO model monographs (140) with statements of nutritional support from notification letters received by FDA. Most Commissioners believe that there are instances when statements concerning treatment such as those found in the WHO model monographs may be more informative to consumers than the less specific language used in some of the statements of nutritional support.

2. NLEA Health Claims

Botanical products, as dietary supplements, are theoretically eligible for the FDA-approved NLEA health claims, provided all of the requirements for health claims can be met. The Commission is not aware that any petition has been filed with FDA to request approval of an NLEA health claim for any botanical, except those used primarily as foods. For example, a health claim for soluble fiber from whole oats was approved in January 1997 and amended in May 1997 to include psyllium husks containing sufficient levels of naturally occurring β-glucan to help lower cholesterol and thus reduce the risk of coronary heart disease (34,35).

In practice, some botanical products may have difficulty meeting the requirements for eligibility as NLEA health claims as set forth in the statute and 21 CFR 101.14 (99). For example:

1. The product may not meet the requirement of providing aroma, taste, or nutritive value.
2. The ingredient(s) may not meet other requirements established in regulations implementing NLEA, including the requirement that use of the ingredient(s) "at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful . . ." (101).
3. The product claim may not relate to a "risk of disease or health-related condition that is diet related, taking into account the significance of the food in the total daily diet . . ." (FDCA Section 403(r)(3)(A)(ii)).
4. The evidence supporting the health claim may be based on historical use rather than current scientific studies and thus may not meet the test of "significant scientific agreement."

The Commission suggests that NLEA health claims be permitted for botanical products where appropriate but recognizes that NLEA health claims will not cover all uses of such products, especially when the use is not diet related or relates to an acute condition or to treatment.

3. Regulation of Botanical Products in Other Countries

Several references regarding the regulation in other countries of botanical products for multiple uses were submitted to and reviewed by the Commission (8,70,137). Botanical pharmacopeias have been established by a number of countries, including Germany, France, the United Kingdom, and Japan. Systems of regulation applicable to therapeutic uses of botanical remedies have been established by the aforemen-

Figure 2

ECHINACEAE PURPUREAE

WHO Model Monograph

"11.1 Uses supported by clinical data.

Herba Echinaceae is administered orally as an immunostimulant, in supportive therapy for colds and infections of the respiratory and urinary tract (1,3,5,7,8,18). Beneficial effects in the treatment of these infections are generally thought to be brought about by stimulation of the immune response (3,5,7). The term 'supportive therapy' denotes that *Echinacea* would ordinarily be administered together with other antibacterial agents, such as antibiotics or sulfa drugs (1).

External uses include: promotion of wound healing, and inflammatory skin conditions (1,5,7,8,9,19). *Echinacea* preparations are used in topical applications for the treatment of chronic superficial wounds and skin inflammations (3,5,7,19).

11.2 Uses described in pharmacopoeias and in traditional systems of medicine.

None.

11.3 Uses described in folk medicine, not supported by experimental or clinical data.

Other medical uses claimed for *Echinacea* preparations include treatment of yeast infections, side effects of radiation therapy, rheumatoid arthritis, blood poisoning, and food poisoning (1,5,7,9)."

(Numbers in parentheses refer to citations of scientific literature in the WHO monograph.)

Statements of Nutritional Support from Notification Letters to FDA

"For immune system function."

"Nutritionally supports healthy immune function."

"Helps stimulate natural resistance."

"Echinacea has been the subject of numerous scientific studies involving its ability to help maintain natural resistance."

"Many Native American tribes have used Echinacea, or purple coneflower, for centuries. The Cheyenne and Comanche gathered this plant for use during cold seasons. It quickly won the favor of early European settlers and has now become a well-loved herb both here and abroad. Scientific research studies on Echinacea abound, documenting its ability to help maintain overall health and well-being."

"Echinacea promotes the body's natural resistance by supporting a healthy immune system. Echinacea continues to be popular in Europe to strengthen and enhance overall well-being."

Figure 3

RHIZOMA ZINGIBERIS

WHO Model Monograph

"11.1 Uses supported by clinical data.

The principal clinical use of ginger is for the prophylaxis of nausea and vomiting associated with motion sickness (20-23), postoperative nausea (24), *hyperemesis gravidarum* (25),[2] and sea sickness (26,27).

11.2 Uses described in pharmacopoeias and in traditional systems of medicine.

Ginger is also indicated for the treatment of dyspepsia, flatulence, colic, vomiting, diarrhea, spasms and other stomach complaints (1,2,4, 9,21). Powdered ginger is further employed in the treatment of colds and flu, to stimulate the appetite, as a narcotic antagonist (1,2,4,6,11,12,21), and as an anti-inflammatory agent in the treatment of migraine headache, and rheumatic and muscular disorders (9,11,12,28).

