

prior authorization of any labeling statement that characterizes the relationship between a substance in the supplement to a "disease or a health-related condition" (section 403(r)(1)(B) of the act; § 101.14(a)(1)). The phrase "disease or health-related condition" was defined in those regulations 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

* * *

Section 101.14(a)(5) (formerly § 101.14(a)(6)). The definition was redesignated as § 101.14(a)(5) effective March 23, 1999 (see 62 FR 49859, 49867).

FDA tentatively concluded that it did not want to retain the older health claims definition because its use of the term "damage" could be interpreted to limit the definition to serious or long-term diseases, and could imply that there needed to be pathological evidence of damage, which is not always present. For example, most mental illnesses have no evidence of anatomic damage, yet are clearly diseases.

In the July 8, 1999, FEDERAL REGISTER notice announcing a public meeting and reopening the comment period, FDA requested additional comment on the definition of disease. The notice listed four questions on which it sought specific comment: (1) What are the consequences, with respect to the range of acceptable structure/function claims, of adopting: (a) The 1993 definition in § 101.14(a)(5), or (b) the definition in the proposed rule? (2) If FDA were to retain the 1993 definition, does the reference to "damage" exclude any conditions that are medically understood to be diseases? Please provide examples. (3) If it does not exclude any such conditions, is the 1993 definition otherwise consistent with current medical definitions of disease? (4) If it does exclude conditions that are medically understood to be diseases, could it be revised in a way that would include such conditions?

(22.) Almost all of the comments from the dietary supplement industry and from individuals objected to the new definition of disease. Most of these comments argued that the new definition is too broad, sweeping in many minor deviations or abnormalities that are not diseases. (Many of these comments did not appear to have understood that the definition required not only a deviation, but one that "is manifested by a characteristic set of one or more signs or symptoms.") One comment said that under the new definition wrinkles and gray hair would qualify as

diseases. Some comments objected to the fact that the proposed definition was not limited to adverse deviations from normal structure or function. Other comments argued that the breadth of the proposed definition is inconsistent with the intent of DSHEA. Some comments objected to the distinction between normal and abnormal functions, and argued that Congress did not intend to limit structure/function claims to normal structure or function. Some comments contended that the definition of disease should not include the phrase "structure or function." Other comments said that Congress should be presumed to have been aware of the 1993 definition of "disease or health-related condition" and to have intended FDA to use that definition. Several comments argued that the new definition of "disease or health-related condition" for health claims would inappropriately broaden the scope of health claims for conventional foods and concomitantly narrow the scope of acceptable structure/function claims for foods. One comment said that redefining "disease or health-related condition" in § 101.14(a)(5) would undermine the existing definition of "statement of nutritional support," and would violate DSHEA and the First Amendment. Most of the comments from the dietary supplement industry and from individuals recommended that FDA return to the 1993 definition.

Most of the comments from health professional groups and groups devoted to specific diseases, including those who

participated in the August 4, 1999, public meeting, supported the new definition of disease as more consistent with a medical understanding of disease than the NLEA definition. Some of these comments criticized the 1993 definition because of its reliance on "damage" and dysfunction and because of its failure to refer to signs and symptoms. While many comments from the dietary supplement industry said that no recognized diseases would be excluded by requiring evidence of "damage," comments from health professionals pointed out a number of recognized disease conditions for which it is not currently possible to identify physical damage to an organ, part, or system of the body, including most psychiatric diseases (depression, bipolar disorder, schizophrenia, and obsessive compulsive disorder, among others), and the early stages of certain metabolic diseases, including diabetes, genetic diseases, and nutritional deficiency diseases.

A few comments offered alternative definitions of disease. A major medical association contended that the proposed definition would be improved by the addition of the phrase "or a state of health leading to such deviation, impairment, or interruption." An OTC drug and dietary supplement trade association offered the following alternative definition of disease, which would modify the proposed definition:

A disease is any adverse deviation from, or 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 that are not characteristic of a natural state or process.

According to this comment, the addition of the word "adverse" appropriately narrows the nature of the deviation, "laboratory or clinical measurements" are appropriately deleted because they are already included under the concept of "signs," and the exclusion of natural states "encompasses Congress' intent to allow health promotion/maintenance claims." One comment suggested that, if FDA were to retain the 1993 definition, it add the word "impairment" after "damage" to cover those recognized disease conditions for which evidence of damage is missing. A pharmaceutical trade association urged FDA to convene a small workshop of physicians, patients, and other stakeholders to develop a consensus on the distinction between disease claims and structure/function claims.

In response to the comments, FDA has reconsidered the proposed definition of disease in § 101.93(g)(1), and has concluded that it is not necessary to change the 1993 health claims definition, because it can be construed in a manner that

covers conditions that are medically understood to be diseases. In light of Congress' desire to increase the number of claims that could be made for dietary supplements without subjecting them to drug regulation, FDA is persuaded that it is therefore appropriate to retain a narrower definition of disease at this time.

FDA has concluded that the older health claims definition, read as a whole, will not exclude any significant conditions that are medically understood to be diseases. For example, the requirement of "damage to an organ, part, structure, or system of the body such that it does not function properly" indicates that a condition may be considered a disease if there is direct evidence of structural damage to an organ, part, structure, or system of the body, or indirect evidence of damage, indicated by the failure of the organ, part, structure, or system of the body to function properly. This interpretation is appropriate because otherwise well-recognized psychiatric diseases, migraine headaches, hypertension, blood lipid disorders, and many other well-accepted diseases, could be excluded from coverage due to the lack of direct evidence of physical damage. The reference to "a state of health leading to such dysfunctioning" also permits the agency to look at evidence other than actual damage to an organ, part, structure, or system of the body.

FDA does not believe that it would be constructive to defer a decision on the definition of disease and seek a "consensus" of stakeholders. The agency believes that it is unlikely that diverse, strongly-held views expressed in written comments and at the public hearing could be forged into a consensus on this issue. FDA also believes that it is important to reach a decision as soon as possible to permit the issuance of clear, uniform rules that will apply to all dietary supplement labeling.

Accordingly, the final rule does not include a new definition of disease, but incorporates the definition of "disease or health-related condition" in § 101.14(a)(5). If experience shows a public health need for a different or broader definition, however, FDA will consider initiating a rulemaking to amend that definition.

