

Two comments contended that changing a claim from "lowers cholesterol" to "maintains healthy cholesterol levels" does not change the effect of the product or its use. Some comments argued that "lowers cholesterol" claims should be permitted for cholesterol levels that are not "abnormal" or are below hypercholesterolemia.

FDA does not agree that claims concerning maintenance of normal cholesterol levels necessarily constitute implied disease claims. Although an elevated cholesterol level is a sign of hypercholesterolemia and an important risk factor for heart disease, a cholesterol level within the normal range is not a sign or risk factor for disease. Moreover, maintaining cholesterol levels within the normal range is essential to the structure and function of the body for reasons other than prevention of heart disease. Although many people think of cholesterol solely in terms of the negative role of elevated cholesterol in heart disease, normal cholesterol levels play a positive role in maintaining a healthy body. Cholesterol is a necessary constituent of cell membranes and of myelin, the sheath that coats nerves. Cholesterol is also required for the synthesis of steroid hormones, which are essential for life. Finally, cholesterol is required for the production of bile in the liver, making possible absorption of dietary fat and fat soluble vitamins. Thus, a claim that a dietary supplement helps

maintain cholesterol levels that are already within the normal range does not necessarily imply disease treatment. FDA also believes that Congress intended to permit dietary supplements to carry claims of this type under section 403(r)(6)(A) of the act.

The agency has concluded, however, that references to "healthy" cholesterol may be misleading to consumers because the phrase "healthy cholesterol" is now frequently used to refer to high density lipoproteins (HDL), a specific cholesterol fraction believed to be beneficial. To avoid this confusion, FDA has concluded that an appropriate structure/function claim for maintaining cholesterol would be "helps to maintain cholesterol levels that are already within the normal range."

FDA continues to believe that "lowers cholesterol," however qualified, is an implied disease claim. As many comments argued, lowering cholesterol is inextricably linked in the public mind with treating elevated cholesterol and preventing heart disease. The agency also believes that "promotes cholesterol clearance" is an implied disease claim because it is directed at lowering cholesterol rather than maintaining levels already determined to be within a normal range. FDA will review all cholesterol claims to determine whether the labeling as a whole implies that the product is intended to lower elevated cholesterol levels. In such cases, FDA would consider the labeling to create an implied disease claim.

(46.) A comment from a former Surgeon General of the United States argued that, given the importance of preventing cardiovascular disease, dietary supplements should be permitted to make claims for cholesterol reduction, because "our citizens deserve the opportunity to know when safe and effective dietary supplements are available to lower cholesterol." A comment from the Nutrition Committee of the American Heart Association argued that current scientific evidence does not support added benefits of dietary supplementation with nutritive substances for prevention of cardiovascular disease in the general population, and expressed concern that dietary supplements also carry risks.

FDA agrees that prevention of heart disease is an extremely important public health goal. Lowering cholesterol with certain drugs has been conclusively shown to be effective in reducing mortality from coronary artery disease. Indeed, the evidence linking the lowering of elevated cholesterol with preventing heart disease is so strong that identifying and using effective therapies to lower cholesterol in patients with elevated cholesterol levels has become of compelling importance. With this in mind, use of possibly ineffective therapies in persons with elevated cholesterol, which can delay or prevent effective treatment, poses significant public health risks. Although DSHEA requires that manufacturers who make structure/function claims have substantiation, manufacturers are not currently required to

submit that substantiation to FDA for premarket review, nor does FDA have the resources to inspect and review the quality of the substantiation in most cases. For this reason, FDA does not believe that permitting "lowers cholesterol" claims on dietary supplements without prior review serves the public health.

(47.) A few comments argued that FDA may not prohibit "lowers cholesterol" claims because the agency had earlier issued an advisory letter permitting such claims if the claim stated that the product was useful in the context of a healthy diet. One of these comments contended that the agency may not change its advice or guidance because it has cited no studies in this rulemaking to support the view that "lowers cholesterol" implies disease treatment.

FDA does not agree that it may not change its position on whether particular cholesterol claims imply disease treatment. The record and analysis in this rulemaking, as well as FDA's experience in implementing DSHEA, provide an ample basis for the conclusions that the agency has reached on cholesterol claims.

#### G. Conditions Associated With Natural States

##### (§ 101.93(q)(2)(iii))

The proposed rule stated that natural states such as aging, menopause, pregnancy, and the menstrual cycle, are not themselves diseases, but can be associated with abnormal conditions that are

diseases. FDA proposed in § 101.93(g)(2)(iii) to treat as a disease claim a statement that a product had an effect on a condition associated with a natural state if the condition presented "a characteristic set of signs or symptoms recognizable to health care professionals or consumers" as an "abnormality." FDA provided as examples of such abnormal conditions the following: Toxemia of pregnancy; premenstrual syndrome; hot flashes; and presbyopia, decreased sexual function, and Alzheimer's disease associated with aging.

In the July 8, 1999, FEDERAL REGISTER notice announcing a public meeting and reopening the comment period, FDA asked for additional comment on this provision of the proposed rule. The agency sought specific comment on the following three questions: (1) If FDA were to treat some conditions associated with natural states as diseases (e.g., toxemia of pregnancy and Alzheimer's disease) but not others (e.g., hot flashes, common symptoms associated with the menstrual cycle, and decreased sexual function associated with aging), what would be an appropriate principle for distinguishing the two groups? (2) For example, would it be appropriate to consider the severity of the health consequences if the condition were to go without effective treatment? (3) If so, how should "severity" be defined?

(48.) Although some comments from disease-specific organizations and health professionals supported this provision,

most of the comments strongly objected to classifying common conditions associated with natural states as diseases. None of the objecting comments argued that toxemia of pregnancy or Alzheimer's disease are not diseases. Almost all of these comments, however, contended that PMS, hot flashes, and various conditions associated with aging, such as decreased sexual function, are so common that they should be considered neither abnormal nor diseases. Some comments argued that any condition suffered by more than 50 percent of the population should be considered normal and not a disease, and gave as an example benign prostatic hypertrophy. Other comments cited prevalence rates for conditions such as PMS and hot flashes, and contended that the cited rates were too high for these conditions to be considered abnormal. A large number of comments asserted that the proposed rule would treat pregnancy, menopause, and aging as diseases. A few comments argued that if menopause, aging, and pregnancy are not diseases, then signs and symptoms associated with these states cannot be diseases. One comment argued that conditions related to natural states are not diseases but "health-related conditions" and that DSHEA permits statements about health-related conditions.

In response to the questions in the July 8, 1999, FEDERAL REGISTER notice, many comments argued that the severity of the condition associated with a natural state was not an appropriate

principle for distinguishing diseases from nondiseases. These comments generally argued that the severity of the symptoms (rather than the severity of the consequences of going without effective treatment) was not an adequate basis to distinguish diseases from nondiseases. One comment from a food industry group argued that this was an inappropriate principle because "all natural states can have severe consequences if left unattended." This comment suggested that conditions that were "universal" should not be treated as diseases. This comment and one other also suggested that the distinguishing principle was whether the cause of the condition was "pathological."

FDA has reconsidered proposed § 101.93(g)(2)(iii), and has concluded that it is not appropriate, under DSHEA, to treat certain common, nonserious conditions associated with natural states as diseases. There are a wide variety of conditions representing impaired function of an organ or system that are associated with particular stages of life or normal physiologic processes. These stages and processes include adolescence, the menstrual cycle, pregnancy, menopause, and aging. (FDA notes that, contrary to the comments, the proposed rule would not have classified these stages or processes themselves as diseases; it classified only certain abnormal conditions associated with these stages or processes as diseases.) The conditions associated with these stages or processes can vary from common, relatively mild

abnormalities, for which medical attention is not required, to serious conditions that can cause significant or permanent harm if not effectively treated.

For example, pregnancy is associated with common and mild abnormalities such as morning sickness and leg edema that cause no permanent harm if left untreated, as well as with such serious conditions as hyperemesis gravidarum, toxemia of pregnancy, and acute psychosis of pregnancy, which can be life-threatening if not effectively treated. The menstrual cycle is commonly associated with mild mood changes, edema, and cramping that do not cause significant or permanent harm if left untreated, but also, more rarely, with serious cyclical depression that can result in significant harm if not effectively treated. Aging is almost invariably associated with characteristic skin and scalp changes, such as wrinkles and hair loss, which do not need medical attention. It is also, however, associated with serious diseases that will result in significant, often irreversible damage, many of which can be effectively treated. These diseases include osteoporosis, glaucoma, and arteriosclerotic diseases of coronary, cerebral, and peripheral vessels. Adolescence is commonly associated with mild acne, which does not cause significant or permanent harm if not treated, and, rarely, with cystic acne, which can produce severe physical and psychological scars if not effectively treated.

Whether all of these conditions represent diseases is, in part, a matter of definition and, in part, depends on the consequences of the conditions if not effectively treated, and on how commonly they occur, i.e., whether they may be considered "normal." Although most people consider the more serious or infrequent conditions referred to above to be diseases, views vary with respect to the common, milder conditions. FDA has reconsidered the position it took in the proposed rule and agrees with the comments that treating as diseases the common, mild symptoms associated with normal life stages or processes would not be consistent with the intent of DSHEA.

FDA does not believe that the frequency with which a condition associated with a natural state occurs is, by itself, sufficient to distinguish diseases from nondiseases. The severity of the consequences of disease, as well as the consequences of ineffective treatment, must also be considered. As noted above, whether common, minor conditions associated with natural states are diseases is a matter of debate, but FDA has decided not to treat them as diseases because the agency believes this approach is consistent with the intent of DSHEA. FDA does not, however, believe that DSHEA was intended to permit unreviewed claims about serious conditions that could cause significant or permanent harm, particularly where effective treatment is available. FDA also does not agree that "all

natural states can have severe consequences if left unattended." FDA has listed a large number of conditions associated with natural states that commonly do not have serious consequences even if not effectively treated. FDA also does not agree that it is helpful in this context to distinguish between diseases and nondiseases by asking which have a "pathological" basis. The term "pathological" is itself defined by reference to disease, namely, "caused by or involving disease; morbid" (Ref. 7).

Accordingly, for purposes of this rule, mild conditions commonly associated with particular stages of life or normal physiological processes will not be considered diseases. Therefore, § 101.93(g)(2)(iii) now states that a statement will be considered a disease claim if it claims that the product "has an effect on an abnormal condition associated with a natural state or process, if the abnormal condition is uncommon or can cause significant or permanent harm." Ordinarily, FDA would follow the suggestion in the comments that conditions associated with a stage of life or a normal physiological process be considered common if they occur in more than one-half of those experiencing that stage or process.

The following are examples of conditions about which structure/function claims could be made under § 101.93(g)(2)(iii): (1) Morning sickness associated with pregnancy; (2) leg edema associated with pregnancy; (3) mild mood

changes, cramps, and edema associated with the menstrual cycle; (4) hot flashes; (5) wrinkles; (6) other signs of aging on the skin, e.g., liver spots, spider veins; (7) presbyopia (inability to change focus from near to far and vice versa) associated with aging; (8) mild memory problems associated with aging; (9) hair loss associated with aging; and (10) noncystic acne. The following are examples of conditions that would remain disease claims: (1) Toxemia of pregnancy; (2) hyperemesis gravidarum; (3) acute psychosis of pregnancy; (4) osteoporosis; (5) Alzheimer's disease, and other senile dementias; (6) glaucoma; (7) arteriosclerotic diseases of coronary, cerebral or peripheral blood vessels; (8) cystic acne; and (9) severe depression associated with the menstrual cycle.