11.3 Uses described in folk medicine, not supported by experimental or clinical data.

Other medical uses for ginger include the treatment of cataracts, toothache, longevity, insomnia, baldness and hemorrhoids (9,10,12).

[2] Although ginger appears to be clinically effective in the treatment of *hyperemesis gravidarum*, it is currently not recommended for use in morning sickness during pregnancy (25), see Precautions section 15.5."

(Numbers in parentheses refer to citations of scientific literature in the WHO monograph.)

Statements of Nutritional Support from Notification Letters to FDA

"Stimulates digestion. Ginger is an aromatic bitter herb that stimulates digestion."

"Ginger is one of the world's most popular spices, and a well researched herb for a healthy lifestyle. The pungent taste of ginger, prized in international cuisine, has been linked to beneficial compounds which warm and soothe the stomach. Ginger has been a favorite of travelers since ancient mariners discovered it in the exotic Orient."

"Ginger root is a soothing and warming herb for the stomach and may help maintain a calm stomach while traveling."

"Eases the discomfort associated with traveling. Ginger is an aromatic bitter herb that eases the discomfort associated with traveling and stimulates digestion to promote gastrointestinal comfort."

tioned countries as well as by Canada and other nations. Twelve of eighteen industrialized countries for which information was available have formal mechanisms allowing therapeutic claims for botanical products based on a combination of historical and scientific information. In some countries, clinical evidence is required to support recommended uses. In other countries, traditional use is sufficient to provide the basis for a limited therapeutic claim, but a disclaimer may be required (Table 3). Some countries have established lists of ingredients that are permitted or not permitted and/or lists of permitted claims for botanical products used for therapeutic purposes. WHO has published guidelines for the regulation of traditional medicines, including botanical remedies (141), and is finalizing a series of model monographs on specific botanicals (140).

Japan, China, and other Asian countries all have long histories of use of botanicals and other natural products. It should be recognized that products defined in the United States as dietary supplements (botanicals, vitamins, minerals, amino acids, hormones, enzymes) are generally regulated as drugs in Japan, China, and other Asian countries (70,121,133). Direct comparison of the Japanese and Chinese regulatory systems with that of the United States is further complicated because of differences in nomenclature and classifications.

In China, traditional Chinese medicine uses more than 6000 natural products. About 500 are most commonly used and of these about 82 percent are derived from plants, 12 percent from animals, and 6 percent are minerals. Most of these are regulated as drugs (70). With regard to foods purported to have special health benefits, recent legislation in The People's Republic of China bans the marketing of unregistered "health foods" and institutes an inspection process for manufacturers of such products (144).

The Commission concluded that a comprehensive evaluation of regulatory systems used in other countries for botanical remedies is needed. Such an evaluation should consider the scope of products covered, the means of assuring safety and preventing deception, the effect of such systems on overall medical care, the issue of defining appropriate OTC uses of products, and the appropriateness and applicability of the different types of disclaimers.

The Commission studied these issues in detail and concluded that although such a study is needed a comprehensive evaluation exceeds the mandate of the Commission. A comprehensive evaluation of the U.S. drug regulatory system and approaches used in other countries to the regulation of drugs, alternative medicines, and traditional botanical remedies is long overdue.

If the study were to suggest the use of botanical remedies under a lower standard of efficacy and a different approval process than that presently required by law for drugs, one member strongly recommends, in such a case, that the review also consider the need for a disclaimer that states: "This product is not generally recognized by experts and has not been approved by FDA

Table 3

EXAMPLES OF DISCLAIMERS USED IN OTHER COUNTRIES

Country	Disclaimer
Belgium	"traditionally used in . . ., even though its activity has *not* been established according to the actual criteria of evaluation of medicines."[1]
Canada	"traditional medicines"[1]
France	"traditionally used for . . ." or "used in . . ."[1]
Germany	"Traditionally used (e.g.) for preventive purposes. This product is not intended for the cure or mitigation of illness, physical deficiencies or ailments. Anyone who has such illness or ailment should consult a physician. This product is used traditionally and it cannot be deduced therefrom whether the product is generally useful."[2]
Greece	Wording frequently used: "possibly effective" and "traditionally used"[1]
Ireland	"The wording on the labeling is mandatory and states the following: i) Do not take in connection with other medications without having consulted a physician. ii) Do not use for longer than two weeks. The drug safety cannot be guaranteed for a prolonged period of use. iii) Should the condition not improve, consult a physician. iv) Allergic reactions are possible. v) Traditional herbal remedy for short-term treatment of slight discomforts and that should . . . not be used for extended periods without the advice of a physician." [1]
United Kingdom	"a traditional remedy for the symptomatic relief of . . ." and "if symptoms persist, consult your doctor"[1]

[1]Gericke, N. 1995. The regulation and control of traditional herbal medicines: an international overview with recommendations for the development of a South African approach. Working draft document. Cape Town, South Africa: Traditional Medicines Programme, University of Cape Town.
[2]Nozari, F. 1994. Dietary supplements. Report to Congress. LL94-3. Washington, DC.

as effective based on adequate and well-controlled studies." A change in the drug approval process or the standards for drug efficacy would require legislative action.