(23.) One comment argued that it is unnecessary for FDA to define disease at all, but that the agency should use a "common sense" approach to distinguishing structure/function claims from disease claims. According to this comment, dietary supplements should be allowed to make any claim that does not contain express references "to specific diseases * * * or which can only be reasonably interpreted to refer to a specific disease (e.g., 'helps prevent tumors')." ."

FDA does not agree that a definition of disease is unnecessary. The comment that made this argument went on to use

the term disease in its "common sense" principle, apparently assuming that there is some common sense understanding of the term. FDA is not aware of any common sense understanding of "disease," and the diversity of comments received in this rulemaking on the appropriate definition of disease supports FDA's view that a definition is needed if FDA is to enforce section 403(r)(6) of the act fairly and consistently.

(24.) One comment argued that any definition of disease should exclude symptoms or diseases that do not normally require a drug or doctor's care because these states could be considered part of "normal" living.

FDA does not agree that DSHEA was intended to permit structure/function claims about diseases that can normally be treated without a physician's care. Nothing in the statute or its legislative history suggests that Congress intended to accord different treatment to this subset of diseases. Diseases that do not ordinarily require a physician's care are generally those for which drugs may be sold over OTC. (OTC drug claims include both disease claims and structure/function claims.) Drugs carrying OTC claims are already regulated under rules different from those applicable to prescription drugs. FDA has undertaken a comprehensive review of OTC drug claims and published monographs on these claims. Had Congress intended to permit dietary supplements to make all OTC claims (both disease claims and

structure/function claims) without prior review, it could easily have so indicated. Because Congress did not do so, FDA does not believe that there is support for treating this subset of diseases differently from other diseases. As discussed elsewhere in this document, the structure/function claims made for OTC drugs also may be made, in appropriate circumstances, for dietary supplements under section 403(r)(6) of the act.

(25.) One comment argued that it was irrelevant whether the 1993 definition excluded conditions that were medically understood to be diseases. According to this comment, the definition of disease should be based on consumer understanding rather than medical understanding, because DSHEA was intended to educate consumers.

FDA does not agree that its interpretation of a medical term like "disease" should ignore medical definitions of the term, unless there is clear guidance from Congress that it intended a nonmedical definition of the term. In any case, the comment provided no argument or evidence that the 1993 definition was based on, or reflects, consumer understanding of the term "disease."

D. Disease Claims (§ 101.93(g)(2))

(26.) Many comments agreed with the statement in proposed § 101.93(g)(2) that, in determining whether a statement is a disease claim, it is appropriate to consider the context in which

the claim is presented. One comment argued, however, that language of the regulation and preamble showed that FDA was biased because the agency would only consider the context of a claim to convert a dietary supplement to a drug.

FDA does not agree that it will consider context only to convert an otherwise acceptable structure/function claim to a disease claim. The context in which a claim appears can provide evidence in either direction.

(27.) One comment argued that the rule should have only the following three criteria: (1) The words "diagnose," "prevent," "treat," "cure," and "mitigate" should not be used in a structure/function claim; (2) the words "stimulate," "maintain," "support," "regulate," and "promote"--or other similar words--may be used in a structure/function claim to distinguish the claim from a specific disease claim; and (3) clinical endpoints that are recognizable to health professionals or consumers as being related to a disease may be used in a structure/function claim.

FDA does not believe that the three suggested criteria provide a sufficient basis to distinguish between structure/function claims and disease claims. Nothing in these criteria would prevent a structure/function claim from discussing a specific disease, explicitly or implicitly, as long as the claim did not contain the specific verbs "diagnose," "prevent," "treat," "cure," or "mitigate."

(28.) Several comments from medical and consumer groups supported the establishment of criteria for structure/function claims, but were concerned that the criteria in the proposed rule were too vague and would fail to protect consumers from misleading claims. A major medical association contended that some of the structure/function claims listed as acceptable in the proposal were debatable and expressed doubt that the public health would be adequately protected. Some of these comments expressed the view that some of the structure/function claims listed in the proposal in fact imply disease prevention. For example, some of these comments argued that health maintenance claims imply disease prevention. On the other hand, a comment from a major dietary supplement trade association argued that the overall impact of the criteria restricts the value of structure/function claims in providing consumers with useful information about dietary supplements.

FDA agrees that consumers should have access to, and be allowed to evaluate for themselves, as much truthful information about dietary supplements as is possible, consistent with the statutory restrictions on disease treatment and prevention claims. FDA believes that the criteria in this rule strike a reasonable balance between these competing goals. Undoubtedly, the criteria will not satisfy everyone. For example, some of the claims considered to be structure/function claims may imply

specific disease prevention to some consumers. Because of the importance of the context in which a claim is presented, it will not always be possible to draw a line between structure/function and disease claims in this rule with great specificity. FDA believes that, within these constraints, the criteria, as finalized, adequately distinguish between structure/function claims and disease claims. In developing final criteria, the agency has tried to pay particularly close attention to claims that might relate to serious health conditions that patients cannot safely evaluate on their own. The question of whether health maintenance claims necessarily imply disease prevention is discussed in more detail below.

(29.) One comment, from a Commission member, said the "dietary relationship" of a structure/function claim is relevant in considering whether such a claim is appropriate. The comment said that statements for dietary ingredients should "relate to the role of the dietary ingredient in the diet in achieving effects like those associated with the effects of foods." The comment added that the claim "should be for an effect that is similar to the non-disease effects of a food on the body" and "phrased to indicate the role of the dietary ingredient in the diet in maintaining or supporting the ordinary functioning of the body in a manner similar to that achieved through foods." Thus, the comment would consider a claim such as "promotes relaxation"

to be appropriate "only if it is indicated to be similar to the effects achieved from foods, such as by indicating that it provides a relaxing calming effect like a cup of tea." While the preamble to the proposed rule considered the claim of "improves absentmindedness" to be a structure/function claim, the comment viewed the same claim as a disease claim "because of the association of absentmindedness with Alzheimer's disease." The comment continued, "That claim should not be permissible for the same reason that a claim that a dietary supplement is an 'oral contraceptive' is not permissible--the claim is simply not one for the effects of a dietary ingredient."

FDA agrees that dietary supplements must be "intended to supplement the diet" (section 201(ff) of the act). In interpreting section 403(r)(6) of the act, however, FDA believes that it is appropriate to focus on the claims made for the product. Unlike section 201(g)(1)(C) of the act, section 403(r)(6) of the act does not limit authorization to make structure/function claims (without triggering drug approval requirements) to substances that are "food." FDA notes that it is developing an overall dietary supplement strategy and will, when a document incorporating the strategy is released, state how the agency plans to address the requirement that dietary supplements be "intended to supplement the diet."