FDA has not included benign prostatic hypertrophy (BPH) on either of these lists, because the agency does not believe that BPH should be considered a consequence of aging. Like many other diseases, e.g., diabetes, prostate cancer, and heart disease, the incidence of BPH is much higher among older men. This does not mean that BPH or prostate cancer is caused by the aging process. Even if BPH were considered a direct consequence of aging, however, claims to treat or prevent it would still be treated as disease claims because failure to obtain effective treatment can cause significant or permanent harm.

FDA notes that it does not base the exclusion of the mild common conditions associated with natural states from § 101.93(g)(2)(iii) on the argument advanced by one of the comments that these are "health-related conditions" and that DSHEA permits structure/function claims about health-related conditions. FDA believes that a "health-related condition" is a state of health leading to disease. As FDA has said previously, "diseases" and "health-related conditions" are "so closely related that no bright-line distinction is practicable" (58 FR 2478, 2481 January 6, 1993). There is nothing in DSHEA, its legislative history, or in the definition of "disease or health-related condition" that would suggest that common conditions associated with natural states are "health-related conditions" within the meaning of section 403(r)(1)(B) of the act. Further, FDA does not agree that section 403(r)(6) of the act authorizes structure/function claims about "health-related conditions." Had Congress intended to authorize structure/function claims about "health-related conditions" it could easily have used that terminology, but did not.

(49.) Some comments concerned specific claims under proposed § 101.93(g)(2)(iii). One comment sought concurrence that the following are acceptable structure/function claims: "supports a normal, healthy attitude during PMS" and "supportive for menopausal women." Another comment argued that a statement

that a product provides nutrients that diminish the normal symptomatology of premenstrual syndrome or menopause is a permissible structure/function claim. Another comment asked whether "helps to maintain normal urine flow in men over 50 years old" is a permissible structure/function claim. One comment urged that only products proven safe when used as directed should be permitted for sale for enlarged prostate and that such products should recommend that a man see his physician. Another comment argued that the claim "for men over 50 years old," which FDA had proposed as an acceptable structure/function claim, is vague and ambiguous and is of no use to consumers.

FDA agrees that "supports a normal, healthy attitude during PMS" and "supportive for menopausal women" are appropriate structure/function claims. "Supports a normal, healthy attitude during PMS" is acceptable because PMS is generally a common, mild condition associated with a normal physiologic process. "Supportive for menopausal women" is acceptable because it is a general statement that does not refer to symptoms of any conditions at all. Claims about diminishing the normal symptomatology of premenstrual syndrome or menopause would also be acceptable structure/function claims, if they did not suggest, for example, prevention or treatment of osteoporosis, or another disease associated with these states. "Helps to maintain normal urine flow in men over 50 years old," however, is an implied

disease claim because, as many comments pointed out, the average or "normal" state in men over 50 years old is diminishing urine flow, in most cases due to BPH, so that the apparent "maintenance" really represents a claim of improvement (treatment).

H. Generally (§ 101.93(g)(2)(iv))

Under proposed § 101.93(g)(2)(iv), FDA stated that a statement would be considered a disease claim if it claimed explicitly or implicitly to have an effect on disease through one or more of the following factors: (1) 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; (2) statements about the formulation of the product, including a claim that the product contained an ingredient that has been regulated by FDA predominantly as a drug and is well known to consumers for its use in preventing or treating a disease (e.g., aspirin, digoxin, or laetrile); (3) citation of a publication or other reference, if the citation 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; (4) use of the term "disease" or "diseased;" or (5) 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, or the prescription symbol (Rx)). The proposed rule stated that a picture of a body would not constitute a disease claim under this criterion.

(50.) A few comments stated that the phrase "has an effect on" in proposed § 101.93(g)(2)(iv) is vague and could be interpreted by the agency to mean almost anything. Some of these comments argued that disease claims should include only those that use the specific terms "diagnose," "prevent," "treat," "mitigate," or "cure."

FDA does not agree that the phrase "has an effect on" is inappropriately vague. FDA believes that it is necessary to use a phrase that encompasses synonyms for the terms "diagnose," "prevent," "treat," "mitigate," or "cure." If disease claims were limited to those that used the specific terms in the statute, it would be possible to make obvious and explicit disease claims simply by using terms that are similar in meaning to the statutory terms, e.g., "relieves arthritis pain" rather than "treats arthritis pain," or "eliminates the risk of cancer" rather than "prevents cancer."

I. Product Name (§ 101.93(g)(2)(iv)(A))

(51.) One comment observed that there is an inconsistency between the statement in the proposed rule that "Heart Tabs" does not imply an effect on a disease and § 101.14(a)(1), which states that:

Health claim means any claim made on the label or in the labeling of a food, including a dietary supplement, that expressly or by implication, including "third party" references, written statements (e.g., a brand name including a term such as "heart"), symbols (e.g., a heart symbol) characterizes the relationship of any substance to a disease or health-related condition \* \* \*

and requested clarification.

FDA agrees, in part, and disagrees, in part, with the comment. FDA does not agree that § 101.93(g)(2)(iv)(A) and § 101.14(a)(1) are inconsistent. Section 101.14(a)(1) was issued in 1993 to implement the health claims provisions of NLEA. In § 101.14(a)(1), use of the term "heart" in a brand name and use of the heart symbol in labeling are offered as examples of health claims, if in the context of the labeling as a whole, the word or symbol suggests that there is a relationship between the product and a disease or health-related condition. Thus, according to the preamble to that final rule (58 FR 2478 at 2486), the heart

symbol might appropriately appear in the labeling of a food product if, in context, it did not suggest a relationship to heart disease, e.g, in conjunction with "Hey, Fudge Lovers." If, however, the heart symbol appeared alone on a food, without further explanation from context, consumers might conclude that the food was beneficial for reducing the risk of developing cardiovascular disease (id.).

Following the issuance of § 101.14(a)(1), Congress enacted DSHEA. DSHEA created a special regulatory regime for dietary supplements. That regime, while closely related to the regime for food, was not identical to the food regime. Section 403(r)(6) of the act specifies certain types of structure/function claims and general well-being claims that may be made for dietary supplements without first obtaining new drug approval or health claim authorization. The types of claims listed in section 403(r)(6) of the act are similar, but not identical to the claims permitted for foods under section 201(g)(1)(C) of the act. Under Nutrilab v. Schweiker, 713 F.2d 335 (7th Cir. 1983), conventional food claims are limited to structure/function effects that derive from the taste, aroma, or nutritive value of the food. Dietary supplement claims are not subject to that limitation. Had Congress intended the scope of the permitted claims to be identical, it could simply have declared that dietary supplements are "foods." In light of

Congress' intent to expand the types of claims authorized for dietary supplements in DSHEA, FDA interprets § 101.14(a)(1) as permitting dietary supplements to have brand names that include the word "heart" or other organs, if, in the context of the labeling as a whole, the name does not imply disease treatment or prevention.

FDA does agree, however, that under § 101.14(a)(1), a dietary supplement name that included the word "heart" could be a health claim, depending on the context. Thus, a dietary supplement could be called "HeartTabs" if its claim was "to maintain healthy circulation," or some other role related to the structure or function of the heart that did not imply treatment or prevention of disease. If, however, the product name was not qualified by any further claim in the labeling, the product could be considered, under § 101.14(a)(1), to be intended for treatment or prevention of cardiovascular disease.

FDA also believes that the heart symbol has become so widely associated with prevention of heart disease that its use in the labeling of a dietary supplement would be ordinarily considered an implied heart disease prevention claim. Consistent with the examples provided in the January 6, 1993, FEDERAL REGISTER document on health claims (58 FR 2486), however, there may be unusual cases in which, in context, the use of a heart symbol does not imply heart disease prevention.

(52.) Several comments agreed with proposed § 101.93(g)(2)(iv)(A) that product names that imply an effect on disease, including implying cure or treatment of a disease, should not be allowed. The comments, however, requested that the agency provide further guidance as to what types of product names are acceptable and what types are not. Some comments questioned whether product names such as "CarpalHealth," "HepatoHealth," "HepataCare," "CircuCure," or "Soothing Sleep" would be acceptable under proposed § 101.93(g)(2)(iv)(A). Other comments disagreed with the agency's examples and stated that it is difficult to distinguish the reasoning behind some of the examples cited. For example, a few comments stated that both "Cardiohealth" and "Heart Tabs" imply that the product prevents heart disease.

Two principles formed the basis for the distinctions in the proposed rule between product names that were considered structure/function claims and those that were considered disease claims. First, the name should not contain the name, or a recognizable portion of the name, of a disease. Second, the name should not use terms such as "cure," "treat," "correct," "prevent" or other terms that suggest treatment or prevention of a disease. Thus, "CarpalHealth" and "CircuCure" would be considered disease claims. In some cases, to determine whether a product name implies an effect on disease, the agency will need

to consider the context in which a term is presented in the labeling as a whole. Thus, "Soothing Sleep" could be considered a claim to treat insomnia, unless the labeling made clear that the product was intended only for occasional sleeplessness.

"HepataCare" and "HepataHealth" could also be considered disease claims because "Hepata" could be read as a reference to hepatitis, unless the labeling made clear that the product was intended for general liver health and not intended to treat or prevent hepatitis.

The agency notes that in the near future, FDA will issue for public comment a draft guidance to provide additional clarification and examples of claims that would and would not be considered disease claims under the final rule. FDA will include in the draft guidance examples of product names.

(53.) Another comment stated that proposed § 101.93(g)(2)(iv)(A) would prohibit the use of the name of the "dispensing institution" if it had the word "Cancer" in it because the agency would interpret the labeling as implying an effect on disease, when in fact the product was listing the institution where the product was dispensed, e.g., ABC Cancer Institute. Other comments were concerned that the proposed rule would prohibit the use of their company trade name, which includes the use of the word "prescription" and its abbreviation "Rx."

The agency reiterates that it will view the name in the context of the entire labeling to determine whether a disease claim is being made. However, a manufacturer may not circumvent the requirements of the act, DSHEA, or this final rule by using the name of an institution or the manufacturer to imply a disease claim.

The agency agrees that the use of the word "prescription" or its abbreviation "Rx" in the name of the product should not automatically be interpreted as a disease claim. Although these terms imply that the product is a prescription drug, some prescription drugs are intended for nondisease conditions. Therefore, if nothing else in the labeling suggests a disease use, the agency will not consider the use of "prescription" or "Rx" to be an implied disease claim. The agency notes, however, that the use of these terms on dietary supplement products may deceive consumers into thinking that they are purchasing a prescription drug without a prescription. Thus, use of the terms "prescription" or "Rx" is misleading and will misbrand the product under section 403(a)(1) of the act if, in the context of the labeling as a whole, the terms imply that the product is a prescription drug.