Some witnesses at Commission hearings suggested that the regulatory system in the United States should accommodate therapeutic claims for products currently marketed as dietary supplements. However, as defined in DSHEA and FDCA, products promoted for the treatment, prevention, mitigation, or cure of disease fall outside of the definition of dietary supplements. To the extent that botanical preparations are marketed for use as dietary supplements, their usage and all aspects of their labeling should comply with the requirements of DSHEA.

4. OTC Drug Uses of Botanical Products

Public testimony before the Commission indicated that many of the recognized traditional uses of botanical products are similar to those classified in the United States as OTC drug uses. Based on the testimony presented, the Commission believes that the history of use and the scientific evidence available for some botanical remedies may be sufficient to justify OTC approval within the U.S. drug regulatory system as it currently exists.

For the past 25 years, FDA has been reviewing the safety and efficacy of OTC drugs. Some botanical ingredients have been reviewed. Of these, six were listed as safe and effective for their intended uses and more than 150 were eliminated from consideration. However, the Commission believes many botanical manufacturers may not have participated in the OTC review, reportedly out of a concern that FDA would not consider approving botanical ingredients.

The Commission understands that petitions for OTC approval of two botanical products (valerian as a sleep aid and ginger as an antiemetic or for relief of symptoms of motion sickness) were submitted in 1992 to FDA by the European-American Phytomedicines Coalition but have not yet been approved.

In light of the increased public interest in botanical remedies, the Commission believes that FDA needs to give special attention to the feasibility of approving botanical remedies for OTC uses in cases in which sufficient evidence is available. The Commission recommends that FDA convene a botanical products review panel to review petitions concerning such products. Such a panel should include experts with an appropriate scientific background in pharmacognosy as well as experts in other applicable disciplines. In its deliberations, this panel should give priority to botanical remedies having the strongest supporting evidence. Initial candidates might include, for example, the botanical products for which the U.S. Pharmacopeial Convention, Inc., is currently establishing standards (132) and/or botanicals for which WHO has prepared draft model monographs (140).

The Commission urges FDA to put a high priority on expediting such a review panel. FDA should also explore whether it would be helpful to convene a scientific con-

ference or workshop on a given product or set of products. The Commission also urges manufacturers of botanical products to prepare and submit scientific data as well as information on the "material time and extent" of use of the ingredient for the relevant purposes to facilitate review when FDA requests such data (39).

To be approved as OTC drugs, products must be generally recognized as safe and effective (116). Proof of safety includes adequate testing by methods reasonably applicable to show that an OTC drug is safe under the prescribed, recommended, or suggested conditions of use. General recognition of safety is ordinarily based on published studies, which may be corroborated by unpublished studies and other data (117). If these standards for safety are not met, submission of a new drug application is required. The U.S. Supreme Court has stated that it "may, of course, be true that in some cases general recognition that a drug is efficacious may be made" without this kind of testing, but "the reach of scientific inquiry" is the same (139).

Proof of effectiveness requires controlled clinical investigations that meet the regulatory criteria for adequate and well-controlled studies (115), unless the requirement is waived because it is not reasonably applicable or essential to the validity of the study and alternative methods of investigation are available (118). Proof of efficacy may also take into account partially controlled or uncontrolled studies, clinical studies by qualified experts, and experiential reports; isolated case reports and random experience are not considered.

FDA has waived requirements for well-controlled clinical studies for some OTC products. For example, in the case of certain OTC drugs used for earwax removal, an FDA advisory panel reviewed studies and clinical data showing that carbamide peroxide in anhydrous glycerin is effective in removing earwax. However, the panel noted that these studies were neither double blinded nor placebo controlled (59). FDA subsequently acknowledged that it agreed with the panel's conclusions and waived the requirement for double-blinded or placebo-controlled studies. FDA stated that the methods of investigation, along with the results of the studies, and human experience justified the waiver. Further, the study subjects were "examined professionally" and the earwax removal product achieved its intended effect by means of "mechanical action" (59). FDA promulgated a final rule based on the panel's conclusions and the agency's concurrence (58).

Some members of the Commission expressed concern that the existing FDA requirements for adequate and well-controlled clinical studies would preclude approval of some botanical remedies as OTC drugs because these types of studies have not been done. However, they also noted that over the past several years, OTC drug review panels and FDA reviewers have occasionally applied standards to some products that differ from those specified in the CFR (116).

