federal register

Wednesday
April 29, 1998

Part VI

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 101

Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Proposed Rule and Dietary Supplements: Comments on Report of the Commission on Dietary Supplement Labels; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101
[Docket No. 98N–0044]

RIN 0910–AA59

Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing regulations defining the types of statements that can be made concerning the effect of a dietary supplement on the structure or function of the body. The proposed regulations also establish criteria for determining when a statement about a dietary supplement is a claim to diagnose, cure, mitigate, treat, or prevent disease. This action is intended to provide direction to the dietary supplement industry and to respond to guidance on this issue provided by the Commission on Dietary Supplement Labels (the Commission).

DATES: Written comments and recommendations by August 27, 1998.

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

FOR FURTHER INFORMATION CONTACT: Jeanne Latham, Center for Food Safety and Applied Nutrition (HFS–456), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–4697.

SUPPLEMENTARY INFORMATION:

I. Introduction

The Dietary Supplement Health and Education Act of 1994 (the DSHEA) authorizes manufacturers of dietary supplements to make certain types of statements about the uses of their products. Among the types of permitted statements are certain claims that, prior to enactment of the DSHEA, could have rendered the product a ''drug'' under the Federal Food, Drug, and Cosmetic Act (the act). Specifically, section 403(r)(6) of the act (21 U.S.C. 341(r)(6)), added by the DSHEA, allows dietary supplement labeling to bear a statement that ''describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans'' or that ''characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function.'' These types of claims are generally referred to as ''structure/function claims.''

Certain other types of statements about dietary supplements continue, under the DSHEA, to cause the product to be regulated as a drug. Statements permitted under section 403(r)(6) of the act ''may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases,'' except that such statements may claim a benefit related to a classical nutrient deficiency disease, provided that they also disclose the prevalence of the disease in the United States. Such statements are generally referred to as ''disease claims.'' FDA notes that certain statements that pertain to a disease or health-related condition are permitted on food products, including dietary supplements. These statements are known as health claims (see section 403(r)(1)(B) of the act) and describe the relationship between a nutrient and a disease or health-related condition. Unlike structure/function claims, health claims must be authorized by FDA before they may be used on the label or in the labeling of a food or dietary supplement (see section 403(r)(3) and (r)(4) and 21 CFR 101.14 and 101.70). Thus, certain claims about disease may be made for foods and dietary supplements without causing these products to be regulated as drugs, provided the claim has been authorized for use by FDA in accordance with the applicable regulations. FDA also notes that a dietary supplement for which only structure/function claims are made in the label or labeling in accord with section 403(r) of the act may nevertheless be subject to regulation as a drug if the agency has other evidence (see 21 CFR 201.128) that the intended use of the product is for the diagnosis, cure, mitigation, treatment, or prevention of disease.

A dietary supplement manufacturer who wishes to make a permitted structure/function statement under section 403(r)(6) of the act must have substantiation that the statement is truthful and not misleading, and must include in the statement 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.'' The DSHEA requires the manufacturer of a dietary supplement bearing a statement under section 403(r)(6) of the act to notify FDA, no later than 30 days after the first marketing of the dietary supplement with the statement, that such a statement is being made for the product. Regulations implementing these requirements were published in the **Federal Register** of September 23, 1997, and are codified at § 101.93 (21 CFR 101.93) (62 FR 49859 at 49883, September 23, 1997, OMB Control Number 0910–0351).

Diseases, by definition, adversely affect some structure or function of the body, and it is possible to describe most products intended to treat or prevent disease in terms of their effects on the structure or function of the body. The DSHEA, thus, does not authorize the use of all claims that describe the effect of a dietary supplement on the structure or function of the body. Instead, section 403(r)(6) of the act authorizes only those structure/function claims that describe an effect of a product on the structure or function of the body but that are not also disease claims. Because the distinction between allowable structure/function claims and disease claims is not always obvious, the dietary supplement industry has requested clarification from FDA on structure/function claims that can be made for dietary supplements under section 403(r)(6) of the act. To develop clarifying criteria for such claims, FDA has reviewed the notification letters that have been submitted to FDA under section 403(r)(6) of the act. In addition, FDA has reviewed the report of the Commission, which was established by the DSHEA to provide guidance and recommendations for the regulation of label claims and statements for dietary supplements.

The Commission issued a draft report (the draft report) on June 24, 1997, among other things, the report included the Commission's views on ''what constitutes an acceptable statement * * * of the structure/function type'' (the draft report, p. 36). The Commission received public comment on the draft report and issued a final report (the report) on November 24, 1997. Guidance in the report ''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'' (the report, p. vi).

The Commission's final report contains the following guidance (the guidance) on the scope of permissible structure/function claims:

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.''

(The report, pp. 38–39).

The guidance thus focuses on the distinction between allowable structure/function claims and claims that a product can diagnose, treat, prevent, cure, or mitigate disease (disease claims), and makes clear that structure/function claims made for dietary supplements should not imply treatment or prevention of disease. The guidance also provides examples of types of structure/function claims that do and do not imply disease claims. In its findings, the Commission expressed the view that ''guidance by FDA to manufacturers making statements [under section 403(r)(6) of the act][1] is appropriate and helpful in clarifying the appropriate scope of these statements'' (the report, p. 38).

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

FDA agrees with the Commission that an acceptable structure/function claim must not imply prevention or treatment of disease. FDA believes that the Commission's guidelines provide a useful framework for clarifying the sometimes difficult distinction between structure/function claims and disease claims. Based upon the Commission's advice and the agency's experience in reviewing notification letters submitted under section 403(r)(6) of the act, FDA has developed proposed regulations to define the types of claims that are ''disease claims'' and thus not acceptable as structure/function claims.