(54.) A few comments cited in a proposed rule published in the FEDERAL REGISTER of March 27, 1974 (39 FR 11298), in which FDA stated that it would challenge brand names only in situations

where clarifying language is incapable of rectifying FDA's concern with the brand name and that excision of a brand name should be a last resort and should be pursued only when all other methods of qualifying the name have failed.

The agency notes that the proposed rule cited in this comment was never finalized and was withdrawn on December 30, 1991 (56 FR 67440), as part of an FDA initiative to reduce the backlog of outstanding proposed rules that have never been finalized. The policies outlined in the March 27, 1974, FEDERAL REGISTER notice are not in effect.

(55.) Several comments sought a statement from FDA that if a product brand name becomes synonymous over time with use for prevention or treatment of a disease, it will still be permitted. As an example, the comments claimed that Kleenex has become synonymous with treatment of nasal congestion, but did not provide support for this assertion.

FDA does not believe that Kleenex is synonymous with treatment of nasal congestion and, absent any supportive data, has no reason to believe that consumers believe them to be synonymous. The agency would agree that Kleenex has become synonymous with "tissue," and that both are used in conjunction with nasal congestion. Neither tissue nor Kleenex, however, treat, prevent, or otherwise affect nasal congestion in any way. Because the agency was not presented with any specific examples

of, nor is it aware of any, names of products that are not intended to treat disease but that have become synonymous with disease treatment or prevention, it does not have reason to believe that there is a real basis for concern.

J. Product Formulation (§ 101.93(g)(2)(iv)(B))

(56.) Several comments questioned whether the inclusion of a dietary ingredient in the ingredient list of a dietary supplement would be interpreted as a disease claim under proposed § 101.93(g)(2)(iv)(B). They argued that to provide truthful labeling, this information must be included. Another comment stated that the proposal fails to distinguish between true claims and false claims. Several comments further argued that ingredient information may be of value to consumers to alert them to potential adverse effects or drug interactions. One comment urged that the presence of a constituent that is naturally occurring in a plant and is also regulated as a drug does not automatically classify the substance as a drug. The comment asserted that 45 percent of drugs are derived from plants, which, according to the comment, would classify a number of dietary ingredients as drugs.

Listing a dietary ingredient in the ingredient list of a dietary supplement will not be considered to imply an effect on disease unless the ingredient is one that has been regulated primarily by FDA as a drug and is well-known to consumers for its

use or claimed use in preventing or treating a disease. (In the proposed rule, the agency gave as examples aspirin, digoxin, and laetrile.) Very few dietary ingredients meet this test. The agency agrees that a certain percentage of drug products are derived from plants. However, only a handful of these drugs are well-known to consumers under the name of the plant or natural plant ingredient from which they were derived. Instead, they are known to consumers under a brand name or generic name, e.g., aspirin. Thus, FDA does not believe that listing dietary ingredients that happen to be related to well-known drugs will fall under this provision, except in unusual circumstances. In those cases where a manufacturer does add a drug ingredient that is well-known to treat or prevent disease to its product and label its presence, however, FDA may consider it a disease claim. The fact that the labeling is truthful does not necessarily mean that it falls within the scope of claims authorized by section 403(r)(6) of the act. For example, the agency believes that there are many dietary ingredients that could be shown to treat or prevent diseases, and for which it could thus be truthful to state that the product treats or prevents a specific disease. Under the act, however, if a manufacturer wants to label its product to treat or prevent disease, it must do so under the drug approval provisions or the health claim provisions of the act. It may not do so under section 403(r)(6) of the act. In drafting

section 403(r)(6) of the act to exclude disease claims, Congress made a judgment that the public health will be served by requiring premarket review of such claims.

FDA agrees that it is important to inform consumers about potential adverse effects or drug interactions for specific dietary supplement ingredients. In fact, dietary supplement labeling, like the labeling of other FDA-regulated products, is required to include all facts that are material in light of consequences that may result from use of the product or representations made about it (sections 403(a)(1) and 201(n) of the act). This provision is not intended in any way to preclude truthful adverse event or drug interaction information from appearing in a dietary supplement's labeling.

(57.) A dietary supplement manufacturer asked FDA to clarify the effect of § 101.93(4)(ii) on a dietary ingredient found in common food(s), whose biological activity is first characterized in a food context, but which is subsequently approved as a drug. The comment asked whether, if indole-3-carbinol, a compound discovered in broccoli and other vegetables, were to be approved as a breast cancer drug, claims to the effect that a vegetable-based dietary supplement product contains indole-3-carbinol would be permitted as structure/function claims under the proposed rule. The comment claimed that the proposed rule would classify such claims as disease claims even if the

biological activity of this dietary ingredient were first identified in the food context.

Where an ingredient has been approved as a drug, section 201(ff)(3) of the act prohibits marketing of the ingredient as a dietary supplement unless the ingredient itself was previously marketed as a food (including a dietary supplement), or unless a food containing the ingredient was previously marketed for the presence of the ingredient. In the example provided in the comment, the isolated ingredient indole-3-carbinol could not be marketed as a dietary supplement, unless a food containing the ingredient had been marketed for the presence of the ingredient before the drug was approved or was the subject of substantial investigations that had been made public. However, to avoid a conflict between this provision and section 201(ff)(3) of the act in a situation where the ingredient was marketed as a food first, FDA has revised § 101.93(g)(2)(iv)(B) to exclude claims about an ingredient that is an article included in the definition of "dietary supplement" under section 201(ff)(3) of the act.

(58.) One comment misunderstood § 101.93(g)(2)(iv)(B) and believed that this provision only applies to the listing of OTC drug ingredients recognized by consumers.

This provision is not limited to the listing of OTC drug ingredients. For purposes of § 101.93(g)(2)(iv)(B), the agency may consider as a disease claim a claim that the product contains

an ingredient that has been regulated by FDA as a drug, whether marketed over-the-counter or by prescription, and that is well known for its use in preventing or treating a disease.

K. Citation of Publication Titles (§ 101.93(g)(2)(iv)(C))

(59.) Many comments objected to this proposed criterion or sought clarification. Many comments said that the proposed criterion undermines DSHEA by prohibiting the use of most journals, is not required by DSHEA, or is contrary to section 403B of the act (21 U.S.C. 343-2), which, the comment said, exempts scientific publications from labeling rules and is intended to allow consumers to be more informed by reading scientific studies. Other comments said that Congress intended to encourage the dissemination of scientific research and truthful, non-misleading information, so FDA should not prohibit titles of scientific studies. Some comments stated that the issue should not be whether a publication's title refers to a disease use, but rather whether, on balance, the entire presentation, including the product label, package insert, and other labeling, represents a disease claim. These comments supported the use of complete citations to scientific literature, including the titles of scientific articles. Some comments suggested that the proposal contradicted earlier FDA positions. One comment referred to the September-October 1998 issue of FDA Consumer which, the comment stated, suggested that consumers

contact companies to obtain scientific articles that the company might have to substantiate a claim. Another comment said the proposal was contrary to FDA policy to recognize and accept valid science. Several comments questioned how to provide substantiation of labeling claims, in compliance with 403(r)(6)(B) of the act, if the supporting articles cannot be cited. One comment stated that there will be more fraud and deception in the marketplace because companies will not cite scientific support for their statements. Several comments stated that the proposed rule will restrict access by consumers and the medical community to important new research results and discourage companies from investing in research. A dietary supplement manufacturer suggested revising the provision to permit companies to cite "bonafide" textbooks and peer-reviewed scientific journals that mention a disease in the title. Another dietary supplement manufacturer suggested revising this provision to permit citation of a publication or reference if the citation "is necessary to present a balanced discussion of the documented mechanism by which a nutrient or dietary ingredient acts to maintain the structure or function of the body."

FDA agrees that in enacting DSHEA, Congress intended to encourage the dissemination of scientific research and truthful, non-misleading information. FDA also agrees that consumers can benefit from reviewing the scientific support used to

substantiate a statement made for a dietary supplement under section 403(r)(6) of the act. In keeping with these goals, FDA has modified § 101.93(g)(2)(iv)(C) to narrow the circumstances under which citation to a scientific reference will be considered a disease claim. Based on Congress' explicit prohibition in section 403(r)(6) of the act of claims to affect disease, however, FDA does not believe that Congress intended to permit scientific references to be used in a way that constitutes an implied disease claim. Consequently, § 101.93(g)(2)(iv)(C) has been revised to state that citation of a title referring to a disease will be treated as a disease claim, if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease, e.g., through placement on the immediate product label or packaging, inappropriate prominence, or lack of relationship to the product's express claims.

The agency continues to believe that placing a citation to a scientific reference that mentions a disease in the title on the immediate product label or packaging should be considered a disease claim for that product, because of the unusual and unnecessary prominence of such placement. For citations to scientific references that refer to a disease use in the title and that are included in other types of labeling (i.e., other than the product label or packaging) the agency will consider the context in which the citation is presented. FDA agrees with the

comments that the totality of all available labeling should be considered to determine the context. One element that the agency will look at is the prominence of the citation in the labeling. If, for example, the citation is simply listed in the bibliography section of the labeling among other titles, it will generally not suggest an implied disease claim. On the other hand, highlighting, bolding, using large type size, or prominent placement of a citation that refers to a disease use in the title could suggest that the product has an effect on disease. The agency will also consider whether the cited article provides legitimate support for a 403(r)(6) of the act statement that appears in the labeling of the dietary supplement. Enhancing the bibliography with citations to scientific references that refer to a disease in the title and that have no reasonable relation to the statement made will be considered a disease claim. Similarly, the agency will consider whether citations are to bona fide research.

FDA also agrees that it is important to provide a balanced discussion of the scientific literature regarding the claim. FDA encourages manufacturers to cite references that provide a balanced discussion of the evidence supporting a structure/function claim.

The agency believes that the final rule strikes a reasonable balance between encouraging the dietary supplement industry to

inform consumers about the substantiation for their claims and preventing abuses of section 403(r)(6) of the act.

(60.) Several comments challenged the basis for the proposed restriction on scientific references. One comment from industry said the proposed restriction on titles is outside DSHEA because the act refers to statements. The comment said titles could be prohibited if they were misleading, but said the rule should not contain a blanket prohibition.

The comment is apparently referring to section 403(r)(6) of the act, which prescribes the terms under which a "statement" may be made for a dietary supplement. FDA believes that the comment's reading is too literal, however. A "statement" does not have to be a declaratory sentence but rather is fairly read to include other kinds of statements, such as citations of scientific authority. In keeping with DSHEA's purpose to broaden the scope of labeling claims that may be made for dietary supplements without subjecting them to regulation as drugs, FDA believes that Congress intended "statement" to refer to any claim made that recommends or suggests a particular use of a dietary supplement. In addition to being under inclusive, a narrower interpretation would not benefit the dietary supplement industry because it would limit the scope of claims authorized under section 403(r)(6) of the act.

(61.) A few comments stated that the agency did not provide any support for the assumption that citations are disease claims rather than substantiation for a claim.

FDA believes that a citation of a title that refers to a specific disease can serve both as a disease claim and as substantiation for a claim. A citation of a publication title that links the product to a particular disease could lead consumers to believe that the product can be used to diagnose, prevent, mitigate, treat, or cure a disease, even if the title also provides substantiation for the product claims.