For example, in a review of slippery elm bark as an antitussive OTC drug, an FDA panel in 1976 observed that there was a long history of safe use but that there were

no well-controlled studies of effectiveness (63). It noted that data to support efficacy were needed. In 1982, another FDA advisory panel, citing the 1976 advisory panel report, recommended that slippery elm bark be approved as a safe and effective oral demulcent (60). The second advisory panel reviewed no new data. Based on the findings of this second panel, FDA proposed that elm bark be recognized as a safe and effective oral demulcent (56).

Similarly, in approving witch hazel as an OTC skin protectant drug, FDA relied on an advisory panel review of data submitted by manufacturers, absence of reports of adverse effects, and long history of use (61). The advisory panel referenced one animal study and one in vitro study of blood clotting efficiency. FDA's approval was based on the advisory panel's review and information published by the U.S. Pharmacopeial Convention, Inc., as sufficient to establish safety and effectiveness (54).

The Commission recommends that the amount of evidence required to support an OTC claim for a botanical product be determined specifically for each type of use being considered. The type of evidence that was required for OTC drugs already approved for certain uses should be the benchmark for determining what is generally recognized as sufficient evidence for botanical products intended for the same uses now. If a higher standard is deemed to be required today than was required historically, justification should be provided by FDA to show that such a higher standard is in the best interest of consumers who are currently using OTC drugs approved under a different standard. The Commission's recommendation regarding creation of an OTC review panel for botanical remedies is based on the assumption that there would be equity in the OTC review process and that it would apply equally to currently approved OTC drugs and to any botanical product covered by a new review.

FINDINGS

The Commission recognizes that DSHEA includes botanicals under the definition of dietary supplements and does not intend to recommend any change in legislation to alter the status of these products as dietary supplements. They should continue to be available as dietary supplements when labeled as dietary supplements in accordance with DSHEA. Manufacturers should make every effort to inform consumers and health professionals of the basis for any statements of nutritional support that are made in the labeling of these products as dietary supplements.

The Commission observed that many botanical products are used traditionally for prevention and treatment purposes. The scientists on the Commission noted that in some cases, current scientific evidence supports such uses. Most Commissioners concluded that consumers would be better served by clear information regarding such uses than by the limited statements of nutritional support permitted by DSHEA. Current efforts to use statements of nutritional support to suggest such uses without overtly stating them may not provide sufficient information to consumers and may also create a climate of deception that

serves neither the industry nor consumers. The Commission believes its recommendation to encourage manufacturers wishing to make claims that go beyond those allowed by NLEA or DSHEA to submit them for OTC review would be in the public interest. Botanicals have always been included as potential candidates for OTC status. The Commission is not recommending a new category of OTC drugs, but believes that a dedicated OTC panel on botanicals would facilitate the review of appropriate OTC claims. In the judgment of the Commission, the extension of the existing OTC process to botanical remedies that are most likely to meet the existing requirements would not require new legislation but could be accomplished within the current legal and regulatory framework for OTC drugs. This concept is consistent with the OTC drug guidelines where there is general recognition of safety and efficacy and adequate current scientific evidence comparable to the evidence that was considered in approving similar OTC uses in the past.

In many other industrialized countries, specific claims for botanical remedies and medicines are permitted, generally in a separate category of nonprescription products within the drug regulatory system. Some Commissioners believe there should be a comprehensive evaluation of the potential applicability of such a system in the United States.

GUIDANCE

- More 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. The study should include the types of disclaimers that might apply and the appropriateness of such a system within the U.S. regulatory framework. Such a comprehensive study would go beyond the mandate of this Commission, which is limited to dietary supplement uses of these products.

- The Commission concluded that a comprehensive evaluation of regulatory systems used in other countries for botanical remedies is needed. Such an evaluation should consider the scope of products covered, the means of assuring safety and preventing deception, the effect of such systems on overall medical care, the definition of appropriate drug uses of products, and the appropriateness and applicability of the different types of disclaimers.

RECOMMENDATIONS

- The Commission recognizes that, under DSHEA, botanical products should continue to be marketed as dietary supplements when properly labeled.

- The Commission strongly recommends that FDA promptly establish a review panel for OTC claims for botanical products that are proposed by manufacturers for drug uses. The panel should have appropriate representation of experts on such products.

ENDNOTES

1. On September 23, 1997, FDA published a final rule that provides guidelines for the content of notification letters. Specifically, the final rule calls for the notification to contain the following information:

   - The name and address of the manufacturer, packer, or distributor of the dietary supplement that bears the statement;
   - The text of the statement that is being made;
   - The name of the dietary ingredient or supplement that is the subject of the statement, if not provided in the text of the statement;
   - The name of the dietary supplement (including brand name), if not provided . . . in the label where the statement appears; and
   - The signature of a responsible individual or the person who can certify the accuracy and completeness of the information presented and contained in the notification letter and that the notifying firm has substantiation that the statement is truthful and not misleading.