II. Provisions of the Proposed Rule and Guidance

As described in section I of this document, the manufacturer of a dietary supplement may make a truthful, nonmisleading labeling statement claiming that the product affects the structure or function of the body, unless the statement expressly or implicitly claims an effect on a disease or class of diseases (other than a classical nutrient deficiency disease). Therefore, to determine the scope of structure/function claims that may be made for a dietary supplement, it is necessary to define the types of claims about the effects of a product that are prohibited disease claims. The proposed rule is designed to provide criteria for determining when a statement about a product constitutes a disease claim.

The agency used several methods and sources to develop the proposed criteria for discerning which categories of labeling statements constitute express or implied claims that a product can diagnose, cure, mitigate, treat or prevent disease. To establish what types of claims the agency had already determined to be disease claims, FDA reviewed the letters it has sent in response to notifications from dietary supplement manufacturers, listing specific claims the agency regards as disease claims, as well as other regulatory actions taken in response to dietary supplement claims. FDA also reviewed the Commission Report's guidance on distinguishing structure/function claims and disease claims. In addition, the agency developed a definition of ''disease.'' As described below, the agency relied upon standard medical and legal definitions of disease as a basis for a proposed regulatory definition. The agency then used the proposed definition of disease to generate workable criteria, by applying the proposed definition to a wide variety of statements currently made by dietary supplement manufacturers to determine whether the statements claimed an effect on ''disease,'' as tentatively defined. Based upon the information derived from these reviews, the agency developed the general criteria below.

The proposed rule applies only to structure/function claims and disease claims within the meaning of section 403(r)(6) of the act. DSHEA generally, and section 403(r)(6) of the act specifically, apply only to dietary supplements for human consumption, and were enacted to provide a unique regulatory regime for these products. Thus, the proposed rule is not intended to apply to products other than dietary supplements for human consumption nor to interpret other provisions of the act.

A. Permitted Structure/Function Claims

Under proposed § 101.93(f), dietary supplement labels and labeling may bear structure/function statements that are not disease claims within the meaning of proposed § 101.93(g) and that otherwise comply with the notification and disclaimer provisions of § 101.93 (a) through (e), including the requirement that any structure/function statement be substantiated.

B. Definition of Disease

To assist in describing what constitutes a disease claim, the proposed rule contains a definition of ''disease.'' The proposed definition is based on standard medical and legal definitions of the term (Refs. 1, 2, 3 and 4). Under proposed § 101.93(g)(1), a ''disease'' is any deviation from, impairment of, or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of one or more signs or symptoms. For purposes of this definition, ''signs or symptoms'' include laboratory or clinical measurements that are characteristic of a disease, such as elevated cholesterol fraction, uric acid, blood sugar, and glycosylated hemoglobin, and characteristic signs of disease, such as elevated blood pressure or intraocular pressure.

To eliminate any inconsistency between this definition of ''disease'' and the definition of ''disease or health-related condition'' found in § 101.14(a)(6) and used for purposes of the agency's regulation of health claims, the proposal would also amend § 101.14(a)(6). That section defines ''disease or health-related condition'' as ''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 * * *'' Under the proposed amendment to 101.14(a)(6), ''disease or health-related condition'' would be defined, in relevant part, as:

''any deviation from, impairment of, or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of one or more signs or symptoms (including laboratory or clinical measurements that are characteristic of a disease), or a state of health leading to such deviation, impairment, or interruption; except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included within this definition * * *.

FDA believes that the proposed amendment of § 101.14(a)(6) is appropriate because experience since the issuance of the health claims regulations has shown that the current definition is too narrow in some respects. The term ''damage'' can be interpreted as limiting the definition to serious or long-term diseases, and as excluding certain conditions that are medically understood to be diseases, such as headaches. The proposed amendment, which covers both ''damage'' to an organ, part, structure, or system leading to dysfunction, and other deviations from, impairments of, or interruptions of the normal functioning of an organ, part, or system, more accurately covers the range of conditions that are medically understood to be diseases. FDA notes that the definition in § 101.14(a)(6) is intended to cover both diseases and ''health-related conditions.'' As amended, the proposed definition in § 101.14(a)(6) would remain broader than the proposed definition of ''disease'' in proposed § 101.93(g)(1) because proposed § 101.14(a)(6) includes the phrase ''or a state of health leading to such deviation, impairment, or interruption.''

C. Criteria for Identifying Disease Claims

Based upon the definition of disease in proposed § 101.93(g)(1), § 101.93(g)(2) of the proposed rule lists criteria for determining whether a statement about a product is a disease claim. To illustrate these criteria, FDA has provided examples of statements that would be considered disease claims under the proposed rule. FDA has also provided examples of statements that would not, by themselves, be considered disease claims. FDA emphasizes that in determining whether a statement about a product constituted a disease claim under these criteria, FDA would also consider the context in which the statement appeared. A statement that by itself would be considered an acceptable structure/function claim could become a disease claim if, in context, an effect on disease were expressed or implied. FDA seeks comment on the examples and the provisions of the proposed rule. To assist the industry, and especially small businesses, if the agency issues a final rule, it will issue an accompanying guidance providing examples of claims that would and would not be considered disease claims under the final rule.