As stated above, citation of a scientific reference will not be treated as a disease claim if, in the context of the labeling as a whole, the reference lacks prominence and if it is appropriate support for the product claim.

(62.) One comment sought clarification of the effect of this provision on multi-ingredient products. The comment asked whether a disease claim for the entire product would be created if the labeling cited an article about only one ingredient of a multi-ingredient product.

Generally, if a citation is presented in the product labeling in such a way as to imply that a specific ingredient can treat or prevent disease, the product, as a whole, will be considered to be intended to treat or prevent disease.

(63.) A few comments requested FDA to clarify how proposed § 101.93(g)(2)(iv)(C) would operate. The comments questioned whether they would have to delete a citation from a list or redact the reference to a disease from the title of the article.

One comment asked whether an article that contains a reference to a disease can be cited if the title is not used in the citation. The comments further questioned whether they can provide the entire article, with the title on it, if requested by a consumer. Some comments asked FDA to clarify that a label may cite a title that appears in a publication whose name includes a disease (such as the publication titled Cancer) or to clarify how scientific studies may be cited. One comment requested that the agency issue further guidance to clarify what is and is not covered by § 101.93(g)(2)(iv)(C).

FDA does not expect a manufacturer to redact portions of the citation or delete a citation from a list of references or bibliography if it is appropriate to include the reference to substantiate a claim. As described above, if the citation to a scientific reference refers to a disease, the agency will consider the context in which the citation is presented, including its prominence in the labeling and whether there is a reasonable relationship between the reference and the express claim. In most cases, the unredacted reference title can be included in the product labeling without subjecting the product to regulation as a drug, as long as the prominence of the reference does not suggest that it is being used to imply disease treatment or prevention. Under revised § 101.93(g)(2)(iv)(C), the only reason a publication title would be considered a disease

claim regardless of prominence would be if the reference is not reasonably related to substantiating the product's express claim. In that case, FDA believes that the reference would be a disease claim, even if the name of the disease is redacted, because the only purpose of including the reference would be to suggest use of the product for treatment or prevention of the disease discussed in the reference.

With regard to citation of titles from journals whose official names include the name of a disease, the same considerations of appropriate prominence and reasonable relationship to the product's express claims apply. FDA expects that accepted conventions of scientific citation will be used for all citations that appear in labeling.

Finally, if specific information about an unlabeled use of a product is requested by a consumer, and the request is not solicited by the manufacturer, providing articles that are responsive to the request will not be considered a disease claim.

FDA will issue further guidance on § 101.93(g)(2)(iv)(C), if necessary.

(64.) Several comments sought modifications to proposed § 101.93(g)(2)(iv)(C). One comment suggested revising the provision to permit companies to cite articles or references that use "intermediate terms" (which the comment said were terms or

phrases that have disease-related endpoints) on the label or labeling.

Whether a citation that refers to a disease-related endpoint will be considered a disease claim under the rule will depend on the context in which the disease-related endpoint is referred to and whether the reference implies that the product has an effect on disease. For example, the title of an article that states that a product was shown to maintain cholesterol levels that were already within the normal range, with no reference to a disease, would be considered a structure/function statement about maintenance rather than a disease claim. However, if the title of the article states that the product was shown to lower elevated cholesterol levels, this implies that the product can be used to have an effect on the disease states hypercholesterolemia and heart disease, because heart disease is associated with high cholesterol levels.

(65.) A trade association suggested that the title should not be considered to be a disease claim unless it uses the terms "treat," "cure," "mitigate," "prevent," or "diagnose."

As stated elsewhere in this document, FDA believes that a disease claim can be made explicitly or implicitly using terms other than those listed in the comment. For example, depending on how it was used in a product's labeling, a scientific reference entitled "Using Ingredient X For Diabetes" could

constitute a claim that the product can diagnose, mitigate, treat, cure, or prevent diabetes, without using any of these specific terms.

(66.) A few comments argued that citation of articles that refer to a disease use should be permitted because consumers have access to these articles in connection with the sale of dietary supplements under section 403B(a) of the act.

As stated above, FDA has revised the proposed rule's treatment of citations to scientific articles. Under the final rule, such citations will not always be considered disease claims. FDA does not agree, however, that section 403B of the act applies to the citation of titles in product labeling. Although section 403B of the act exempts certain publications from the labeling provisions of the act, section 403B(a)(2) states that the exemption applies only when, among other requirements, the publication is "used in connection with the sale of a dietary supplement to consumers when it \* \* \* does not promote a particular manufacturer or brand of a dietary supplement." If the reference or the title of the reference was disseminated by a particular manufacturer of the dietary supplement discussed in the reference, the agency would conclude that it was being used to promote that manufacturer's brand of the dietary supplement. Therefore, the exemption in section 403B of the act would not apply.

Furthermore, to qualify for the exemption in section 403B of the act, a publication must be "an article, a chapter in a book, or an official abstract \* \* \* reprinted in its entirety" and must be "displayed or presented, or \* \* \* displayed or presented with other such items on the same subject matter, so as to present a balanced view of the available scientific information of a dietary supplement." A citation to an article alone could not meet these requirements.

L. Use of Disease or Diseased (§ 101.93(g)(2)(iv)(D))

(67.) Many comments agreed with proposed § 101.93(g)(2)(iv)(D), stating that the terms "disease" or "diseased" should classify a statement as a disease claim. Several comments urged that a statement referring in a general way to the concept of "health promotion and disease prevention" not cause the statement to be considered a disease claim, as long as no specific disease was mentioned. One comment asked that the agency permit general discussions of the concept of disease prevention, citing the following example from the U.S. Public Health Service Healthy People 2000 initiative: "Better dietary and exercise patterns can contribute significantly to reducing conditions like heart disease, stroke, diabetes, and cancer, and could prevent 300,000 deaths."

FDA agrees that general statements about health promotion and disease prevention may be acceptable, as long as the

statements do not imply that a specific product can diagnose, mitigate, cure, treat or prevent disease. Accordingly, FDA has revised § 101.93(g)(2)(iv)(D) to permit general statements about disease prevention that do not refer explicitly or implicitly to a specific disease or class of diseases or to the specific product or ingredient. For example, the statement "a good diet promotes good health and prevents the onset of disease" would not be considered a disease claim. On the other hand, the claim "Promotes good health and prevents the onset of disease" would refer implicitly to the product and would constitute a disease prevention claim. FDA also believes that the particular statement offered by one of the commenters would constitute a disease claim. The example cites four specific diseases. If that statement were included in the labeling for a dietary supplement, a consumer would reasonably assume that the statement applies to the product and that taking that dietary supplement contributes to preventing the diseases listed. If, however, the statement said "better dietary and exercise patterns can contribute to disease prevention and better health," FDA would not consider it a disease claim.

M. Pictures, Vignettes, and Symbols (§ 101.93(g)(2)(iv)(E))

(68.) Many comments agreed that certain pictures, vignettes, and symbols can explicitly or implicitly convey that the product has an effect on disease. A few comments agreed that a diseased organ should be considered a disease claim. They argued, however,

that a picture of a healthy heart, healthy artery, or other healthy organ should be permitted because such pictures do not in and of themselves depict a disease. A few comments stated that a healthy electrocardiogram (EKG) tracing should not be considered a disease claim. One comment requested that the agency clarify whether a picture of an organ is permitted if the claims are appropriate and within the scope of permitted structure/function claims. The comment offered as an example a statement that a product maintains cardiovascular health accompanied by a picture of a heart and circulatory system.

FDA agrees that in most cases, a picture of a healthy organ would not be considered a disease claim, if, in the context of the labeling as a whole, it did not imply treatment or prevention of disease. As described in response to comment 51 of section II.I of this document, however, there may be symbols for organs, like the heart symbol, that have become so widely recognized as symbols for disease treatment or prevention, their use in labeling would constitute an implied disease claim. FDA also believes that a picture of a healthy EKG tracing is an implied disease claim. Because most consumers cannot distinguish a healthy EKG tracing from an unhealthy one, both types may be viewed as references to diagnosis or treatment of unhealthy heart conditions.

N. Membership in Product Class (§ 101.93(g)(2)(v))

Some product class names are so strongly associated with use to treat or prevent a specific disease or class of diseases that claiming membership in the product class implies disease treatment or prevention. Under proposed § 101.93(g)(2)(v), a statement would have been 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. The preamble provided the following examples of class names that would imply disease treatment or prevention: Claims that the product was an "antibiotic," a "laxative," an "analgesic," an "antiviral," a "diuretic," an "antimicrobial," an "antiseptic," an "antidepressant," or a "vaccine." These examples were not intended to constitute an exclusive list of product class names that convey disease claims. Under the proposed rule, 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 would not have constituted a disease claim under this criterion. The preamble provided as examples of acceptable structure/function claims: Claims that the product was an "energizer," a "rejuvenative," a "revitalizer," or an "adaptogen." In light of the agency's decision that claims for

relief of "occasional constipation" should not be considered disease claims, the term "laxative" will not be considered a disease claim under the final rule, as long as the remainder of the labeling makes clear that the product is not intended to treat chronic constipation.

(62.) Most of the comments on proposed § 101.93(g)(2)(v) were generally supportive, but some wanted to ensure that the provision would be applied in specific ways. One comment urged that "appetite suppressant" be treated as a disease claim, while another comment urged that "tonic" be treated as a structure/function claim.

FDA does not agree that "appetite suppressant" should be considered a disease claim. As discussed elsewhere in this document, although obesity is a disease, overweight is not. An appetite suppressant may be intended for ordinary weight loss, rather than as a treatment for obesity. Therefore, "appetite suppressant" would only be considered a disease claim in a context where it implies use for obesity. FDA agrees that "tonic" is not a disease claim. "Tonic" is commonly understood as a general term for anything that refreshes, and, by itself, would not be considered to constitute a disease claim.

(70.) Some comments stated that various class names should be allowed when they describe the mechanism by which a supplement has its effect, or when they are present in a product and it is

truthful and not misleading to name them. One comment offered as examples of class names that might be used to describe a product's mechanism of action: A statement that a product that is soothing to the stomach achieves its effects as a result of its "carminative (antispasmodic) properties" or as a result of its "anti-inflammatory effect on the gastrointestinal tract." This comment stated that it is not membership in a given class of compounds that should make a product a drug, but rather the intended use of the product. One comment asked whether this criterion precludes a statement that daily consumption of vitamins and minerals may prevent the onset of disease or other physical ailments.

Nothing in this provision would preclude a manufacturer from truthfully declaring the ingredients contained in a product. In fact, FDA regulations require the ingredients in a dietary supplement to be listed on its label. (See § 101.4(a)(1) and (g) (21 CFR 101.4(a)(1) and (g)), and § 101.36). The rationale for § 101.93(g)(2)(v) is that certain product class names (not particular ingredients) are so strongly associated with use to diagnose, treat, mitigate, cure, or prevent disease that claiming membership in the class would constitute a disease claim. FDA does not believe that claiming membership in a product class is necessary in order to provide an accurate list of the ingredients present in a product.