(30.) One comment said FDA should develop a list of "acceptable subclinical, pre-disease, and normal states" that may be used in structure/function claims.

FDA declines to adopt the comment's suggestion. However, this rule contains many examples of acceptable structure/function claims and FDA intends to issue further guidance listing acceptable claims.

(31.) One comment argued that all statements about effects on structure or function should be deemed permissible unless they are already approved drug claims. The comment noted that "reduces joint pain" and "relieves headache" would not be structure/function claims because they are OTC monograph claims.

FDA does not agree that such a criterion would appropriately discriminate between structure/function claims and disease claims. One kind of valid drug claim is a claim related to the effect of the product on the structure or function of the body (section 201(g)(1)(C) of the act) but not related to disease prevention or treatment. In other words, not all drug claims are disease claims. Congress specifically provided that structure/function claims authorized by section 403(r)(6) of the act do not, in themselves, subject a dietary supplement to regulation as a drug under 201(g)(1)(C) of the act. It thus would not be appropriate to exclude from the scope of acceptable structure/function claims OTC monograph claims or other approved

claims for products classified as drugs under section 201(g)(1)(C) of the act.

(32.) A national pharmacy group stated that the examples of structure/function and disease claims in the proposal were reasonable and based on good science and logic, but should be evaluated and revised as necessary over time.

FDA agrees that it will be necessary to evaluate the examples over time and to revise them as experience dictates.

(33.) Some comments argued that the types of claims permitted under the proposal may discourage serious approaches to substantiation because the terms used are not scientifically verifiable. Stating that the preferred method of substantiation is an adequate and well-controlled trial, one comment contended that the claims permitted under the rule are not amenable to such proof. According to this comment, this rule may preclude companies from meeting the substantiation rules of the Federal Trade Commission (FTC). A few comments said that manufacturers cannot substantiate claims that a product maintains healthy status. One of these comments stated that it was impossible to show by adequate studies that "cranberry extract supports healthy urinary tract functioning," and that companies should instead be able to show that cranberry extract reduces frequency of urinary tract infections in susceptible people. Similarly, because it is "impossible" to test whether St. John's Wort "supports mood" in

the general population, companies need to be able to test its effect on depressed people.

FDA agrees that some structure/function claims that are acceptable under DSHEA may be difficult to substantiate. For example, some structure/function claims currently in the marketplace use terms that do not have clear scientific meaning. Other claims concern health maintenance in the general population and therefore could require studies in a large population for substantiation. FDA believes, however, that such claims are within the intended scope of section 403(r)(6) of the act. Difficulty in substantiating them does not alter the terms of the statute. Manufacturers are responsible for determining whether claims for their products can be appropriately substantiated, and to use only those claims for which they have substantiation. FDA does not agree that difficulty in substantiating a particular claim justifies the use of express or implied disease claims for which methods of substantiation may be more straightforward. Such an approach would turn section 403(r)(6) of the act on its head.

FDA also does not agree that it is impossible to substantiate the claims described in the comments. For example, to substantiate the claim "supports mood," it is not necessary to study the effects of a substance on clinical depression. Instead, it is quite possible to assess the effects of a

substance on mood changes that do not constitute clinical depression.

E. Effect on Disease or Class of Diseases (§ 101.93(g)(2)(i))

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. FDA included the following examples of such disease claims: "Protective against the development of cancer," "reduces the pain and stiffness associated with arthritis," "decreases the effects of alcohol intoxication," or "alleviates constipation." FDA included the following examples of claims that do not refer explicitly or implicitly to an effect on a specific disease state: "Helps promote urinary tract health," "helps maintain cardiovascular function and a healthy circulatory system," "helps maintain intestinal flora," and "promotes relaxation." FDA proposed to treat both express and implied disease claims as disease claims that could not be made for dietary supplements without prior review either as health claims or as drug claims. Implied disease claims do not mention the name of a specific disease, but refer to identifiable characteristics of a disease from which the disease itself may be inferred. There are many possible ways to imply treatment or prevention of disease, from listing the characteristic signs and symptoms of the disease to providing images of people suffering from the disease. Nine of

the 10 criteria proposed by FDA for identifying disease claims could be considered methods of implying disease treatment or prevention.

In the July 8, 1999, FEDERAL REGISTER notice announcing a public meeting and reopening the comment period, FDA sought additional comment on the applicability of the rule to implied disease claims. The discussion in the notice offered three examples of possible implied disease claims: (1) "shrinks tumors of the lung" or "prevents development of malignant tumors" ("treats cancer" would be the corresponding express claim); (2) "prevention of seizures" ("treatment of epilepsy" would be the corresponding express claim); (3) "relief of sneezing, runny nose, and itchy watery eyes caused by exposure to pollen or other allergens" ("treatment of hayfever" would be the corresponding express claim). The notice listed four questions related to implied disease claims on which the agency sought specific comments: (1) If implied disease claims should be permitted, has FDA correctly drawn the line between what constitutes an express disease claim and what constitutes a permitted implied claim? (2) If such claims should be permitted, what are representative examples of the types of implied disease claims that should be permitted without prior review? (3) Are the examples of implied claims mentioned in the July 8 notice appropriate structure/function claims? (4) Is a claim that a product

"maintains healthy function" an implied disease claim in all cases? If not, under what circumstances is such a claim not an implied disease claim?

(34.) Many comments agreed with proposed § 101.93(g)(2)(I) that structure/function statements should not explicitly or implicitly mention specific diseases or class of diseases. These comments contended that consumers cannot distinguish between implied and express disease claims and that permitting implied disease claims poses significant dangers to consumers with diseases. According to these comments, permitting implied disease claims on dietary supplements may cause consumers to delay or forego effective treatment for serious diseases without assurance that the dietary supplement that has been substituted is safe or effective for the disease. Some comments also argued that permitting implied disease claims on dietary supplements will undermine the drug approval process by permitting dietary supplement manufacturers to market products for essentially the same indications for which pharmaceutical companies have spent millions of dollars obtaining approval.