1. Under proposed § 101.93(g)(2)(i), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect on a specific disease or class of diseases. Examples of such disease claims include: ''protective against the development of cancer,'' ''reduces the pain and stiffness associated with arthritis,'' ''decreases the effects of alcohol intoxication,'' or ''alleviates constipation.'' Claims that do not refer explicitly or implicitly to an effect on a specific disease state would not be disease claims under this criterion. Examples include: ''helps promote urinary tract health,'' ''helps maintain cardiovascular function and a healthy circulatory system,'' ''helps maintain intestinal flora,'' and ''promotes relaxation.'' FDA has tentatively concluded that these examples do not contain express or implied references to specific diseases. Instead, they refer broadly to body systems or functions without sufficient reference to specific abnormalities or symptoms to be understood as references to particular diseases.

2. Proposed § 101.93(g)(1) defines disease as any one of several types of abnormalities that are ''manifested by a characteristic set of one or more signs or symptoms.'' FDA believes that reference to a characteristic set of signs or symptoms, even in the absence of the name of the disease, can be understood as a reference to the disease itself. Under proposed § 101.93(g)(2)(ii), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect (using scientific or lay terminology) on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific disease or of a number of diseases. Examples of such disease claims include: ''improves urine flow in men over 50 years old'' (characteristic symptoms of, e.g., benign prostatic hypertrophy); ''lowers cholesterol'' (characteristic sign of, e.g., hypercholesterolemia); ''reduces joint pain'' (characteristic symptom of, e.g., arthritis); and ''relieves headache'' (characteristic symptom of, e.g., migraine or tension headache). In each of these cases, the symptoms described are sufficient to characterize one or more specific diseases. To determine whether a reference to a set of signs and symptoms constituted a disease claim, FDA would interpret the reference in context. Claims of an effect on symptoms that are not recognizable as characteristic of a specific disease or diseases would not constitute disease claims. Examples include: ''reduces stress and frustration,'' ''inhibits platelet aggregation,'' and ''improves absentmindedness.'' In these examples, the signs or symptoms noted may be broadly associated with a number of diseases, but are not, by themselves, sufficient to characterize a specific disease or diseases. If the context did not suggest treatment or prevention of a disease, a claim that a substance helps maintain normal function would not ordinarily be a disease claim. Examples include: ''helps maintain a healthy cholesterol level,'' or ''helps maintain regularity.''

FDA requests comment on the distinction between maintaining normal function, which is potentially the basis for an allowable structure/function claim, and preventing or treating abnormal function, which is potentially a disease claim. This can be a difficult distinction conceptually, especially if the only reason for maintaining normal function is to prevent a specific disease or diseases associated with abnormal function. According to the report, ''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 * * *'' (the report, pp. 36–37).

The Commission concluded that ''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'' (the report, p. 38). This is consistent with the criterion proposed by FDA. As the report illustrates, however, there can be disagreement about the circumstances in which a reference to maintaining normal function implies disease treatment or prevention. Therefore, FDA welcomes

comment on the basis for the distinction between maintaining normal function and preventing or treating abnormal function and on factors that help distinguish between claims relating to normal, healthy function that do not imply disease treatment or prevention and those that do. Because of the Commission's concerns that claims relating to maintaining healthy cholesterol levels raise particularly difficult issues (the report, p. 37), FDA seeks comment on these claims.

3. Certain natural states, such as pregnancy, aging, or the menstrual cycle, that are themselves not ''diseases,'' are sometimes associated with abnormalities that are characterized by a specific set of signs or symptoms, and thus meet the proposed definition of disease. Under proposed § 101.93(g)(2)(iii), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect on a consequence of a natural state that presents a characteristic set of signs or symptoms recognizable to health care professionals or consumers as constituting an abnormality of the body, such as toxemia of pregnancy, premenstrual syndrome, or abnormalities associated with aging such as presbyopia, decreased sexual function, Alzheimer's disease, or hot flashes. Claims that did not refer to a recognizable abnormality resulting from a natural state or to its signs or symptoms (e.g., ''for men over 50 years old,'' and ''to meet nutritional needs during pregnancy'') would not be disease claims under this criterion. These examples do not include references to specific abnormalities or symptoms. FDA thus believes that they would not be understood as references to particular diseases.

4. Various aspects of a product's labeling may be used to express or imply that the product will diagnose, cure, mitigate, treat, or prevent disease. Under proposed § 101.93(g)(2)(iv), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect on disease through one or more of the following factors:

(a) The name of the product (e.g., ''Carpaltum'' (carpal tunnel syndrome), ''Raynaudin'' (Raynaud's phenomenon), ''Hepatacure'' (liver problems)). Names that did not imply an effect on a disease, such as ''Cardiohealth'' and ''Heart Tabs,'' would not constitute disease claims;

(b) Statements about the formulation of the product, including a claim that the product contained an ingredient that has been regulated primarily by FDA as a drug and is well known to consumers for its use in preventing or treating a disease (e.g., aspirin, digoxin, or laetrile). FDA notes that this proposed rule is not intended to interpret section 201(ff)(3)(A) of the act (21 U.S.C. 321(ff)(3)(A)), and that a product may be included in or excluded from the definition of ''dietary supplement'' under that provision regardless of whether the statement made for the product under section 403(r)(6) of the act meets the criteria specified here;

(c) Citation of a title of a publication or other reference, if the title refers to a disease use. For example, labeling for a vitamin E product that included a citation to an article entitled ''Serial Coronary Angiographic Evidence That Antioxidant Vitamin Intake Reduces Progression of Coronary Artery Atherosclerosis,'' would create a disease claim under this criterion;

(d) Use of the term ''disease'' or ''diseased;'' or

(e) Otherwise suggesting an effect on disease by use of pictures, vignettes, symbols, or other means (e.g., electrocardiogram tracings, pictures of organs that suggest prevention or treatment of a disease state, the prescription symbol (Rx), or any reference to prescription use). A picture of a body would not constitute a disease claim under this criterion.