2. See Chapter I Endnote.

Chapter IV

ADDITIONAL ISSUES AND RECOMMENDATIONS IDENTIFIED BY THE COMMISSION

INFORMATION FOR CONSUMERS AND HEALTH PROFESSIONALS

The Commission devoted considerable attention to the need for assessment of consumer understanding and to the use of dietary supplement labeling. The information needs of consumers and health professionals must be met appropriately to ensure that the purposes of labeling are achieved.

The principle of using food labels to communicate messages that encourage a healthful diet and inform consumers of foods that may meet various nutritional objectives is well established (126). The emphasis has been on ensuring that the message on any given food label is of high quality, understandable, based on sound scientific information, and consistent with national nutrition policy. A review of issues related to consumer understanding of conventional food label claims is instructive because it is potentially analogous to the understanding of dietary supplement label claims.

Ippolito & Mathios (76) provide evidence that in the ready-to-eat cereal market, producer advertising and labeling are a significant source of information and reach consumers who are not being as well informed by government and general information sources. They confirm the ability of producer advertising and labeling to effectively communicate the link between diet and health to the public. However, it is important to note that the investigators evaluated consumers' changes in cereal choices during a time (1985 and 1986) when cereal manufacturers promoted their products using fiber-related health claims and that, at that time, there was no significant agreement in the scientific community on the relationship between dietary fiber and cancer. Another economic analysis of the regulation of health claims addresses the credibility of these claims on labels (10). Citing studies by Deighton in 1983 and 1984 (16,17), these authors assert that consumers tend to base their decisions on a "portfolio" of health information rather than on marketing information alone. That is, they tend to treat advertising claims with skepticism and check the truthfulness of claims against neutral sources of information, such as newspapers, magazines, books, physicians, and government sources.

A recent review on communication of food, nutrition, and health messages did not include dietary supplement labeling specifically but did address consumer understanding of nutrient content and health claims on food labels (80). In an appendix to this report, Levy (83) indicates that consumers in focus groups were interested in having information about the relationship between diet and disease. Some Commissioners interpret this study as suggesting that consumer research has not yet established a "mandate" for having health information on food labels as opposed to obtaining such information from health care providers, books, or the print and telecommunications media. Moreover, considering that food labels are viewed by consumers as reflective

of the manufacturer's interest in selling the product, consumers are skeptical about the veracity of health messages on food labels.

This skepticism may be exacerbated by the prevailing climate in which many consumers have a sense that they are constantly being bombarded with conflicting information about nutrition. In this context, the study (83) may suggest that the precautions taken to make nonmisleading food label claims involving any aspect of the diet-health relationship may satisfy policy makers but may be ineffective in reassuring consumers that label statements are reliable. In addition, while nutrient content claims can be verified by reference to the Nutrition Facts panel on the label, most other types of claims cannot be verified without further information, which by its very nature is too extensive to include on a label.

After several years of deliberations, FDA approved a number of health claims for use in food labeling and set forth "model health claims" to guide manufacturers. Recent research on consumer understanding of food label claims suggests that perceptions formed from label claims may differ from those intended in setting regulatory criteria. In focus groups conducted by FDA relating to health claims on food products, consumers did not discriminate between health claims and nutrient content claims when asked about statements on food packages that described possible health benefits of particular products (83). This conclusion was confirmed in a subsequent quantitative study of consumers' perceptions when exposed to food packages with various health claims and claim formats (84). When asked which food packages contained any "health" information, more than 90 percent of respondents identified products with only nutrient content claims. Further, at least four times as many respondents described the health benefits of the product in terms of its nutrient characteristics as in terms of its effects in alleviating disease. When asked closed-ended questions about the possible health benefits of the products, consumers generalized positive impressions conveyed by a nutrient content or health claim to benefits other than those explicitly identified in the message (sometimes referred to as a "halo" effect). However, fewer of them did so in response to open-ended questions (84). As was also evident in FTC studies (10,76), consumers do not tend to look at label claims or advertising claims in isolation.

In contrast to the situation with food labels, in which policy makers seemed to be leading the public, support by consumers and industry for passage of DSHEA suggested that consumers want more flexibility in label claims for dietary supplements (136). The interest of policy makers in meeting this consumer need is reflected in DSHEA's provision for the establishment of the Commission on Dietary Supplement Labels to address "how best to provide truthful, scientifically valid, and not misleading information to consumers." Among the findings identified by Congress in DSHEA was the concern that "although the Federal government should take swift action against products that are unsafe or adulterated, the Federal government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers." In the view of those who promote dietary supplements, the interest in allowing flexibility in making label claims for supplements seems to be

more urgent than for foods. One reason for this is that while foods are consumed for many reasons, including health, anticipated health benefits are the only reason for consuming supplements. Thus, labeling with respect to potential health benefits may be more important in supplement choice than in food choice.