FDA agrees that dietary supplements may carry statements that characterize "the documented mechanism of action by which a nutrient or dietary ingredient acts to maintain \* \* \* structure or function," but only to the extent that such a statement does "not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases" (section 403(r)(6) of the act). In the examples provided in the comment, FDA is unaware of evidence establishing that the claims actually describe "documented" mechanisms by which the products "maintain" a calm stomach. Nevertheless, assuming that these statements met the other requirements of section 403(r)(6)(A) of the act, FDA would not consider the term "antispasmodic" to constitute a disease claim because the agency does not believe that it is closely associated with treatment or prevention of gastrointestinal disease. The term "anti-inflammatory" is, however, strongly associated with treatment of certain serious gastrointestinal diseases, and would constitute a disease claim.

FDA agrees with the statement that it is not membership in a given class of compounds that makes a product a drug, but rather the intended use of the product. This criterion sets forth FDA's conclusion that claiming membership in certain product classes that are strongly associated with use to treat or prevent disease is evidence that the product is intended to treat or prevent disease.

Although this provision does not itself treat as a disease claim a statement by a vitamin manufacturer that the product prevents the onset of a disease, such a statement would be considered a disease claim under § 101.93(g)(2)(I), which covers statements that a product has an effect on a specific disease or class of diseases. In addition, a general statement that a product prevents the onset of disease would be considered a disease claim under § 101.93(g)(2)(iv)(D), as noted in the discussion of that provision. Claiming membership in the class of vitamins or minerals would not constitute a disease claim under this criterion.

(71.) A food manufacturers' trade association and an individual manufacturer opposed the provision, arguing that it goes beyond the intent of DSHEA and would prohibit the use of any term associated with a drug product.

FDA does not agree that this provision goes beyond the intent of DSHEA nor that it would prohibit the use of any term associated with a drug product. DSHEA precludes statements under section 403(r)(6) of the act from claiming to treat or prevent disease. This provision constitutes FDA's conclusion that some drug class names (but not all terms associated with drug products) are so strongly associated with disease prevention or treatment that claiming membership in the class constitutes a

claim that the product, like other members of the class, treats or prevents disease.

(72.) One pharmaceutical company argued that proposed § 101.93(g)(2)(v) would violate DSHEA, because DSHEA specifically defines as a dietary supplement an article that is approved as a new drug under section 505 of the act, if it was, prior to approval, marketed as a dietary supplement.

FDA agrees that the dietary supplement definition includes the provision cited by the comment (section 201(ff)(3)(A) of the act), but believes that the definition and § 101.93(g)(2)(v) are not inconsistent. Section 101.93(g)(2)(v) would treat as a disease claim a labeling statement that the supplement is a member of a product class when that class is so recognizable for its disease treatment or prevention use that the labeling statement would be understood as a disease claim for the supplement. The criterion would not treat inclusion of an ingredient in a dietary supplement as a disease claim merely because the ingredient had been approved under section 505 of the act nor would it preclude listing the ingredient in the Supplement Facts panel or ingredient list.

0. Substitute for Disease Therapy (§ 101.93(g)(2)(vi))

Under proposed § 101.93(g)(2)(vi), a statement would have been 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. FDA offered "Herbal Prozac" as an example of such a claim. A claim that did not identify a specific drug, drug action, or therapy (e.g., "use as part of your weight loss plan") would not constitute a disease claim under this criterion.

(73.) There was general support for the provision, particularly for considering terms that make a direct connection with an approved drug, like "Herbal Prozac" and "Herbal Phenfen," disease claims. Several organizations noted that associating dietary supplements with regulated drug products is deceptive and dangerous because it can signal to consumers that because the product is "herbal" it is safer. Several medical associations, however, objected to the interpretation that "use as part of your weight loss plan," is nonspecific and would be acceptable. They maintained that the term implies treatment of a disease, obesity. A comment from a manufacturer also strongly objected to the statement in the proposal that "Use as part of your weight loss plan" would be an acceptable structure/function claim. The comment contended that the legislative history of the act shows that Congress intended weight loss claims to be treated as disease claims. Finally, the comment argued that even if FDA decides to permit weight loss claims as structure/function claims, the legislative history of the act and case law require that FDA classify products containing "antinutrients" as drugs.

FDA agrees with these comments that obesity is a disease, and that obesity claims are not acceptable structure/function claims. Being overweight, i.e., being more than one's ideal weight but less than obese, however, is not a disease. FDA believes that it is commonly understood that "weight loss plans" relate to a broad range of overweight statuses. Therefore, weight loss plans are not so narrowly associated with disease treatment that a reference to use as part of a weight loss plan should be considered a disease claim.

FDA does not agree that either the legislative history of the act or the case law interpreting section 201(g) of the act or DSHEA require a determination that FDA classify as drugs products making weight loss claims. The legislative history of section 201(g)(1)(C) of the act shows that Congress added the structure/function definition of "drug" in part to capture obesity claims that were not covered by section 201(g)(1)(B) because obesity was not, at that time, considered a disease. FDA believes that the legislative history in fact supports FDA's view that weight loss claims are properly considered structure/function claims. Although obesity claims are now covered by section 201(g)(1)(B) of the act because obesity is now considered a disease, section 201(g)(1)(C) was added to cover conditions, like overweight, that are not considered diseases, but that affect the structure or function of the body.

Structure/function claims under section 403(r)(6) of the act are closely related to structure/function claims under section 201(g)(1)(C) of the act and therefore should encompass weight loss claims.

FDA also does not agree that cases cited by the comment compel the conclusion that weight loss products must be regulated as drugs. In Nutrilab v. Schweiker, 713 F.2d 335 (7th Cir. 1983), American Health Products Co. v. Hayes, 574 F. Supp. 1498 (S.D.N.Y. 1982), aff'd, 744 F.2d 912 (2d Cir. 1984), and United States of America v. Undetermined Quantities Of "CAL-BAN 3000", 776 F. Supp. 249 (E.D.N.C. 1991), the courts held that certain weight loss products were drugs under section 201(g)(1)(C) of the act because they were labeled to affect the structure or function of the body, and did not qualify for the "food" exception to section 201(g)(1)(C). At the time these cases were decided, the only issue was whether these products were "foods" or "drugs." Since then, however, DSHEA created a new statutory category of products, dietary supplements. Section 403(r)(6) of the act, which was added by DSHEA, permits structure/function claims to be made for dietary supplements without subjecting them to regulation as drugs, even if they could not qualify for the "food" exception in section 201(g)(1)(C) of the act. Therefore, these cases do not establish that dietary supplements making weight loss claims must be regulated as drugs. To the contrary,

because the products were held to be drugs under section 201(g)(1)(C) of the act rather than section 201(g)(1)(B), these cases support treatment of weight loss claims for dietary supplements as structure/function claims authorized under section 403(r)(6) of the act.

Finally, FDA does not agree that, under United States v. Ten Cartons, More or Less, of an Article \* \* \* Ener-B Vitamin B-12, 72 F.3d 285 (2d Cir. 1995), dietary supplements making weight loss claims must necessarily be regulated as drugs. The court in Ener-B held that a dietary supplement that makes a structure/function claim may nevertheless be regulated as a drug, under certain circumstances. In that case, the court found that FDA could regulate a product as a drug, based on its method of intake (nasal administration). Nothing in that case suggests that FDA must regulate dietary supplements making weight loss claims as drugs.

(74.) Several comments reiterated that general statements about the nature of a product or its mechanism of action should not be disease claims, or should be structure/function claims as long as they are truthful and not misleading. One comment objected to the provision as duplicative of proposed § 101.93(g)(2)(v). Another comment sought to delete the provision, arguing that dietary supplement manufacturers have the

right to communicate to consumers that their products have fewer side effects than drugs.

FDA does not believe that this provision precludes general statements about the function or mechanism of action of a dietary supplement. It is not necessary to claim that the product is a substitute for a drug or therapy to describe its function or its mechanism of action. Nor is § 101.93(g)(2)(vi) duplicative of § 101.93(g)(2)(v). Claiming that a product is a substitute for a specific drug or therapy, e.g., "Herbal Prozac," is a different means of communicating that a dietary supplement is intended to treat a disease than claiming that the product belongs to a class of drugs associated with treatment or prevention of that disease, e.g., "antidepressant."

FDA does not agree that section 403(r)(6) of the act permits a dietary supplement manufacturer to claim that its product has fewer side effects than a drug, if the drug is intended to treat or prevent disease, because the clear implication is that the dietary supplement is intended for treatment or prevention of the same disease. If, however, the drug is not intended to treat or prevent disease, a dietary supplement manufacturer is free to make truthful, non-misleading comparisons between the drug and the dietary supplement.

P. Augmentation of Therapy or Drug for Disease

(§ 101.93(g)(2)(vii))

Under proposed § 101.93(g)(2)(vii), a statement would have been considered a disease claim if it explicitly or implicitly claimed that the product augmented a particular therapy or drug action. The preamble offered the following example of a disease claim under this criterion: "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 would not constitute a disease claim under this criterion. The preamble gave the following example of an acceptable structure/function claim: "use as a part of your weight loss plan."

(75.) Several comments supported this provision. A few comments requested that FDA withdraw the provision, arguing that dietary supplements are often useful in providing nutritional support to complement drug therapy or medical treatment and that the agency should encourage such information to be communicated to consumers. One comment stated that as long as the statement makes it clear that the product is being recommended for its nutritional impact on structure or function "as part of the therapy and not as the therapy itself," FDA should permit the statement. According to the comment, "use as part of your diet when taking insulin to help maintain a healthy blood sugar level" should be acceptable because the product is being recommended for its nutritional impact on structure or function as part of the

therapy and not as the therapy itself. Another comment asked whether removing the words "when taking insulin" from the statement would make it an acceptable structure/function claim.

The agency agrees that dietary supplements may be useful in providing nutritional support. Associating such a statement with an express or implied claim that the dietary supplement augments a therapy or drug action, however, implies that the dietary supplement has a role in treating or preventing the disease for which the drug or other therapy is used.

The agency does not agree that the proposed claim involving insulin is an acceptable structure/function claim. Persons who take insulin have a disease, namely, diabetes. By referring to the use of the dietary supplement in conjunction with and for the same purpose ("to maintain a healthy blood sugar level") as a drug (insulin), which is used to for a disease (diabetes), the statement implies that the dietary supplement will help treat diabetes.

A general statement that a dietary supplement provides nutritional support would be an acceptable structure/function claim, provided that the statement does not suggest that the supplement is intended to augment or have the same purpose as a specific drug, drug action, or therapy for a disease. In the example, if the statement were changed to "use as part of your diet to help maintain a healthy blood sugar level," the claim

would be considered acceptable. Deleting the reference to the drug, insulin, would remove the implication that the dietary supplement is used to augment the insulin to treat, mitigate, prevent, or cure diabetes.

On its own initiative, FDA is modifying § 101.93(g)(2)(vii) to limit its applicability to claims for augmentation of drugs or therapies that are intended to diagnose, mitigate, treat, cure, or prevent disease.

(76.) Another comment noted that the agency did not address the use of synonyms for "augment," such as "strengthen," "reduce," "improve," "modify," "inhibit," "protect," or "defend."

Use of these terms may be appropriate in some contexts, i.e., when the statements do not suggest disease prevention or treatment use. If, however, the use of these terms implies that the dietary supplement augments a particular therapy or drug action or otherwise suggests an effect on disease, the agency will consider the statement a disease claim.