Many other comments objected to treating implied disease claims as disease claims, arguing that dietary supplements should be allowed to carry any truthful claim that does not explicitly refer to a specific disease. Some comments argued that Congress intended consumers to have access to as much information about

supplements as possible. Other comments contended that barring implied disease claims eliminates any meaningful claims for dietary supplements. Other comments argued that treating implied claims as disease claims gives FDA "unlimited discretion" to treat structure/function claims as disease claims. Some comments, however, agreed that disease claims may be implied as well as express, and said that it is appropriate to consider a structure/function statement in context to determine whether it conveys a disease claim.

FDA continues to believe that structure/function claims should not imply disease treatment or prevention. Most disease treatment or prevention claims, including claims about serious and life-threatening diseases, can be described in a manner that will be easily understood by consumers without express reference to a specific disease. The following examples of implied disease claims demonstrate that it is not difficult to convey prevention or treatment of a specific disease or class of diseases without actually mentioning the name of the disease, which are given in parentheses: "Relieves crushing chest pain" (angina or heart attack), "prevents bone fragility in post-menopausal women" (osteoporosis), "improves joint mobility and reduces joint inflammation and pain" (rheumatoid arthritis), "heals stomach or duodenal lesions and bleeding" (ulcers), "anticonvulsant" (epilepsy), "relief of bronchospasm" (asthma), "prevents wasting

in persons with weakened immune systems" (AIDS) (acquired immune deficiency syndrome), "prevents irregular heartbeat" (arrhythmias), "controls blood sugar in persons with insufficient insulin" (diabetes), "prevents the spread of neoplastic cells" (prevention of cancer metastases); "antibiotic" (infections), "herbal Prozac" (depression). The distinction between implied and express disease claims is thus, in many cases, a semantic one that has little, if any, practical meaning to consumers. The argument that Congress intended to encourage the free flow of information about dietary supplements and therefore intended to permit implied disease claims is illogical. If Congress wanted to ensure that consumers receive information about how these products can treat or prevent diseases, it is difficult to imagine why it would have specifically denied the right to make such claims expressly, and allowed manufacturers to make the claims only by implication.

There are also serious public health questions raised by implied disease claims. Treatment and prevention of disease are serious matters, and the statute reflects a congressional judgment that consumers deserve to have claims for such uses reviewed by experts for proof of safety and effectiveness. In addition, permitting dietary supplement manufacturers to make implied disease claims without prior review would allow them to compete unfairly with prescription and OTC drugs, which are

required to establish their safety and effectiveness for disease treatment and prevention before being marketed. Pharmaceutical manufacturers, faced with this competition, might be less likely to undertake future research and development, compromising one of the nation's most important sources of therapeutic advances. Had Congress intended to allow implied disease claims when it authorized dietary supplement manufacturers to make structure/function claims without prior review, it could easily have made clear its intention through express statutory language or legislative history. As discussed below, Congress did not do so.

FDA does not agree that the final rule eliminates all meaningful claims for dietary supplements. FDA believes that there are many meaningful structure/function claims that can be made without implying disease treatment or prevention, and has listed a number of such claims in this preamble.

FDA does not agree that treating implied claims as disease claims gives the agency unfettered discretion to treat all structure/function claims as disease claims. The purpose of this rule is to clarify which claims are structure/function claims permitted under section 403(r)(6) of the act and which are disease claims. Both in the proposed rule and in this final rule, FDA has provided many examples of specific claims that would be acceptable structure/function claims.

(35.) Many comments pointed to three provisions of DSHEA as evidence that Congress intended to include implied disease claims among structure/function claims permitted under section 403(r)(6) of the act. First, the "Findings" section of DSHEA refers to the relationship between dietary supplements and disease prevention. Many comments argued that Congress would not have made statutory findings linking dietary supplements to disease prevention if it intended that FDA could prohibit such references.

Second, section 403(r)(6) of the act states that structure/function statements may not "claim" to treat or prevent disease, and, according to the comments, this term should be read to refer only to express claims. Some comments noted that section 403(r)(6) of the act does not use the word "implied" to qualify the term "claims," and contrasted the language of the drug definition in section 201(g)(1)(B) of the act ("articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease") with the language of section 403(r)(6)(C) of the act, which states that a structure/function statement may not "claim" to diagnose, cure, mitigate, treat, or prevent disease. One comment agreed with the proposal's statement that while DSHEA authorizes structure/function claims that are not also disease claims, but nevertheless asserted that the statute authorizes structure/function claims that imply "some protection against disease." This comment reasoned that the act,

as amended by DSHEA, allows dietary supplements to be "intended" to affect the structure or function of the body, provided that the product does not "expressly claim to prevent, etc. disease" (emphasis in original) and the product bears "an express, formal disclaimer of an intent to prevent, etc. disease." The comment also said that the Commission report only referred to express claims.

Third, DSHEA requires structure/function claims to be accompanied by a disclaimer that reads, in part: "[T]his product is not intended to diagnose, treat, cure, or prevent any disease." According to some comments, Congress understood that specific disease treatment or prevention effects can also be described as effects on the structure or function of the body, and resolved the tension by requiring the disclaimer. In contrast, however, another comment argued that the drug definition in section 201(g)(1)(B) of the act still applies to dietary supplements because the exemption for dietary supplements added to section 201(g)(1) applies only to the structure/function definition in section 201(g)(1)(C). Many comments argued generally that DSHEA was intended to promote the free flow of truthful information about dietary supplements, and that prohibiting implied disease claims is contrary to this legislative goal.

FDA does not agree that DSHEA authorizes dietary supplement manufacturers to make implied disease claims without prior review of the claims. There is no express provision of DSHEA that authorizes implied disease claims, and a construction of DSHEA that permitted such claims would be fundamentally incompatible with important provisions of the act that were squarely before Congress when it passed DSHEA, including the definitions of "drug" and "new drug" and the health claims provisions of NLEA.