5. Certain product class names are so strongly associated with diagnosis, cure, mitigation, treatment or prevention of a disease or diseases, that a claim that a product belonged to such a class would be understood as a disease claim. Under proposed § 101.93(g)(2)(v), a statement would be considered a disease claim if it claimed that the product belonged in a class of products recognizable to health care professionals or consumers as intended for use to diagnose, mitigate, treat, cure, or prevent a disease (e.g., claims that the product was an ''antibiotic,'' a ''laxative,'' an ''analgesic,'' an ''antiviral,'' a ''diuretic,'' an ''antimicrobial,'' an ''antiseptic,'' an ''antidepressant,'' or a ''vaccine''). The foregoing examples do not constitute an exclusive list of product class names that convey disease claims. Claiming that a product was in a class that is not recognizable to health care professionals or consumers as intended for use to diagnose, mitigate, treat, cure or prevent disease (e.g., an ''energizer,'' a ''rejuvenative,'' a ''revitalizer,'' or an ''adaptogen'') would not constitute a disease claim under this criterion.

6. A statement may imply that a dietary supplement has an effect on disease by claiming that the effect of the dietary supplement is the same as that of a recognized drug or disease therapy. A statement may also imply an effect on disease by suggesting that the dietary supplement should be used as an adjunct to a recognized drug or disease therapy in the treatment of a disease. In both cases, the statement implies that the dietary supplement is intended for the same purpose as the drug or disease therapy, i.e., for the diagnosis, cure, mitigation, treatment, or prevention of disease. Under proposed § 101.93(g)(2)(vi) and (g)(2)(vii), a statement would be considered a disease claim if it explicitly or implicitly claimed that the product was a substitute for another product that is a therapy for a disease (e.g., ''Herbal Prozac'') or that it augmented a particular therapy or drug action (e.g., ''use as part of your diet when taking insulin to help maintain a healthy blood sugar level''). A claim that did not identify a specific drug, drug action, or therapy (e.g., ''use as a part of your weight loss plan'') would not constitute a disease claim under this criterion.

7. A statement may contain an express or implied disease claim if it suggests that the product cures, mitigates, treats or prevents a disease or diseases by augmenting the body's own disease-fighting capabilities. Under proposed § 101.93(g)(2)(viii), a statement would be considered a disease claim if it explicitly or implicitly claimed a role in the body's response to a disease or to a vector of disease. A vector of disease is an organism or object that is able to transport or transmit to humans an agent, such as a virus or bacterium, that is capable of causing disease in man. A claim that a product ''supports the body's antiviral capabilities'' or ''supports the body's ability to resist infection'' would constitute a disease claim under this criterion. Infections are well-known disease states that result from the action of pathogenic (disease-causing) microorganisms, such as bacteria and viruses, and are deviations from and impairments of the normal structure and/or function of the body with characteristic signs and symptoms. Claims that a product is intended to affect the body's ability to kill or neutralize pathogenic microorganisms, or to mitigate the consequences of the action of pathogenic microorganisms on the body (i.e., the signs and symptoms of infection) are disease claims because they are claims exclusively associated with the body's ability to prevent or respond to infectious diseases. A more general reference to an effect on a body system that has several functions, only one of which is resistance to disease, would not constitute a disease claim under this criterion (e.g., ''supports the immune system'').

8. Many adverse reactions to drugs or medical procedures meet the proposed definition of disease because they are abnormalities of structure or function manifested by a characteristic set of signs or symptoms. In addition, the clinical management of adverse events that are consequences of medical intervention is an integral part of the overall medical management of the underlying disease state for which the therapeutic intervention is intended. Therefore, claims that a product is intended to counter adverse events resulting from medical intervention are claims that the product is intended as a part of the treatment program and, as such, are claims that the product is to mitigate, treat, or cure the disease state. Under proposed § 101.93(g)(2)(ix), a statement would be considered a disease claim if it explicitly or implicitly claimed to treat, prevent, or mitigate adverse events associated with a medical therapy or procedure and manifested by a characteristic set of signs or symptoms (e.g., ''reduces nausea associated with chemotherapy,'' ''helps avoid diarrhea associated with antibiotic use,'' and ''to aid patients with reduced or compromised immune function, such as patients undergoing chemotherapy''). A claim that did not mention a therapy for disease (e.g., ''helps maintain healthy intestinal flora'') would not constitute a disease claim under this criterion.

9. Under proposed § 101.93(g)(2)(x), a statement would be considered a disease claim if it otherwise suggested an effect on a disease or class of diseases.

III. Legal Authority

This proposed rule is authorized under sections 201, 403(r), and 701(a) of the act (21 U.S.C. 321, 343(r), and 371(a)).