(77.) A trade association maintained that under the proposal, bread, crackers, and other baked goods used in conjunction with prescription drugs and/or other therapy would not be considered a food, but a drug, under certain circumstances.

Section 101.93 is intended to provide regulatory criteria for statements made for dietary supplements. Under section 201(ff)(2)(B) of the act, a dietary supplement does not include a

product represented for use as a conventional food or as a sole item of a meal or the diet. If statements made for breads, crackers, and other baked goods characterize the relationship between a substance in the food and a disease or health-related condition, they must comply with the health claims provisions for foods under section 403(r)(1)(B) and (r)(3) through (r)(4) of the act.

Q. Role in Body's Response to Disease or Disease Vector

(§ 101.93(g)(2)(viii))

Under proposed § 101.93(g)(2)(viii), a statement would have been 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. The preamble to the proposal defined a vector of disease as 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. The preamble offered as examples of disease claims under this criterion claims that a product "supports the body's antiviral capabilities" or "supports the body's ability to resist infection." A more general reference to an effect on a body system that did not imply prevention or treatment of a disease state would not have constituted a disease claim under this criterion. FDA provided as an example of an acceptable structure/function claim under this criterion "supports the immune system."

(78.) Two comments from health associations supported this provision. One comment from a manufacturer argued that it should be deleted because a number of nutrients and dietary supplements "have a role in the body's response to disease." One comment argued that the body has natural defenses to disease, that these are normal functions of the body, and that therefore, statements such as "enhances disease resistance" should be allowable as structure/function claims. Comments from a consumer organization and a member of the President's Commission on Dietary Supplement Labels asserted that the provision made too many claims allowable. These comments stated that as long as a claim includes a disease-fighting function of the body, e.g., "supports the immune system," it should be considered a disease claim, regardless of other functions that might be involved.

FDA agrees that nutrients and dietary supplements may play a role in the body's response to disease. This does not mean, however, that disease prevention claims are acceptable structure/function claims. The act requires dietary supplement manufacturers who wish to make disease prevention claims to do so by obtaining authorization for a health claim or by obtaining new drug approval. Although FDA agrees that claims that a product fights disease, or enhances disease-fighting functions of the body, are disease claims, FDA does not agree that claims such as

"supports the immune system" are specific enough to imply prevention of disease.

(79.) Several comments argued that there was no significant difference between "supports the immune system" (identified as a structure/function claim in the proposal) and "supports the body's antiviral capabilities" (identified as a disease claim in the proposal). One view was that both should be considered structure/function claims. Conversely, other comments contended that "supports the immune system" is a disease claim, because it could be interpreted as a claim for treatment or prevention of human immunodeficiency virus (HIV) disease. Another comment recommended that "supports the body's antiviral capabilities" be allowable as a structure/function claim, stating that the broader "supports the immune system" statement was vague and useless to consumers because the immune system has many functions.

The distinction between the two claims is one of specificity. An intact immune system has several functions. In addition to their role in the defense against pathogens, certain components of the immune system, namely white blood cells, have other important functions. For example, white blood cells play an essential role in the phagocytosis and disposal of aging red blood cells or otherwise damaged cells. A statement of support for the immune system, by itself, conveys no specific reference to disease treatment or prevention. The claim that vitamin A is

necessary to maintaining a healthy immune response does not imply that a specific disease or class of diseases will be prevented. In contrast, a claim that a product "supports the body's antiviral capabilities" represents a claim of treatment or prevention of a specific class of diseases, those caused by viruses (e.g., colds, hepatitis, or HIV infection).

R. Treatment/Prevention of Adverse Events (§ 101.93(g)(2)(ix))

Under proposed § 101.93(g)(2)(ix), a statement would have been considered a disease claim if it explicitly or implicitly claimed to treat, prevent, or mitigate adverse events associated with a therapy for a disease (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 have constituted a disease claim under this criterion.

(80.) Comments from two large health organizations supported this provision, while two large business organizations and several other comments criticized it. Those opposing the provision argued that the proposal incorrectly categorized adverse reactions as diseases. Opposing comments also contended that dietary supplements may be useful as an adjunct to therapy by counterbalancing the effects of a drug in depleting a nutrient

or interfering with the metabolism of a nutrient, and that this should be considered a structure/function role.

FDA believes that some of these comments may have misconstrued the provision. The criterion is not intended to capture every adverse event claim, but only claims about adverse events that satisfy the definition of disease. In the proposed rule, this limitation was conveyed by the phrase "and manifested by a characteristic set of signs or symptoms." Because the final rule uses a different definition of disease, § 101.93(g)(2)(ix) has been revised to state that claims about adverse events are disease claims only "if the adverse events constitute diseases." FDA believes that a claim that a product is useful because it counterbalances the effects of a drug in depleting a nutrient or interfering with the metabolism of a nutrient would be acceptable as a structure/function statement. Such a claim would not suggest treatment of an adverse reaction that meets the definition of disease. However, as discussed above, if the claim expressly or impliedly suggests that the supplement is intended to augment a specific drug, drug action, or therapy for a disease, or serve the same purpose as a specific drug or therapy for a disease, then the statement may be considered a disease claim.

(81.) A dietary supplement manufacturer requested that FDA clarify why a statement that refers to a drug but not a disease,

such as "helps individuals using antibiotics to maintain normal intestinal flora" is a disease claim, but a general statement, such as "helps maintain intestinal flora" is a permissible structure/function claim.

Although the statement "helps individuals using antibiotics to maintain normal intestinal flora" does not explicitly refer to a disease, there is an implicit claim that use of the dietary supplement while taking antibiotics will prevent or mitigate a disease. Persons using certain antibiotics are at risk of developing overgrowth in the gut of a pathogenic organism because along with fighting the target organisms in the body the antibiotic can suppress normal intestinal flora that are used to prevent infection in the intestinal tract. A firm that markets its product to address this concern, with claims that the product can be used to maintain normal intestinal flora while taking antibiotics, is making an implied disease prevention claim. Conversely, the statement "helps maintain intestinal flora" alone, without any reference to a disease, drug, drug action, or therapy, does not imply an effect on disease and would be considered a structure/function claim about general health maintenance.

S. Otherwise Affects Disease (§ 101.93(g)(2)(x))

Under proposed § 101.93(g)(2)(x), a statement would have been considered a disease claim if it suggested an effect on a

disease or class of diseases in a manner other than those specifically enumerated in the first nine criteria.

(82.) A food manufacturers' trade association commented that this provision is of no regulatory importance, whereas a dietary supplement trade association and several other comments considered it an over-reaching "catch-all" provision that would allow FDA to treat any claim as a disease claim. These comments provided examples of a number of claims that they believed would be disease claims under this provision, e.g. "provides nutritional support for women during premenstruation by promoting proper fluid balances and breast health," and "ginger supports the cardiovascular system by inhibiting leukotriene and thromboxane synthesis, substances associated with platelet aggregation."

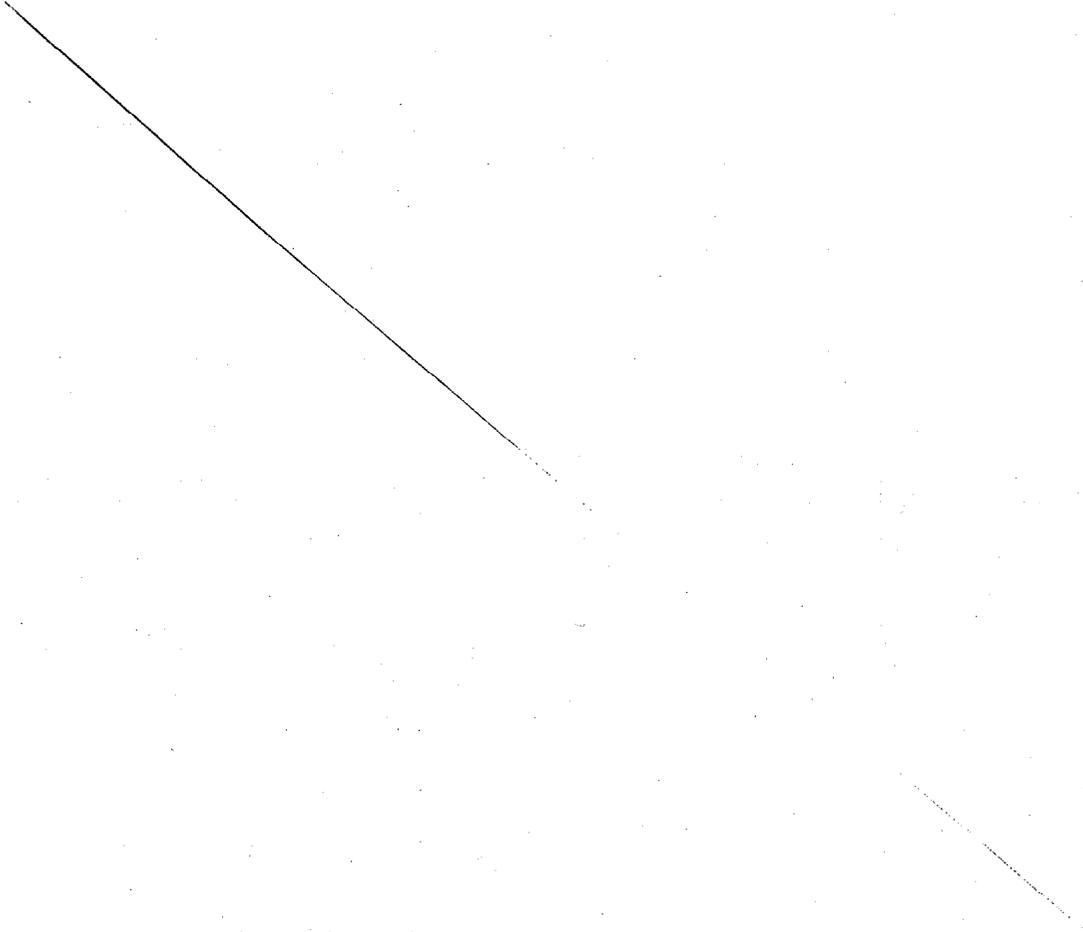
FDA believes that this provision is necessary to allow for implied disease claims that may not fit into the nine enumerated criteria. The nine criteria are examples, and not an exhaustive list, of types of claims that the agency believes would constitute disease claims, based on past experience. Rather than attempting to evaluate or categorize statements that have not yet been presented to FDA, § 101.93(g)(2)(x) recognizes the possibility that other types of statements may also imply disease treatment or prevention. FDA does not believe that the provision will cause the agency to classify any structure/function

statement as a disease claim. To regulate a statement as a disease claim under this provision, the agency would have to show that the statement implied an effect on disease. The two examples quoted in the comments do not appear to the agency to constitute disease claims.

T. Specific Claims Not Mentioned in the Proposed Rule

(83.) One comment contended that a dietary supplement called "pain free" or "pain product," that is labeled "to support and maintain joints," should not be regulated as an internal analgesic drug product under the OTC drug review because it is intended to maintain or support "normal well-being and pain levels." According to this comment, however, products sold as "pain relief" or "otherwise indicated to relieve temporary occurrences of arthritis pain" could be regulated as drug products under the OTC review, because the tentative final monograph for internal analgesics requires that such products be labeled for the "temporary relief of minor aches and pains" (53 FR 46204). At the same time, this comment argued that pain, in and of itself, is not a disease and therefore that pain claims should not be regulated as disease claims unless accompanied by an explicit reference to a specific disease.