A syndicated study of 2,010 men and women (71) indicated that 58 percent of vitamin and/or mineral supplement users read the supplement label always, almost always, or most of the time. Of these, 33 percent looked for an explanation of benefits to be gained from taking supplements and 23 percent looked for scientific findings supporting use of the supplement (e.g., health claims). However, 78 percent of regular users believed that scientific information on package labels was very or somewhat important. The study indicated that scientific information and/or functional or health claims on product labels are important to and wanted by consumers. However, the study pointed out that this information is viewed by consumers in the context of information from other sources and their own knowledge and experience. The effective use of scientific information on labels may require a certain amount of education and personal experience on the part of the consumer (71).

FINDINGS

The Commission recognizes that evaluation of consumer information needs relating to dietary supplements is an important issue and makes several recommendations intended to provide more useful label information to consumers. Recent studies of consumer perceptions of food label claims illustrate the potential for miscommunication despite the efforts of policy makers to establish clear labeling guidelines and of manufacturers to comply with them. The Commission believes that there is value in providing information about nutrition and health to consumers on the product label, as authorized by NLEA and DSHEA. Reports on consumer research indicate that adequate effort must go into providing information that consumers understand. Clear, nonmisleading communication of dietary supplement attributes may pose unique challenges. The understanding by older adults of information relating to dietary supplements merits particular attention because older adults represent a substantial proportion of the users of dietary supplements (142).

Consumer comprehension of the uses of dietary supplements may be hampered by a lack of attention to dietary supplements by the traditional sources of consumer information about diet and health. Although surveys show that substantial numbers of Americans consume dietary supplements, the Commission believes that guidance provided by some scientific, health, and nutrition societies on supplement use is often limited. Evidence suggests that the American public obtains more information about diet and health from the media than from physicians and dietitians (85,127). Also, nutritional guidance by the Federal government provides limited discussion of supplements that may help consumers make appropriate decisions about supplement use (135). Current policy statements say that conventional foods should provide needed nutrients and that supplements are largely unnecessary in the context of a well-chosen diet.

The Commission believes that some professionals in medicine and nutrition devote more effort to refuting unsubstantiated and unrealistic claims than to providing sound information on appropriate, scientifically valid uses of dietary supplements. Research is needed on the attitudes of health and nutrition professionals toward supplements and the extent to which these attitudes are sufficiently specific (i.e., differentiating among different types and uses of dietary supplements) and informed. Such research may reveal ways in which health and nutrition professionals can better help the public interpret label information and scientific literature on dietary supplements. Health professionals need to take into account scientific developments that demonstrate the benefits of dietary supplements. There now are scientific studies and significant scientific agreement to support health claims on some dietary supplements. Dietary supplements are also permitted under DSHEA to make statements of nutritional support when the claims are substantiated and not misleading. To enable health professionals to evaluate these uses of dietary supplements, and to advise consumers about the uses, the health professionals need to have access to adequate information about the scientific basis for the statements.

In Section E of Chapter III of this report, the Commission suggests that manufacturers affirm in the notification letter, or in a separate public notice, that they have evidence to document statements of nutritional support and that the product is safe for its intended use. The Commission also concludes that some synopsis of the scientific evidence regarding statements of nutritional support and product safety should be available to potential buyers of dietary supplements. This conclusion is based primarily on the mandate in DSHEA which indicates that a major role of the Commission is to "evaluate how best to provide truthful, scientifically valid, and not misleading information to consumers so that such consumers may make informed and appropriate health care choices for themselves and their families." Thus, the Commission concludes that the dietary supplement industry has a responsibility not only to affirm that such evidence exists, but also to make summaries of information about the scientific evidence for statements of nutritional support and product safety available to the public. The Commission is suggesting that these summaries include evaluation of evidence from observational and experimental scientific studies on the effects of the specific dietary supplement or its active ingredient(s), if known.

Further, the dietary supplement industry should be responsive to requests for such summaries of evidence by interested parties. These summaries could be provided by manufacturers or independent organizations. A publicly accessible database might be a more efficient means of communication. Summaries or the database could be developed and maintained by a government agency such as ODS, a trade association, a consumer organization, or a partnership of such organizations. Criteria for inclusion of data should be stated in each summary. Data summaries on specific dietary supplements themselves, or a database, would help consumers, health professionals, and health care organizations in evaluating the extent of scientific evidence that supports label statements. In addition, publicly available data summaries on specific dietary supple-

ments or a publicly accessible database of these would have considerable educational value to all users.

For example, it would be important for consumers and health professionals to know whether a statement of nutritional support for a dietary supplement relating to a structure or function of the body is based on clinical data or on a long history of use of the supplement for the purpose mentioned in the statement of nutritional support. Similarly, it would also be important to know whether a statement relating to a biochemical mechanism is based primarily on in vitro studies of the physiological function of active compounds in the supplement or whether observational or experimental animal and human data are available to support the reputed effects.