IV. Effective Date and Implementation Plan

The agency proposes that any final rule based on this proposal will become effective 30 days after the date of publication of the final rule in the **Federal Register**. However, for a product marketed by a small business (as defined below) that was on the market as of the date of publication of the final rule, the agency is proposing to allow an additional 17 months within which claims made about such product as of the date of publication of the final rule must be brought into compliance with the final rule, provided that the small business has notified FDA of the claim as required by section 403(r)(6) of the act and § 101.93(a) and that FDA has not objected to the claim. A ''small business'' for purposes of this proposal is a business with total annual revenues of less than $20 million. For all other products that were on the market as of the date of publication of the final rule, the agency is proposing to allow an additional 11 months within which claims made about such products as of the date of publication of the final rule must be brought into compliance, again provided that the firm has notified FDA of the claim as required by section 403(r)(6) of the act and § 101.93(a) and that FDA has not objected to the claim. Any product that is marketed for the first time after publication of the final rule, and any new claims made for an existing product for the first time after publication of the final rule, will be expected to be in compliance beginning 30 days after publication of the final rule.

During the pendency of this rulemaking, manufacturers will continue to be under an obligation to comply with section 403(r)(6) and other applicable provisions of the act and applicable regulations. FDA will continue to respond to notifications submitted under section 403(r)(6) of the act, and the agency will continue to enforce that provision and all other applicable legal requirements.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h), (k) and 25.34(f) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Analysis of Economic Impacts

A. Benefit—Cost Analysis

FDA has examined the economic implications of this proposed rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory approach which maximizes net benefits (including potential economic, environmental, public health and safety effects; distributive impacts; and equity). According to Executive Order 12866, a rule is significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. Because it raises novel policy issues, FDA finds that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

In addition, FDA has determined that this rule does not constitute a significant rule under the Unfunded Mandates Reform Act of 1995 requiring cost-benefit and other analyses. A significant rule is defined in Section 1531(a) as ''a Federal mandate that may result in the expenditure by State, local, and tribal governments in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation) in any 1 year * * *''.

Finally, in accordance with the Small Business Regulatory Enforcement Fairness Act, the administrator of the Office of Information and Regulatory Affairs of the Office of Management and Budget has determined that this proposed rule is not a major rule for the purpose of Congressional review.

There are several different types of products that may be considered to be dietary supplements. These products include but are not limited to vitamin and mineral supplements, herbal products, and products that contain other similar nutritional substances. Estimates of the number of dietary supplements are approximate because no one source collects information on all types of dietary supplements. In fact, until the DSHEA, there was no agreed upon definition of a dietary supplement. Some sources include only dietary supplements of vitamins and minerals, others include herbals or botanicals, and still others include other types of products that may or may not be dietary supplements, such as sports nutrition products and ''functional foods,'' a term for which there is no regulatory definition. FDA's preliminary estimate of the number of such products is approximately 29,000. FDA's estimate of the number of stockkeeping units (skus), a more accurate count of the number of labels, is approximately 75,000.

In its analysis of the rule establishing nutrition labeling requirements for dietary supplements (62 FR 49826 at 49843), FDA provided an estimate of the number of dietary supplement firms. According to Dun's Market Identifiers (Ref. 5), there are approximately 250 manufacturers of vitamin and mineral products. According to Nutrition Business Journal (Ref. 6), the dietary supplement industry includes 850 supplement manufacturing companies. The Journal reports 1995 industry revenues at $4.5 billion. The Journal's estimate of 850 firms is an overestimate of the dietary supplement industry as defined by FDA because it includes homeopathic products, which are drugs by statutory definition, and ''functional

foods'' and sports nutrition products, which may be either conventional foods or dietary supplements depending on how they are marketed and used. Although the Journal does not break down the number of firms by the type of dietary supplement produced, it does specify that 250 firms produce herbal or botanical products.

For purposes of determining the costs of regulation, FDA has used 850 as an upper bound estimate of the number of firms. As a lower bound estimate, FDA has used 500 (250 vitamin/mineral firms plus 250 herbal/botanical firms). Since publication of the nutrition labeling final rule in September 1997 (62 FR 49826), FDA has not been challenged on these estimates. Therefore, the same range of estimates is used in this analysis.

In this proposed rule, FDA is clarifying the distinction between disease claims and structure/function claims in dietary supplement labeling. If the proposed rule becomes final, any firm currently making a claim that was not previously classified as a disease claim but is classified as a disease claim by the rule will be required to change the claim to an acceptable structure/function claim, remove the claim from labeling, petition and be granted permission to carry a health claim, or bear the consequences of being classified as an unapproved drug. FDA has received approximately 2,300 notifications of structure/function claims and has sent objection letters for approximately 150 of the notifications. FDA believes that those firms have made the necessary changes to make their claims come into compliance. FDA has estimated the number of additional notifications to which it would have objected under the criteria in this proposed rule. Using conservative, worst-case estimates, FDA estimated that it would have objected to approximately 60 additional notifications. The firms making these 60 products will have to change their claims if the proposal becomes final; these firms would bear the costs of this proposed rule.

FDA is aware that, despite the notification requirements in section 403(r)(6) of the act and § 101.93(a), some firms that have not sent notifications are in fact marketing products whose labeling contains structure-function claims. If the labels contain claims that are unacceptable under the criteria FDA is proposing to adopt, and if the firms change those labels in response to this proposed rule, then the costs of those labeling changes can be attributed to the rule.