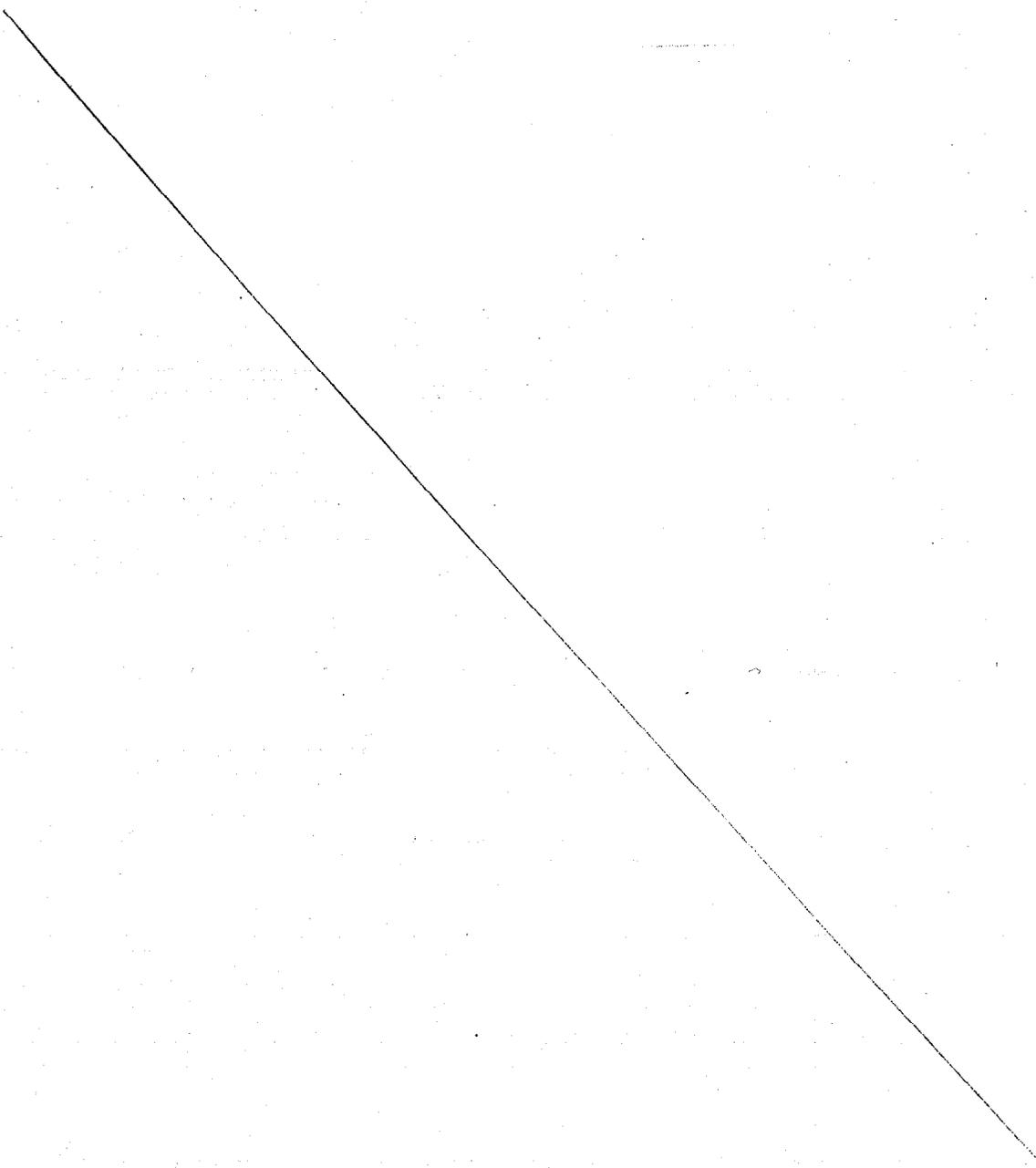
FDA agrees in part and disagrees in part with this comment. FDA agrees that some minor pain relief claims may be appropriate structure/function claims for dietary supplements. A claim that a product is intended to treat minor pain, without reference to any other conditions, symptoms, or parts of the body that would imply disease treatment or prevention, would be an appropriate structure/function claim, because minor pain, by itself, can be caused by a variety of conditions, not all of them disease-related.



FDA does not agree, however, that general well-being or health maintenance claims would encompass such pain claims. Pain is not a normal state, nor are there "normal pain levels." The claim is thus clearly one of pain treatment or prevention. FDA also does not agree that section 403(r)(6) of the act authorizes a product whose name promises freedom from or relief of pain ("pain-free" or "pain product") and whose labeling includes claims related to maintenance or support of joints. While the latter claims alone are appropriate structure/function statements, in conjunction with a name that includes the term "pain," the product is clearly making a claim related to treatment or prevention of joint pain. As explained elsewhere in this document, joint pain is a characteristic symptom of arthritis, and joint pain claims are therefore disease claims. Acceptable structure/function claims could be made, however, for pain associated with nondisease states, e.g., muscle pain following exercise.

(84.) One comment listed several claims and sought concurrence that they were acceptable structure/function claims: "Boosts stamina, helps increase muscle size, and helps enhance muscle tone"; "deters bacteria from adhering to the wall of the

bladder and urinary tract"; and "dietary support during the cold and flu season." Another comment asked whether "promotes general well-being during the cold and flu season" is a permissible claim.



FDA agrees that "boosts stamina, helps increase muscle size, and helps enhance muscle tone" are acceptable structure/function claims, because they do not refer to any disease. However, the agency notes that a claim to increase muscle size implies an effect that may subject the product regulation as an anabolic steroid under the Controlled Substances Act (see 21 U.S.C. 802(41)). "Deters bacteria from adhering to the wall of the bladder and urinary tract" is not an acceptable structure/function claim because it implies prevention of bacterial infections of the bladder and urinary tract. The claims "dietary support during the cold and flu season" and "promotes general well-being during the cold and flu season" are disease claims because they imply that the product will prevent colds and flu or will mitigate the symptoms of those diseases.

(85.) One comment asked that the FDA clarify that dietary supplements can bear "smoking-alternative" claims if they avoid references to nicotine, nicotine withdrawal symptoms, and tobacco-related disease. The comment sought concurrence that the following types of claims were permitted: "Smoking alternative," "temporarily reduces your desire to smoke," "to be used as a dietary adjunct in conjunction with your smoking cessation plan;" and "mimics the oral sensations of cigarette smoke."

FDA agrees that certain smoking alternative claims may be acceptable structure/function claims, if they do not imply

treatment of nicotine addiction, relief of nicotine withdrawal symptoms, or prevention or mitigation of tobacco-related illnesses. "Smoking alternative," "temporarily reduces your desire to smoke" and "mimics the oral sensations of cigarette smoke" may be acceptable (for products that otherwise meet the definition of a dietary supplement), if the context does not imply treatment of nicotine addiction, e.g., by suggesting that the product can be used in smoking cessation, or prevention or mitigation of tobacco-related diseases. For example, such claims would not be disease claims if the context made clear that they were for short-term use in situations where smoke is prohibited or socially unacceptable. "To be used as a dietary adjunct in conjunction with your smoking cessation plan," however, is a disease claim because it is a claim that the product aids in smoking cessation, thereby implying that the product is useful in treating nicotine addiction. As noted earlier, a claim that the product is useful in counterbalancing the effects of a drug in depleting a nutrient or interfering with the metabolism of a nutrient would be acceptable as a structure/function statement.

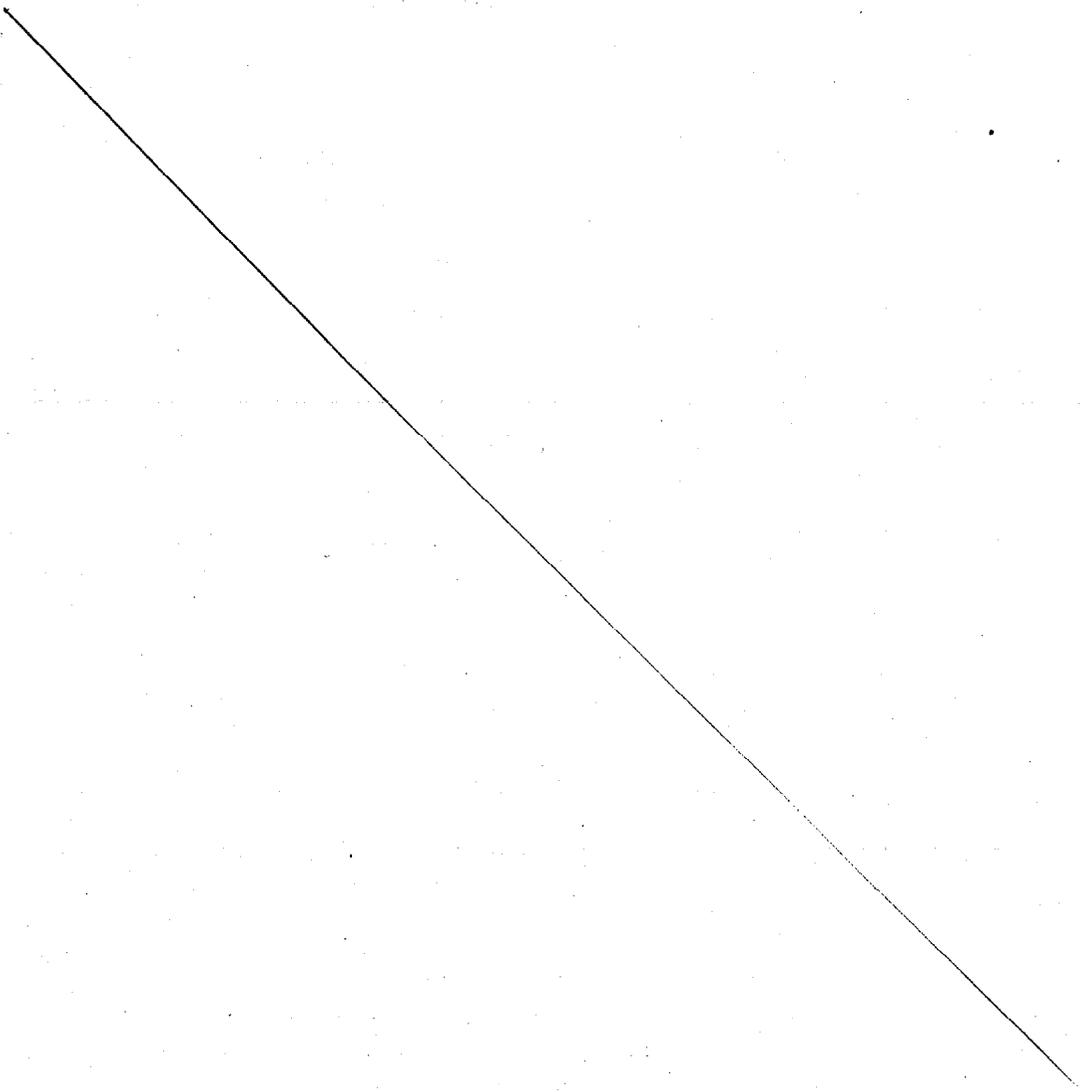
(86.) One comment offered as acceptable structure/function claims a long list of OTC drug claims provided for in the monographs for antacids, antiflatulents (antigas), antiemetics, nighttime sleep-aids, stimulants (alertness aids), daytime sedatives, aphrodisiacs, products for relief of symptoms of

benign prostatic hypertrophy, anticholinergics (products that, at low doses, depress salivary and bronchial secretions), and products for certain uses. Two comments sought clarification that inclusion of a claim in an OTC monograph does not preclude its use as a structure/function claim.