The Commission recognizes that the summaries would need to be prepared with care in order to provide consumers and health professionals with responsible information. Summaries should be balanced and not misleading. Because statements of nutritional support cannot, under the provisions of DSHEA, claim to prevent or treat a disease or disorder, the summaries should similarly not make these types of claims.

The Commission believes that consumers and health professionals should have full access to the information supporting statements of nutritional support. The summaries should also indicate how health professionals can obtain access to the studies and evidence that support the statements. Full access would facilitate the ability of health professionals and consumers to evaluate these statements.

There may be a need to clarify whether these summaries are labeling or are publications exempt from classification as labeling. Currently, experience with such publications is quite limited, and any legislative or regulatory determination of this sort should be made on the basis of adequate experience. If the summaries are classified as labeling, they should bear the same disclaimer required by DSHEA for statements of nutritional support.

As indicated previously, Congress made it clear, in passing DSHEA, that these products and information about these products should be available so that consumers could make "informed and appropriate health care choices for themselves and their families." The Commission believes that providing consumers and health professionals with appropriate and nonmisleading summaries of scientifically valid evidence regarding substantiation of statements of nutritional support and product safety for specific dietary supplements would support this goal.

GUIDANCE

- The Commission urges that dietary supplement labeling be evaluated in additional consumer research to determine whether consumers actually want and can utilize the information provided by existing FDA regulations, by the requirements of DSHEA, and in the recommendations of this Commission. The Commission recognizes that consumer understanding of statements of nutritional support and health claims, as well as consumer perception of dietary supplement use based on literature at the point of sale, are important aspects

of the use of information that require additional and continued assessment.

- The Commission believes that it is important for health and nutrition professionals to become more knowledgeable about all types of dietary supplements and to assist the consumer in making appropriate health care choices with respect to use of dietary supplements.

- The Commission urges manufacturers to make available publicly balanced and nonmisleading summaries of the evidence substantiating statements of nutritional support and product safety for the intended use at the stated dosage. The summary should not claim use for prevention or treatment of disease.

NEED FOR INDUSTRY EXPERT ADVICE ON SAFETY, LABEL STATEMENTS, AND CLAIMS

The Commission believes the industry should be more proactive in incorporating scientific input to its decision-making regarding the safety and benefits of dietary supplements. The establishment of one or more expert advisory committees could be a productive way of obtaining such scientific input for the industry. Such committees might serve in an advisory role to individual companies, to members of specific trade associations, or to the industry as a whole, depending on the nature of the support available and the mechanism used for establishing such committees. Public comments received on the Commission's draft report expressed concern that these advisory committees might take over the role of reviewing NLEA health claims, but that was not the Commission's intent. The outside expert review that the Commission urges FDA to seek when evaluating health claims is an entirely separate topic from the industry's internal need for more scientific guidance, and the two topics are treated separately in this report. This section of the report addresses the need for industry to develop one or more mechanisms for strengthening its scientific basis for making label statements.

Dietary supplements are eligible for a variety of label statements and claims, each of which is subject to unique regulatory requirements. Despite differing regulatory provisions, in a practical sense, messages conveyed to consumers by label statements of nutritional support, NLEA health claims, and OTC drug claims are often similar. Manufacturers of dietary supplements have several options in determining which type of statement or claim is appropriate for a given product, in evaluating the degree of substantiation required for the statement or claim, and in deciding whether the evidence is sufficient to substantiate a statement of nutritional support under DSHEA or to justify a petition to FDA for approval of an NLEA health claim or an OTC drug claim.

The Commission believes the dietary supplement industry and consumers alike would benefit from an increased level of scientific input into decisions regarding label statements for dietary supplements. In addition, as emphasized elsewhere in this report, the Commission considers it axiomatic that dietary supplements must be safe for their intended uses, and scientific input is essential in making such determinations. Accordingly, the Commission recommends that the industry consider establishing an

expert advisory committee on dietary supplements to provide scientific review of label statements and claims and to provide guidance to the industry regarding the safety, benefit, and appropriate labeling of specific products. Such a committee might be supported by one or more industry trade associations or might be established as an independent entity funded by extramural grants and/or fees for services.

A number of models illustrate the value and reliability of expert outside review as a means of helping to resolve issues relating to the safety and/or benefits of specific products or groups of products. The Flavor and Extract Manufacturers Association (FEMA) has conducted its own GRAS review of flavor compounds and the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA) has conducted its own Cosmetic Ingredient Review. In these two instances, the reviews are organized and funded by industry but involve extramural scientists with appropriate expertise and experience who conduct quality reviews that are made available publicly.