1. Costs

Only those firms who must change their labeling will bear the costs of this rule. Categories of costs for relabeling include administrative, analytical, printing, and inventory disposal. FDA will first estimate compliance costs for the 60 products for which the agency has received notifications of claims that would be classified as disease claims under the criteria in the proposed rule. These costs will be the lower-bound costs of the proposed rule. FDA will then estimate the compliance costs for the products for which FDA has not received notification, but whose labeling contains claims that would be classified as disease claims under the criteria in the proposed rule. The sum of the compliance costs for the two categories of products will be the upper-bound costs of the proposed rule.

a. Lower-bound Estimate

The administrative costs associated with a labeling regulation result from the incremental administrative labor expended in order to comply with a regulation. FDA estimates administrative costs at approximately $425 per firm for a 1-year compliance period and approximately $320 for an 18-month compliance period. Longer compliance periods decrease administrative effort because firm executives often delegate downward decisions that are less immediate. FDA will assume that the number of firms affected by the proposed rule is proportional to the number of labels affected. FDA therefore estimates the number of firms affected by multiplying the upper-bound estimate of total firms in the industry by the fraction of the labels in violation, or 850 x (60/2,300) = 22. Total administrative costs are estimated to be $7,040 (22 x $320) with an 18-month compliance period and $9,350 (22 x $425) with a 1-year compliance period.

Based on an average of the estimates provided in comments to earlier rules, FDA estimates that the average redesign cost for a 1-year compliance period is $1,700 per dietary supplement label. Redesign costs associated with an 18 - month compliance period are typically 3/4 of those for a 1 year compliance period, or $1,300 per dietary supplement label. Therefore, FDA estimates total redesign costs to be $102,000 (60 x $1,700) for a 12-month compliance period and $78,000 (60 x $1,300) for an 18-month compliance period.

FDA received information from an earlier rule affecting the entire dietary supplement industry indicating that inventory disposal costs would be $8 million for an 18-month compliance period and $15 million for a 12-month compliance period. FDA has some experience suggesting that some firms will experience minimal inventory disposal costs due to the rapid frequency with which they change labels or move product. Because FDA is assuming that 0.08 percent (60/75,000) of the industry will incur costs as a result of this rule, total inventory disposal costs are estimated to be $6,400 (0.0008 x $8 million) for an 18-month compliance period and $12,000 (0.0008 x $15 million) for a 12-month compliance period.

FDA has estimated the impact of the proposed regulation and has determined that, for a 1-year compliance period, lower-bound total costs would be approximately $123,400. Alternatively, if FDA were to provide 18 months for compliance, lower-bound total costs would be approximately $91,400. The components of lower-bound total costs are shown in the following table.

Cost Category	12-month compliance	18-month compliance
Administrative	$9,400	$7,000
Redesign	$102,000	$78,000
Inventory	$12,000	$6,400
Total	$123,400	$91,400

b. Upper-bound Estimate

Some manufacturers of dietary supplements may not have notified FDA that their product labels contain structure-function claims. Because these manufacturers have not complied with the existing legal requirement to notify FDA of the claims they are making for their products, FDA believes that it is unlikely that they would change their labels to comply with new regulations defining acceptable structure/function claims. However, to ensure that all possible costs are considered in this impact analysis, the agency is including costs that might be incurred by such manufacturers as an upper bound on its estimate of the costs of this proposed rule. Based on visual observation of dietary supplements sold in retail establishments (grocery, drug, and health food stores), FDA estimates that up to 30 percent of all labels contain structure-function claims. FDA therefore estimates that up to 22,500 (0.3 x 75,000) dietary supplement labels may contain structure-function claims. Although it is uncertain how many of these labels contain claims that would be disease claims under the proposed rule, if the proportion of all labels containing such claims is the same as the proportion of notifications containing such claims, then there may

be up to 585 [(60/2,300) x 22,500] labels that would need to be changed if the proposed rule becomes final. Subtracting the 60 unacceptable labels for which FDA has received notifications leaves about 525 additional labels that may be affected by the rule.

Based on its model of food labeling compliance costs, FDA assumes that compliance costs per label double with each halving of the compliance period (Ref. RTI Final Report, ''Compliance Costs of Food Labeling Regulations''). The cost per label for a 12-month compliance period is approximately $2,000 ($123,400/60). The compliance period for claims for which no notification has been received is 30 days. Based on the model, FDA expects that compliance costs will double as the compliance period falls from 12 to 6 months, and double again as the compliance period falls to 3 months. Although the model does not predict compliance costs for periods shorter than 3 months, FDA assumes that as the compliance period falls from 3 months to 30 days, compliance costs are likely to double again. Estimated costs per label should therefore be approximately 8 times (2 x 2 x 2) higher for a compliance period of 30 days than for a compliance period of 12 months. FDA therefore estimates compliance costs per label for current structure-function claims for which no notification has been received to be $16,000 (8 x $2,000). The total costs for 525 label changes would be $8.4 million (525 x $16,000). Although FDA believes that it is very unlikely that all of these label changes would be made, the upper-bound total cost of this proposed rule is the sum of the costs for the 60 unacceptable claims for which notifications have been received and the costs of the additional unacceptable claims. The total cost will thus range between approximately $0.1 million and $8.5 million.

2. Benefits

Most of the benefits from this rule will come from the reduced uncertainty associated with structure/function claims in dietary supplement labeling. Some manufacturers of dietary supplements, as shown by the submission of a significant number of notifications for purported structure/function statements that are clearly disease claims, are uncertain about what constitutes an acceptable structure/function claim. This proposed rule establishes clarifying criteria that will reduce and perhaps eliminate this uncertainty.

FDA cannot quantify the benefits from this proposed rule. Because of the uncertainty about what constitutes an acceptable structure/function claim, some manufacturers of dietary supplements may have hesitated to attempt to make structure/function claims. These clarifying criteria will enable those firms to go forward with those claims. To the extent that the lack of these claims has caused consumers to seek out the information from other sources, this rule will benefit consumers by reducing the cost of searching for information and ensuring that the information provided to consumers is appropriate.