As described above, Congress created a partial exemption for dietary supplements from the definition of drug in section 201(g)(1)(C) of the act by providing that truthful and non-misleading claims under section 403(r)(6) of the act do not in themselves trigger drug regulation. Congress did not, however, create any exemption from section 201(g)(1)(B) of the act for dietary supplements. Thus, dietary supplements that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" are subject to regulation as drugs under the act. It has been FDA's longstanding interpretation of section 201(g)(1)(B) of the act that the phrase "intended for use" refers to the objective intent of the manufacturer, which is not limited to a manufacturer's express representations. See § 201.128 (21 CFR 201.128); NNFA v. Weinberger, 557 F.2d 325, 334 (2d Cir. 1977) ("the FDA is not bound by the manufacturer's subjective claims of intent," but may establish intent "on the

basis of objective evidence"). Evidence of objective intent can come from a variety of sources, and may include both implied and express claims (United States v. Undetermined Quantities * * * Pets Smellfree, 22 F.3d 235 (10th Cir. 1994); United States v. Storage Spaces Designated Nos. "8" and "49", 777 F.2d 1363, 1366 (9th Cir. 1985) ("intent may be derived or inferred from labeling, promotional material, advertising, or any other relevant source"), cert. denied, 479 U.S. 1086 (1987); United States v. Kasz Enterprises, Inc. 855 F. Supp. 534, 539, 543-44 (D.R.I. 1994), modified on other grounds, 862 F. Supp. 717 (D.R.I. 1994); United States v. Articles of Drug * * * Neptune, 568 F. Supp. 1182 (N.D. Ca. 1983); United States v. Vitasafe, 226 F. Supp. 266 (D.N.J. 1964); United States v. 14 105 Pound Bags * * * Mineral Compound, 118 F. Supp. 837 (D.C. Idaho 1953); United States v. 43 ½ Gross Rubber Prophylactics, 65 F. Supp. 534, 535 (D. Minn. 1946), aff'd sub nom. Gellman v. United States, 159 F.2d 881 (8th Cir. 1947); 59 FR 6084, 6088 (February 9, 1994) (terms "antibacterial," "antimicrobial," "antiseptic," or "kills germs" constitute implied drug claims that cause products carrying them to be drugs); 58 FR 47611, 47612 (September 9, 1993) (labeling indicating that "hormones" are present in a product constitutes implied drug claim); 58 FR 28194, 28204 (May 12, 1993) (products carrying term "sunscreen"

are drugs because "sunscreen" implies disease prevention, even if not expressly promoted for prevention of skin cancer)).

Thus, interpreting section 403(r)(6) of the act as permitting implied disease claims would be irreconcilable with FDA's longstanding interpretation of section 201(g)(1)(B) of the act, which treats such claims as drug claims.

Permitting implied disease claims as structure/function claims would also conflict with the health claims scheme established in section 403(r)(1) through (r)(1)(5) of the act, which requires food and dietary supplement manufacturers to obtain health claim authorization before making a claim "which expressly or by implication" characterizes the relationship of a nutrient to a disease or health-related condition. Under this provision, a claim that characterized, by implication, the relationship between a dietary supplement ingredient and a disease would require authorization as a health claim.

Interpreting section 403(r)(6) of the act as permitting the same implied claim without authorization of a health claim directly conflicts with 403(r)(1) through (r)(1)(5) of the act.

None of the statutory provisions relied on by the comments provides persuasive support for the conclusion that structure/function claims can imply disease treatment or prevention.

FDA agrees that the Findings section of DSHEA includes statements linking dietary supplements and disease prevention. However, in addition to the types of claims authorized for dietary supplements in section 403(r)(6) of the act, the act specifically authorizes dietary supplements to bear health claims. Health claims are expressly described in the statute as claims that characterize the link between a nutrient and a disease or health-related condition (section 403(r)(1)(B) of the act). The statements in the "Findings" section of the DSHEA are entirely consistent with this scheme and do not compel the conclusion that claims linking dietary supplements and disease prevention may be made as structure/function claims.

The use of the word "claim" rather than "intended for use" in section 403(r)(6) of the act also does not show that Congress intended to permit implied disease claims. First, the comment cites no authority, and FDA is aware of none, for the proposition that the meaning of the word "claim" is limited to "express claim." More importantly, section 403(r)(6) of the act does not stand by itself. As Congress recognized when it provided that dietary supplements making appropriate claims under section 403(r)(6) of the act do not thereby become drugs under section 201(g)(1)(C) of the act, section 403(r)(6) must be read in conjunction with section 201(g)(1). As described above, section 201(g)(1)(B) of the act continues to apply to dietary supplements

and treats them as drugs if they are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." FDA has interpreted section 201(g)(1)(B) of the act to cover both express and implied claims for more than 50 years. Had Congress intended 403(r)(6) of the act to permit any claims covered by section 201(g)(1)(B) of the act, it would have had to provide an exemption from the latter section.

Further, FDA does not agree that the Commission report referred only to express claims. In its guidance on statements under section 403(r)(6) of the act, the Commission specifically said that such statements "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" (the report, p. 38) (emphasis added). In addition, the Commission cautioned that claims using terms such as, e.g., "support," "maintain," or "promote" are appropriate only if they 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) (emphasis added). Clearly, the Commission was concerned about implied claims as well as express claims.

FDA also does not agree that the required disclaimer demonstrates an intention to permit implied claims. To the contrary, FDA believes that the disclaimer language ("This

product is not intended to diagnose, treat, cure, or prevent any disease"), which is virtually identical to the language of section 201(g)(1)(B) of the act, provides further evidence that Congress did not intend section 403(r)(6) of the act claims to overlap section 201(g)(1)(B) claims. As a practical matter, it is unreasonable to interpret section 403(r)(6) of the act as inviting a communication to consumers like the following: "This product prevents bone fractures in post-menopausal women due to bone loss. This product is not intended to diagnose, treat, cure, or prevent any disease." The comments suggested that the addition of the disclaimer would somehow clarify the product's purpose to consumers. The comments provided no support, however, for their view that consumers reading the disclaimer would interpret it as eliminating implications in the remainder of the labeling that the product treats or prevents disease. FDA believes that the two statements simply contradict one another and could confuse consumers. Indeed, FDA is concerned that juxtaposing two such contradictory statements is likely to cause consumers to ignore the disclaimer required by section 403(r)(6) of the act, undermining its effectiveness.

(36.) A few comments addressed the examples of implied claims listed in the July 8, 1999, FEDERAL REGISTER notice. Some comments said that all of the examples were appropriate structure/function claims. Two comments suggested that "shrinks

tumors," "prevents development of malignant tumors," and "prevents seizures" are express disease claims because they employ "synonyms" for specific diseases. According to these comments, "tumor" is a synonym for cancer, and "seizure" is a synonym for epilepsy. Another comment said that FDA should treat as implied disease claims only those claims "where there is a direct causal relationship between the structure/function parameter identified in the claim and a specific known disease." According to this comment, a tumor is a "direct manifestation of cancer" and therefore reference to a tumor is a disease claim. In contrast, risk factors for disease, in which the comment includes elevated cholesterol, are not direct manifestations of a disease, and therefore may be the subject of structure/function claims. Another comment contended that disease claims should be limited to express claims and to terms or measurements that are "surrogates for the disease itself." According to this comment, tumors are a surrogate for cancer, but elevated cholesterol is not a surrogate for heart disease. One comment argued that "relief of sneezing, runny nose, and itchy watery eyes caused by exposure to pollen or other allergens" is an acceptable structure/function claim, but did not explain why.