AHPA proposed a botanical ingredient review to FDA as an alternative mechanism for approving NLEA health claims for botanical ingredients. Although the agency declined to incorporate such an outside review into its procedures for approving health claims, the Commission believes there would be value in the industry's undertaking such reviews in the spirit of self-regulation and with the goal of increasing consumer confidence in both the safety and the efficacy of dietary supplements. Some Commissioners believe that an expert outside review would also enhance the quality of petitions submitted to FDA for approval of an NLEA health claim or an OTC drug claim for a product.

To assure the credibility of an expert advisory committee, any such committee should be composed of scientific experts with appropriate specialties in nutrition, pharmacognosy, pharmacology, health promotion and disease prevention, medicine, and toxicology. Some Commissioners believe it would be desirable to include participation by the U.S. Pharmacopeial Convention, Inc., FDA, the National Academy of Sciences, and international bodies such as WHO. Regardless of the composition of the committee, procedures should be in place to avoid conflict of interest.

The Commission recognizes that the support of an expert advisory committee in the pursuit of a comprehensive review of dietary supplement ingredients would be a major and costly undertaking. However, the success of the CTFA and FEMA reviews indicates that the value of the undertaking might be well worth the investment.

GUIDANCE

- The Commission recommends that the dietary supplement industry consider establishing an expert advisory committee on dietary supplements to provide scientific review of label statements and claims and to provide guidance to the industry regarding the safety, benefit, and appropriate labeling of specific products. Such a committee might be supported by one or more industry trade associations or might be established as an independent entity funded by extramural grants and/or fees for services.

RESEARCH ISSUES

DSHEA recognizes the importance of research in relation to dietary supplements. In the findings section of the legislation, Congress indicated that the importance of nutrition and the benefits of dietary supplements to health promotion and disease prevention have been increasingly documented in scientific studies. The Commission endorses the continuation of these types of studies. DSHEA establishes ODS within NIH to promote scientific studies of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions. Thus, it seems clear that Congress recognized that use of dietary supplements should be based on a strong foundation of scientific research.

As discussed elsewhere in this report, the Commission considered the availability of scientific evidence supporting the benefits of dietary supplements and deliberated on the type of evidence that may be used to substantiate health claims and statements of nutritional support. In the course of these deliberations, it became evident that the research base for supporting various types of statements for dietary supplements is highly variable.

Over the past several decades, the Federal government has supported a significant body of basic research on ingredients used in dietary supplements, specifically vitamins, minerals, and amino acids. In addition to the basic work on most of the vitamins and minerals, in recent years large clinical or epidemiologic studies have been carried out dealing with the relationship between nutrients and diseases (e.g., vitamins E and C and cardiovascular disease and cancer, selenium and cancer, β-carotene and cancer, calcium supplements and osteoporosis).

The Commission is unable to ascertain with certainty the magnitude of federally supported basic and applied research associated with dietary supplements due to difficulties in retrieving such data. However, some estimates can be derived from existing information.

According to data provided from the Human Nutrition Research and Information Management System (HNRIMS), in fiscal year 1995, expenditures by Federal agencies on human nutrition, research, manpower development training, and education totaled about $540 million (82) (Table 4). Comparison of data from 1986 to 1995 (Table 5) suggests a progressive increase in Federal funding for nutrition research and training (74,82). However, the portion of research directly applicable to dietary supplements cannot be determined. ODS is defining a series of codes for dietary supplements to allow inclusion of data on dietary supplement research expenditures in the HNRIMS databases. This effort will be completed later this year or in 1998.

There has been relatively little Federal support of basic research dealing with the mechanism of action of botanical products. In view of the public's interest in dietary supplements, the Commission believes that additional Federal funding should be directed toward evaluation of the potential health benefits and safety of a wide range of dietary supplements, including botanical products. Such research results can provide information that consumers can use to make informed decisions about their health.

Table 4

FISCAL YEAR 1995 EXPENDITURES AND NUMBER OF PROJECTS IN HUMAN NUTRITION RESEARCH, MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION BY FEDERAL AGENCIES

Agency	Expenditures (Dollars in Thousands)	Percent of Total Expenditures	Number of Projects	Percent of Total Projects
Department of Health and Human Services (DHHS):				
National Institutes of Health	428,687	79	2,620	60
Food and Drug Administration	1,464	<1	15	<1
Centers for Disease Control	4,713	1	3	<1
Health Resources and Services Administration	344	<1	2	<1
Total DHHS	435,208	81	2,640	60
Agency for International Development	6,104	1	14	<1
National Science Foundation	41	<1	8	<1
Department of Veterans Affairs	9,962[a]	2	558	13
Department of Commerce	502	<1	1	<1
Department of Defense	3,545	<1	6	<1
National Aeronautics and Space Administration	855	<1	8	<1
U.S. Department of Agriculture	84,217	16	1,137	26
Total Federal Expenditures[b]	540,436	100	4,372	100

a Estimate
b Totals may be imprecise due to rounding

Source: This table was modified from information provided by the Human Nutrition Research and Information Management System (82).