Manufacturers who were considering making claims that would be considered unacceptable will be provided with clear criteria showing that the claims are unacceptable. As evidenced by notifications of structure/function claims already received by FDA, several firms have had to bear the cost of redesigning labeling to incorporate the changes recommended by the agency. By providing criteria to firms before they submit notifications to FDA, this rule will reduce costs to firms by reducing the probability of having to redo labels. Government costs will also be lessened by reducing the number of letters informing firms of inappropriate label statements.

3. Regulatory Alternatives

FDA considered, but did not adopt, other regulatory options. First, the agency considered treating a statement about a dietary supplement as a disease claim only if the statement included an express reference to a specific disease. This option would have resulted in a significantly larger number of permitted claims for dietary supplements, and reduced costs for dietary supplement manufacturers. FDA did not adopt this option for several reasons. First, it would be inconsistent with FDA's longstanding policy of considering both express and implied claims when determining whether a product falls within various definitions under the act. Second, it would be inconsistent with the interpretation of ''disease claims'' that FDA has used in administering section 403(r)(6) of the act prior to issuing this proposed rule. Finally, because many implied claims, e.g., claims that list the symptoms of a disease without naming the disease, are well-understood by consumers as disease treatment or prevention claims, this option would be inconsistent with the intent of section 403(r)(6).

Second, FDA considered treating any mention of an abnormality of the structure or function of the body as a disease claim, even if the abnormality was not characterized by a set of signs or symptoms recognized as a disease. This option would have resulted in a significantly smaller number of permitted claims for dietary supplements, and greater costs for dietary supplement manufacturers. FDA did not adopt this option because section 403(r)(6) of the act prohibits only claims of an effect on a disease. Because not all abnormalities are recognized by health professionals or consumers as diseases, this option would have been overbroad, and would have prevented manufacturers from making claims permitted by the statute.

Finally, FDA considered taking no new regulatory action. This option would have resulted in no immediate change in the number of permitted claims, and no costs for dietary supplement manufacturers. FDA rejected this option because there is substantial confusion among dietary supplement manufacturers and consumers about what types of claims are permitted for dietary supplements, and the agency has been called upon to provide clarification of permitted and prohibited claims. In the absence of direction from the agency, an increasing number of products in the marketplace carry express and implied disease claims, misleading consumers and creating unfairness to those manufacturers who have attempted to comply with advice from FDA.

B. Small Entity Analysis

According to the Regulatory Flexibility Act, the definition of a small entity is a business independently owned and operated and not dominant in its field. The Small Business Administration (SBA) has set size standards for most business categories through use of four-digit Standard Industrial Classification (SIC) codes. Dietary supplements of vitamins and minerals are included in the industry group Pharmaceutical Preparations (SIC 2834); a business in that classification is considered small if it has fewer than 750 employees. According to Dun's Market Identifiers, there are approximately 250 producers of vitamin and mineral supplements, of which 200 have fewer than 750 employees. The remaining dietary supplement products—mainly herbs, other botanicals, and amino acids—do not fit in any classification, but come closest to the industry groups Food Preparations Not Elsewhere Classified (SIC 2099) and Medicinal Chemicals and Botanical Products (SIC 2833). The SBA size standards are 500 or fewer employees for food preparations and 750 or fewer employees for medicinal and botanical products.

According to Nutrition Business Journal (Ref. 6), 11 of the 850 dietary supplement manufacturing firms have

total revenues over $100 million, accounting for 53 percent of total sales; 30 firms have sales revenues between $20 and $100 million, accounting for 28 percent of industry sales; and 809 firms have sales under $20 million, accounting for 19 percent of industry sales. The 809 firms in the under $20 million category have an average sales revenue of $800,000 and will be considered small by FDA.

No employment data are available for some of these firms. Many of the firms are in the SIC codes 2833 and 2834, however. According to Dun's Market Identifiers, no firms for which both employment and sales data are available in SIC code 2833 have less than $20 million in annual sales and more than 500 employees. Indeed, 96% of the firms in that sales category have fewer than 100 employees. By contrast, over 90% of the firms in SIC codes 2833 and 2834 (vitamin and minerals sub-category) with annual sales greater than $100 million have more than 750 employees. If the relationship between sales and employment for SIC codes 2833 and 2834 holds for other sectors of the dietary supplement industry, then the proportion of firms with sales under $20 million should be approximately the same as the proportion of firms with fewer than 500 employees, an employment category that is classified as small for any SIC code involving the manufacture of foods, chemicals and kindred or allied products. FDA concludes therefore that as many as 809 firms in the dietary supplement industry, or 95 percent of firms, could be considered small (sales under $20 million). As stated previously in this analysis, 809 small firms may be an overestimate because it counts firms that produce homeopathic products, which are drugs, and sports nutrition products and ''functional foods,'' which may be either foods or dietary supplements. If there are as few as 500 dietary supplement firms, there may be 475 small dietary supplement firms.