FDA has considered these comments, but does not believe that any of them have provided a principle that distinguishes between claims that consumers will understand as disease claims and those

that will not be understood as disease claims. According to the comments, some of the claims that FDA offered as examples of implied disease claims should not be allowed as structure/function claims. FDA agrees that claims that refer to synonyms for disease, direct manifestations of disease, and surrogates for disease are disease claims. Each of these principles, however, would permit many types of implied disease claims that would be clearly understood by consumers as disease claims, e.g., "Herbal Prozac" and "antibiotic."

(37.) Some comments argued that it is impossible to construct a structure/function claim that does not imply disease prevention or treatment. Several of these comments claimed that health promotion claims inevitably imply disease prevention.

FDA does not agree that every structure/function claim implies disease prevention or treatment. In the proposed rule, FDA provided examples of many types of claims that the agency would not consider implied disease claims, and has expanded that list in the final rule.

(38.) Some comments disagreed with FDA's examples of disease claims in the proposed rule. These comments stated that intoxication and constipation are not in and of themselves diseases, and that these conditions are not readily understood by consumers as diseases. A few comments argued that alcohol intoxication is a "self-induced condition" and not a disease.

FDA continues to believe that alcohol intoxication, like all poisonings (mushroom, digitalis, or any drug overdose), meets the definition of disease, albeit a transient disease. The definition in § 101.14(a)(5), which FDA is incorporating in this rule, states, in part, that a disease is "damage to an organ, part or structure, or system of the body such that it does not function properly * * *" All poisonings, like alcohol intoxication, cause dose-related dysfunctioning and damage, ranging from mild impairments to death. Alcohol intoxication causes temporary damage to brain function, causing impairments of judgment, attention, reflexes, and coordination. The fact that it is "self-induced" does not remove it from the definition of disease. Deliberate barbiturate overdoses are also self-induced, but clearly meet the definition of disease.

FDA has considered the comments on constipation and agrees that certain constipation claims should not be treated as disease claims. Constipation has a variety of causes, many of them unrelated to disease. For example, constipation can be caused by changes in diet and schedule, and by travel. Constipation can also, however, be a symptom of such serious diseases as bowel obstruction and irritable bowel syndrome. FDA is aware that there may be differences of opinion about whether occasional constipation, alone, constitutes a disease, but believes that treating it as a disease would not be consistent with the intent

of DSHEA. "For relief of occasional constipation" would therefore not be considered a disease claim under the rule. The labeling of a product that claimed to treat occasional constipation should make clear, however, that the product is not intended to be used to treat chronic constipation, which may be a symptom of a serious disease.

(39.) One comment questioned whether a claim that begins, "According to the National Cancer Institute" would be a disease claim because it used the word "cancer."

Although the National Cancer Institute (NCI) is associated with the treatment and prevention of cancer, such a statement will be considered a disease claim only if, within the context of the total labeling, the statement can be reasonably understood to relate the product to the disease listed in the organization's name, e.g., cancer. For example, FDA would regard as a disease claim "According to the National Cancer Institute, ingredient X protects smokers' lungs."

F. Signs or Symptoms of Disease (§ 101.93(g)(2)(ii))

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. FDA provided as examples of such disease claims: "Improves urine flow in men over 50 years old," "lowers cholesterol," "reduces joint pain," and "relieves headache." Stating that claims of an effect on symptoms that are not recognizable as characteristic of a specific disease or diseases would not constitute disease claims, FDA provided the following examples of acceptable structure/function claims: "Reduces stress and frustration," "inhibits platelet aggregation," and "improves absentmindedness." The agency also stated that 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 included: "Helps maintain a healthy cholesterol level," or "helps maintain regularity."

FDA specifically requested comment on the distinction between maintaining normal function, which is potentially the basis for an acceptable structure/function claim, and preventing or treating abnormal function, which is potentially a disease claim. FDA noted that the members of the Commission were divided on this issue, but that the final report 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).

Recognizing that claims relating to maintaining healthy cholesterol levels raise particularly difficult issues, FDA sought specific comment on these claims.

(40.) Many comments from manufacturers and individuals objected to proposed § 101.93(g)(2)(ii). Some of these comments argued that basing the criterion on which signs and symptoms were "recognizable" to health care professionals or consumers was too vague, and that it was unclear what proportion of health care professionals or consumers would be necessary to establish recognition. Some comments asked whether FDA expected manufacturers to conduct consumer surveys. Other comments urged that FDA itself conduct consumer surveys to determine which signs and symptoms were recognizable to consumers as implied disease claims. Other comments argued that the proposed provision would create a moving target because "as soon as consumers understood that certain signs and symptoms are characteristic of a disease--that is, as soon as consumers understood why they should take a particular supplement--FDA could * * * prohibit a product label from bearing the substantive claims information."

FDA agrees with these comments that the proposal's focus on recognition of signs and symptoms by consumers or health professionals might have made the provision difficult to apply,

both for manufacturers and for the agency. Accordingly, the agency has substituted a more objective criterion. The final rule eliminates the reference to recognition, and focuses simply on whether the labeling suggests that the product will produce a change in the characteristic signs or symptoms of a specific disease or class of diseases. FDA believes that it will be easier for manufacturers to verify whether symptoms are in fact characteristic of a disease. FDA and manufacturers may look to medical texts and other objective sources of information about disease to determine whether a label implies treatment or prevention of disease by listing the characteristic signs and symptoms of a disease or class of diseases.

FDA notes that the standard in the rule may be met if characteristic signs and symptoms are referred to either in technical or lay language. It also would not be necessary to mention every possible sign or symptom of a disease to meet this standard. Instead, the standard focuses on whether the labeling suggests that the product will produce a change in a set of one or more signs or symptoms that are characteristic of the disease.

FDA does not agree with the comment that objected to the recognition standard because it would prohibit a claim "as soon as consumers understood that certain signs and symptoms are characteristic of a disease--that is, as soon as consumers understood why they should take a particular supplement * * *."

This comment assumes that the only reason people take dietary supplements is to treat or prevent disease and that it is appropriate to market supplements by implying that they can do so. Many people take dietary supplements for health-related reasons that do not involve treatment or prevention of specific diseases. As discussed elsewhere in this document, FDA does not believe that the act permits structure/function claims to imply treatment or prevention of specific diseases.

(41.) Several comments contended that the recognition standard was too restrictive because all signs or symptoms relating to the structure or function of the body are potentially recognizable to health care professionals and educated consumers as characteristic of some specific disease. Another comment argued that the proposal to treat references to signs and symptoms as disease claims was arbitrary and artificial. The comment said that specific examples of disease claims used in the proposal could as easily refer to nondisease states, e.g., "reduces joint pain" could refer to over-exercise. Conversely, "stress and frustration" could refer to anxiety and depression. Another comment contended that "reduces joint pain" is an acceptable structure/function claim if other language or graphics in the labeling clearly communicated treatment of conditions unrelated to arthritis. One comment asked whether "helps support cartilage and joint function" would constitute a permissible

structure/function claim. Some comments said that references to signs and symptoms should not be evidence of a disease claim because signs and symptoms can be associated with a number of varying conditions. One comment claimed that "inhibits platelet aggregation" does not mean anything to most consumers. On the other hand, some medical groups, groups devoted to specific diseases, and others expressed concern that the examples of structure/function claims provided by FDA permitted references to signs or symptoms that imply disease treatment or prevention. According to one comment, "inhibits platelet aggregation" could be interpreted to mean "prevents heart attack," and "improves absentmindedness" could be interpreted as a treatment for Alzheimer's disease.

FDA believes that removing the reference to recognition by consumers or health professionals from § 101.93(g)(2)(ii) will permit a clearer distinction between those signs and symptoms that imply a disease and those that do not. The focus will be on whether specific signs or symptoms are characteristic of a disease, based on objective sources. FDA does not believe that "improves absentmindedness" or "relieves stress and frustration" are characteristic of the specific diseases mentioned in the comments. FDA agrees that some signs and symptoms are associated with such a wide variety of diseases and nondisease states that they may not imply a specific disease or class of

diseases. For example, FDA would not interpret "improves absentmindedness" as implying treatment of Alzheimer's disease because absentmindedness is not as serious as the type of memory loss characteristically suffered by Alzheimer's patients; absentmindedness is, in fact, suffered predominantly by people who do not have Alzheimer's disease or any other disease. Stress and frustration, while associated with some anxiety disorders, are not the characteristic symptoms of those disorders; in addition, these symptoms are equally associated with many other nondisease states.

The agency does agree, however, with the comment that "inhibits platelet aggregation" is an implied disease treatment or prevention claim. Although platelet aggregation is a normal function needed to maintain homeostasis, inhibiting or decreasing platelet aggregation is a well-recognized therapy for the prevention of stroke and recurrent heart attack (see, e.g., 63 FR 56802, October 23, 1998 (final rule for professional labeling of aspirin for cardiovascular, cerebrovascular, and rheumatologic uses); 53 FR 46204, November 16, 1988, (internal analgesic tentative final monograph)). Inhibiting or decreasing platelet aggregation is the mechanism of action of a number of drug products approved for the treatment or prevention of stroke and heart attack. Thus, the agency would consider a claim to inhibit

normal platelet function to be an implied claim to treat or prevent these disease conditions.

FDA also believes that "joint pain" is characteristic of arthritis. According to the Merck Manual, joint tenderness is the most sensitive physical sign of rheumatoid arthritis (Ref. 6). The claim "helps support cartilage and joint function," on the other hand, would be a permissible structure/function claim, because it relates to maintaining normal function rather than treating joint pain.

(42.) One comment suggested that claims about a physiologic marker or symptom should be regarded as disease claims in two situations: (1) If the physiologic marker or symptom of a disease is described as being quantifiably linked to that disease in an official government health agency summary statement or consensus report, or (2) if most clinicians treating patients with the condition prescribe prescription drugs to modify the marker and historically do so without including nutritional or dietary intervention as part of the treatment. According to this comment, references to cholesterol lowering or blood pressure reduction would be regarded as disease claims under the first suggested criterion, and white cell counts and fever would be disease claims under the second. This comment also suggested that FDA develop a list of disease markers and symptoms that fall under each of the proposed criteria.

FDA agrees in part and disagrees in part with this comment. The agency agrees that references in dietary supplement labeling to physiologic markers or symptoms of a disease that are quantifiably linked to that disease in an official government health agency summary statement or consensus report would be appropriately treated as implied disease claims. Indeed, in the cases described, elevated blood pressure (hypertension) and elevated cholesterol (hypercholesterolemia) are diseases themselves, with subsequent events (heart attack, stroke) the late consequences of those diseases. Although FDA agrees that fever and elevated white cell counts are almost always evidence of a disease, FDA does not agree that the second criterion appropriately describes the remaining circumstances in which references to signs or symptoms should be treated as disease claims. The appropriate test is whether: (1) The condition to be treated or prevented is a disease and (2) the signs and symptoms referred to in the labeling, in context, are characteristic of a disease and thus permit the inference that the product is intended to treat or prevent the disease. The second criterion offered by the comment does not provide information on either of these elements.

(43.) Some comments that objected to the proposed definition of disease argued that the inclusion of "signs or symptoms" as part of the definition of disease should not mean

that a reference to the signs and symptoms of a disease in dietary supplement labeling constitutes a disease claim. Another comment argued that because signs and symptoms do not appear in the definition of "drug," FDA is not authorized to treat a reference to characteristic signs and symptoms as a drug claim.

The health claims definition of "disease or health-related condition" in § 101.14(a)(5), which is being adopted as the definition of "disease" in this regulation, does not include reference to the signs and symptoms of disease. Nonetheless, dietary supplement labeling that refers to the characteristic signs or symptoms of a specific disease or class of diseases will still be considered to have made an implied disease claim. Labeling that claims a product "prevents bone fragility in postmenopausal women," clearly implies that the product prevents osteoporosis. Similarly, labeling that claims a product "prevents shortness of breath, an enlarged heart, inability to exercise, generalized weakness, and edema" has made a congestive heart failure claim.