Because virtually all firms affected by this rule will be classified as small under SBA standards, FDA assumes that small entities will bear 100 percent of the costs. Because per firm labeling costs are probably burdensome for small firms and because the costs of this rule are borne entirely by small firms, FDA tentatively concludes that this rule will result in a significant economic impact on a substantial number of small entities. In section VI. A. of this document, entitled Benefit—Cost Analysis, FDA estimated that, as a lower-bound, 22 firms would be affected by this proposed rule and that the lower-bound costs with a compliance period of 12 months would be approximately $123,400, or about $5,600 per small firm. FDA estimated upper-bound costs, $8.5 million, by adding the costs of changing 525 additional labels (with a 30-day compliance period) to the lower-bound costs. If the number of additional firms affected is proportional to the number of additional labels changed, the upper-bound number of firms affected by this proposed rule is 215, for an upper-bound average cost of about $40,000 per small firm.

The Regulatory Flexibility Act requires agencies to examine regulatory alternatives that would minimize the impact on small entities. FDA considered exempting small entities from this rule, which would eliminate the costs borne by small entities. FDA rejected this option for several reasons. First, the agency has no authority to exempt small entities from their statutory obligations, and this proposed rule merely clarifies a statutory requirement. Second, as described above, virtually all manufacturers covered by this proposal are small entities. Exempting small entities would thus eliminate the benefits of the proposed rule. Finally, some of the benefits of the rule, such as reducing the uncertainty associated with structure/function claims and reducing the probability of having to re-do labels, will accrue to small entities.

FDA has examined the impact of different compliance periods and has determined that extending the compliance period from 12 to 18 months for firms that have notified the agency of a claim and have not received an objection reduces the burden on small entities in this category. Extending the compliance period from 12 to 18 months reduces lower-bound estimated costs borne by small firms by $32,000, and average costs per firm would fall from $5,600 to about $4,200. Extending the compliance period beyond 18 months could provide additional relief to these small entities. Based on FDA's experience with the dietary supplement industry, however, the agency believes that labels are changed more often than every 18 months; therefore, FDA believes that this additional relief would be small. FDA has tentatively concluded that the compliance period for those firms whose products contain structure/function claims but who have not complied with the legal requirement to notify FDA of those claims should not be extended.

VII. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Comment Request

Interested persons may, on or before August 27, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. *Dorland's Illustrated Medical Dictionary*, 28th Edition, W.B. Saunders Co., Philadelphia, p. 478, 1994.

2. *Stedman's Medical Dictionary*, 26th Edition, Williams & Wilkins, Baltimore, p. 492, 1995.

3. *The Encyclopedia Americana, International Edition*, Grolier Inc., Danbury, p. 168, 1985.

4. *Black's Law Dictionary*, 6th Edition, West Publishing Co., St. Paul, p. 467, 1990.

5. *Dun's Market Identifiers*, Knight-Ridder Information, Inc., Mountain View, CA, 1998.

6. *Nutrition Business Journal*, 1(1):15, 16, 1996.

List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371.

2. Section 101.14, as currently in effect, is amended by revising paragraph (a)(6) to read as follows:

§ 101.14 Health claims: general requirements.

(a) * * *

(6) *Disease or health-related condition* means any deviation from, impairment

of, or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of one or more signs or symptoms (including laboratory or clinical measurements that are characteristic of a disease), or a state of health leading to such deviation, impairment, or interruption; 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 this section or § 101.70).

* * * * *

3. Section 101.93, as currently in effect, is amended by revising the section heading and by adding paragraphs (f) and (g) to read as follows:

§ 101.93 Certain types of statements for dietary supplements.

* * * * *

(f) *Permitted structure/function statements*. (1) Dietary supplement labels or labeling may, subject to the requirements of this section, bear statements that describe the role of a nutrient or dietary ingredient intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, but may not bear statements that are disease claims under paragraph (g) of this section.

(g) *Disease claims*. (1) *Definition of disease*. For purposes of 21 U.S.C. 343(r)(6), a ''disease'' is any deviation from, impairment of, or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of one or more signs or symptoms, including laboratory or clinical measurements that are characteristic of a disease.

(2) *Disease claims*. FDA will find that a statement about a product claims to diagnose, mitigate, treat, cure, or prevent disease (other than a classical nutrient deficiency disease) under section 403(r)(6) of the act if it meets one or more of the criteria listed in this paragraph (g)(2). In determining whether a statement is a disease claim under these criteria, FDA will consider the context in which the claim is presented. A statement claims to diagnose, mitigate, treat, cure, or prevent disease if it claims, explicitly or implicitly, that the product:

(i) Has an effect on a specific disease or class of diseases;

(ii) Has an effect, using scientific or lay terminology, on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific disease or of a number of different specific diseases;

(iii) Has an effect on a consequence of a natural state that presents a characteristic set of signs or symptoms recognizable to health care professionals or consumers as constituting an abnormality of the body;

(iv) Has an effect on disease through one or more of the following factors:

(A) The name of the product;

(B) A statement about the formulation of the product, including a claim that the product contains an ingredient that has been regulated by FDA as a drug and is well known to consumers for its use in preventing or treating a disease;

(C) Citation of the title of a publication or reference, if the title refers to a disease use;

(D) Use of the term ''disease'' or ''diseased''; or

(E) Use of pictures, vignettes, symbols, or other means;

(v) Belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease;

(vi) Is a substitute for a product that is a therapy for a disease;

(vii) Augments a particular therapy or drug action;

(viii) Has a role in the body's response to a disease or to a vector of disease;

(ix) Treats, prevents, or mitigates adverse events associated with a therapy for a disease and manifested by a characteristic set of signs or symptoms; or

(x) Otherwise suggests an effect on a disease or diseases.

Dated: April 22, 1998.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 98–11294 Filed 4–24–98; 4:27 pm]

BILLING CODE 4160–01–F