The basis for determining whether such a reference to signs or symptoms constitutes an implied disease claim is not whether the definition of disease includes mention of signs or symptoms. Rather, FDA looks at whether the objective evidence shows that the product is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" within the

meaning of section 201(g)(1)(B) of the act and § 201.128, or the claim constitutes a health claim within the meaning of section 403(r)(1)(B) of the act and § 101.14(a)(1). For example, § 201.128 provides that the objective intent of those responsible for the labeling of drugs "is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article." Section 101.14(a)(1) provides that "[i]mplied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition." Both of these provisions permit FDA to look at whether a reference to the characteristic signs or symptoms of a disease constitute an implied disease claim.

(44.) Many comments argued that the distinction between claims that a product maintains healthy function and that it prevents or treats abnormal function is artificial, and that consumers understand both types of claims as disease treatment or prevention claims. Comments from dietary supplement manufacturers and some consumer groups argued that both types of claims should be permitted either because they are not implied disease claims or because implied disease claims are permissible. Conversely, most of the comments from health professional groups,

groups devoted to specific diseases, pharmaceutical companies, and other consumer groups argued that neither type of claim should be permitted, because permitting implied disease claims to be made without prior review would jeopardize the public health by encouraging substitution of unproven remedies for proven ones. One comment argued that analysis of health maintenance claims is no different than analysis of any other structure/function claim: They are disease claims if they imply disease prevention or treatment. According to this comment, health maintenance claims are permissible unless they relate to endpoints that are understood to be disease markers, such as blood pressure and cholesterol. Comments from a former Commission member and from a consumer group argued that many health maintenance claims will be perceived as disease treatment or prevention claims, and urged that FDA follow the Commission's guidelines, under which the seriousness of the condition and the ability of the consumer to evaluate it are key factors in deciding whether a disease claim has been made. One comment argued that FDA may not prohibit a claim that a dietary supplement "maintains normal function" even if it implies a disease claim because 403(r)(6)(A) of the act expressly authorizes such claims.

One comment said that the proposed rule would frustrate the "orphan drug" process. The comment contended that if dietary supplement labeling may claim to promote or maintain "healthy"

endpoints that are related to signs and symptoms of specific diseases, then incentives to conduct research on orphan drugs would be undermined. The comment explained that dietary supplements do not require the same financial investment as drugs do (because drugs must be approved as safe and effective for their intended uses and meet quality controls), and could undercut sales of a more heavily regulated and more expensive approved drug. The comment said that a dietary supplement manufacturer's ability to make a disease prevention claim by characterizing the product as promoting good health "cannot become a license to sell an active ingredient in a product that is functionally a drug but is labeled as a dietary supplement."

FDA has carefully considered these comments and has concluded that the distinction drawn in the proposal between maintaining normal function and treatment or prevention of abnormal function is supported by the statute and the Commission report. FDA does not agree that health maintenance claims must always be treated as implied disease claims. Section 403(r)(6)(A) of the act demonstrates that Congress intended to treat as structure/function claims some claims concerning maintenance of normal structure or function, because it expressly permits statements that "characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function."

FDA also believes that many claims concerning the maintenance of "normal" or "healthy" structure or function do not imply disease prevention in the context of dietary supplement labeling, unless other statements or pictures in the labeling imply prevention of a specific disease or class of diseases. There may be cases, however, in which a statement of health maintenance can be understood only as a claim of prevention of a specific disease, in which case it will be considered a disease claim. Thus, any reference to "maintaining a tumor-free state" would be a disease claim. Similarly, a claim to "maintain normal bone density in post-menopausal women" is a disease claim because post-menopausal women characteristically develop osteoporosis, a disease whose principal sign is decreased bone mass.

FDA has added a sentence to § 101.93(g)(2) clarifying that the criteria in that paragraph are not intended to preclude structure/function claims that refer to the maintenance of healthy structure or function, unless they imply disease treatment or prevention.

For the reasons described elsewhere in this document, however, FDA does not believe that DSHEA permits claims concerning treatment or prevention of abnormal function, where such abnormal function implies a specific disease or class of diseases. Accordingly, FDA believes that the statutory scheme is consistent with treating many health maintenance statements as

structure/function claims, while treating as health claims or new drug claims statements that imply disease treatment or prevention by reference to an effect on abnormal structure or function.

The Commission report also supports the distinction drawn by FDA between maintaining healthy function and preventing or treating abnormal function. The report's Guidance states:

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.

(Report at pp. 38 and 39.)

FDA agrees that if a health maintenance claim implies disease treatment or prevention, it would not be acceptable. (In FDA's view, a claim promoting "use for a serious health condition that is beyond the ability of the consumer to evaluate" is simply one form of implied disease claim.) FDA believes that many health maintenance claims are acceptable. In some cases, a health maintenance claim could use terms that are so closely identified with a specific disease or that so clearly refer to a particular at-risk population that FDA would consider the claim to be an implied disease prevention claim, e.g., "maintains healthy lungs in smokers" would imply prevention of tobacco-related lung cancer and chronic lung disease. "Maintains healthy lung function," alone, however, would be an acceptable structure/function claim.

In response to the comment contending that dietary supplements undercut sales of orphan drugs by making health promotion claims for active ingredients already approved as orphan drugs, FDA notes that section 201(ff)(3) of the act excludes from the definition of "dietary supplement" articles that have been approved as drugs or for which substantial clinical investigations conducted under an investigational new drug application (IND) have been made public, before they were marketed as dietary supplements or foods.

(45.) Many comments responded to FDA's specific request for comment on whether it is appropriate to treat "maintains healthy cholesterol levels" as a permissible structure/function claim, while treating "lowers cholesterol" as a disease claim. A few comments supported the distinction drawn in the proposed rule. Many did not, however. One comment from a major trade association claimed that the distinction between lowering and maintaining cholesterol levels is ambiguous, asking "What is a healthy cholesterol level, but a lower cholesterol level?" Another comment from a food industry group contended that "cholesterol" itself is a sign or symptom, and thus that both types of claims refer to a sign or symptom of disease. Several comments argued that lowering cholesterol is inextricably linked to cardiovascular disease. Some comments argued that the distinction between maintaining normal cholesterol and lowering cholesterol is arbitrary because both have as their purpose preventing heart disease, and consumers link cholesterol levels with disease prevention. Other comments, however, argued that cholesterol claims do not imply disease prevention. A comment from an organization devoted to prevention and treatment of heart disease argued that if any cholesterol claims were to be permitted, a claim like "promotes cholesterol clearance" would be a more accurate structure/function statement than "maintains healthy cholesterol" and less likely to imply disease prevention.