FDA agrees that some of the claims on the comment's list of OTC drug claims may be acceptable structure/function claims, but believes that others on the list are disease claims. Of the claims listed in the comment from the "Antacids" monograph, "relief of sour stomach" and "upset stomach" are acceptable structure/function claims, because they refer to a nonspecific group of conditions that have a variety of causes, many of which are not disease-related. Thus, they are not characteristic of a specific disease or class of diseases. Although "relief of heartburn" and "relief of acid indigestion" without further qualification are not appropriate structure/function claims, the agency has concluded that "occasional heartburn" and "occasional acid ingestion" can also be considered nonspecific symptoms, arising as they do in overindulgence and other sporadic situations. These claims could be appropriate structure/function claims. In contrast, "recurrent" or "persistent" heartburn and acid indigestion can be hallmarks of significant illness, and are therefore disease claims.

All of the claims listed in the comment from the "Antiflatulents" (antigas) monograph are acceptable structure/function claims, because the symptoms in the claims are not sufficiently characteristic of specific diseases:

"Alleviates the symptoms referred to as gas," "alleviates bloating," "alleviates pressure," "alleviates fullness," and "alleviates stuffed feeling." The claim listed in the comment



from the "Antiemetics" monograph, "for the prevention and treatment of the nausea, vomiting, or dizziness associated with motion," is also a permitted structure/function claim.

Of the claims listed in the comment from the "Nighttime" sleep-aids monograph, "for the relief of occasional sleeplessness" is an acceptable structure/function claim, because occasional sleeplessness is not a characteristic symptom of a disease. "Helps you fall asleep if you have difficulty falling asleep," and "helps to reduce difficulty falling asleep" are disease claims because, unless the context makes clear that the product is only for occasional sleeplessness, they imply treatment of insomnia, a disease. The claim listed in the comment from the "Stimulants" (alertness aids) monograph, "helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness," is an acceptable structure/function claim because occasional fatigue and drowsiness are not characteristic symptoms of a specific disease or class of diseases. FDA notes, however, that chronic fatigue or daytime drowsiness can be symptoms of chronic fatigue syndrome and narcolepsy, respectively. Products labeled "to help restore mental alertness or wakefulness when experiencing fatigue or drowsiness" should not imply treatment of either of these diseases.

Of the claims listed in the comment from the "Daytime" sedatives monograph, almost all are acceptable structure/function

claims. "Occasional simple nervous tension," "nervousness due to common every day overwork and fatigue," "a relaxed feeling," "calming down and relaxing," "gently soothe away the tension," "calmative," "resolving that irritability that ruins your day," "helps you relax," "restlessness," "nervous irritability," and "when you're under occasional stress, helps you work relaxed" are all acceptable structure/function claims, because all suggest occasional rather than long-term or chronic mood changes.

Although occasional or acute symptoms can be characteristic of diseases in other settings, none of the occasional symptoms referred to here is characteristic of a specific disease.

"Nervous tension headache" is a disease claim because tension headache meets the definition of a disease.

Of the claims listed in the comment from the "Aphrodisiacs" monograph, "arouses or increases sexual desire and improves sexual performance" is an acceptable structure/function claim because it does not imply treatment of a disease. "Helps restore sexual vigor, potency, and performance," "improves performance, staying power, and sexual potency," and "builds virility and sexual potency" are disease claims because they use the term "potency," which implies treatment of impotence, a disease. If, however, these claims made clear that they were intended solely for decreased sexual function associated with aging, they could be acceptable structure/function claims. The claim from the

"Products for relief of symptoms of benign prostatic hypertrophy" monograph ("To relieve the symptoms of benign prostatic hypertrophy, e.g., urinary urgency and frequency, excessive urinating at night, and delayed urination") is a disease claim, because benign prostatic hypertrophy meets the definition of a disease.

The claim listed in the comment from the "Anticholinergics" monograph is a disease claim. "Relieve excessive secretions of the nose and eyes" refers to the characteristic signs or symptoms of hay fever. Of the claims listed in the comment from the "Products for certain uses" monograph, "digestive aid," "stool softener," "weight control," and "menstrual" are, by themselves, acceptable structure/function claims if the labeling does not otherwise imply treatment or prevention of a disease. None mentions a characteristic symptom of a disease. "Laxative" is a not a disease claim, if the labeling makes clear that the intended use is for treatment of occasional rather than chronic constipation. "Nasal decongestant," "expectorant," and "bronchodilator" are disease claims. "Nasal decongestant" is a treatment for a characteristic symptom of colds, flu, and hay fever. "Expectorant" is a treatment for a characteristic symptom of colds, flu, and bronchitis. "Bronchodilator" is a treatment for bronchospasm, a characteristic symptom of asthma.

The claim from the "Products for the treatment and/or prevention of nocturnal leg muscle cramps" monograph ("treatment and/or prevention of nocturnal leg muscle cramps, i.e., a condition of localized pain in the lower extremities usually occurring in middle life and beyond with no regular pattern concerning time or severity") is an appropriate structure function claim. Nocturnal leg cramps do not meet the definition of disease.

As is clear from this response, FDA agrees that inclusion of a claim in an OTC monograph does not preclude its use as a structure/function claim. FDA notes, however, that in light of the statutory requirement that dietary supplements bear all information that is material in light of consequences that may result from use of the product or representations made about it, dietary supplements that contain or are labeled as containing ingredients covered by an OTC monograph and that are being sold for the claims covered by the monograph may be misbranded to the extent that they omit material information required under the monograph. For example, if the OTC monograph required a label statement that products containing a particular ingredient should not be used by persons taking a prescription monoamine oxidase

inhibitor, a dietary supplement containing that ingredient would be misbranded if its label did not include such statement.

U. Substantiation of Claims

(87.) Several comments requested that the final rule explicitly state that structure/function statements must be adequately substantiated and that FDA provide guidance on what constitutes adequate substantiation. One comment maintained that adequate substantiation is critical to ensuring that consumers receive truthful and accurate information about the benefits of dietary supplements. Another comment argued that this final rule should focus on adequate substantiation of claims rather than on delineating the boundaries between structure/function claims and disease claims. Other comments maintained that substantiation is not as effective in preventing consumer fraud as preapproval of the claims because consumers will be using the products long before the label claims are investigated.

FDA agrees that the statutory requirement to substantiate claims is important. FDA does not agree, however, that it is necessary to state in the regulatory text of the final rule that structure/function claims must be adequately substantiated. Section 101.93(a)(3) requires a firm notifying FDA of a claim under section 403(r)(6) of the act to certify that the firm has substantiation that the claim is truthful and not misleading. FDA also does not agree that substantiation is an appropriate

alternative to distinguishing structure/function claims from disease claims. The requirement that structure/function statements and other statements for dietary supplements under section 403(r)(6) of the act be adequately substantiated is distinct from the requirement that such statements not claim to diagnose, treat, mitigate, cure, or prevent disease. Both of these requirements are imposed by the statute and must be complied with.

(88.) Several comments offered advice on what types of evidence should constitute adequate substantiation. A consumer health organization suggested that health claims and structure/function claims for dietary supplements be based on the totality of the publicly available scientific evidence, including results from well-designed studies conducted in a manner consistent with generally recognized scientific principles and procedures. The comment added that consumers would be better served if standards for support applied to both health claims and structure/function claims. Another consumer health organization suggested that substantiation be based on "significant scientific agreement."

Many of the comments suggested that the agency adopt FTC standards for substantiation. A comment from FTC explained that FTC typically applies a substantiation standard known as "competent and reliable scientific evidence" to claims about the

safety and effectiveness of dietary supplements, after first looking at the overall context to determine what the claim is. The comment further stated that FTC's approach to substantiation is consistent with the guidance provided by the President's Commission on Dietary Supplement Labels, and, because FDA concurred with the Commission's guidance on substantiation, the comment suggested that FDA refer to the Commission guidance in the final rule.

As stated above, the agency does not believe that this final rule is the appropriate venue to address the substantiation requirement. FDA does, however, agree that claims under section 403(r)(6) of the act should be supported by adequate scientific evidence and may provide additional guidance regarding substantiation for 403(r)(6) statements at a future date.

The Commission report included guidance on what quantity and quality of evidence should be used to substantiate claims made under 403(r)(6) of the act. It also contained guidance on the content of the substantiation files for such statements, including the 30-day notification letter to FDA, identification of the product's ingredients, evidence to substantiate the statements, evidence to substantiate safety, assurances that good manufacturing practices were followed, and the qualifications of the person(s) who reviewed the data on safety and efficacy. In a notice published in the FEDERAL REGISTER (63 FR 23624 at 23633),

FDA stated that it agreed with the guidance of the Commission. FDA encourages manufacturers of dietary supplements making a 403(r)(6) of the act statement for a dietary supplement to follow this guidance.

(89.) A food manufacturer suggested that the agency require dietary supplement manufacturers making structure/function claims to disclose in labeling any and all scientific studies supporting the claim. In addition, the comment advocated requiring that these studies be performed using the marketed formulation. The comment also urged FDA to determine how contrary studies should be addressed.

DSHEA does not require dietary supplement labeling that carries a statement under section 403(r)(6) of the act to include in the labeling "any and all scientific studies supporting the claim." Section 403(r)(6)(B) of the act requires only that the "manufacturer have substantiation that such statement is truthful and not misleading." Contrary studies should be considered when deciding whether to make and how to word a 403(r)(6) of the act statement to ensure that any statements made are truthful and not misleading. Additionally, in response to a request for substantiation for the statement, the agency would expect manufacturers to provide a requester with contrary as well as supporting studies.

There is no specific statutory requirement that the studies substantiating the statement be performed using the actual marketed formulation. However, many ingredients and factors influencing the formulation can affect the safety and effectiveness of the dietary supplement. These variations from the marketed product should be considered before using a study to substantiate a statement made for a particular product.

#### V. Enforcement Issues

(90.) One comment said that the proposal shifts the burden of proof to manufacturers to show that their files match and support the claims made for their products.

The regulations issued by this final rule do not address or affect the burden of proof during enforcement actions. However, section 403(r)(6)(B) of the act clearly states that manufacturers must have substantiation to show that the statements that they make under section 403(r)(6) of the act are truthful and not misleading. This indicates that manufacturers must be prepared to demonstrate to the court that they have support for each claim.

(91.) One comment predicted widespread noncompliance with the rule because of its complexity and limited FDA resources.

FDA disagrees with the comment. FDA believes that most of the rule is straightforward, and the comments received on the proposed rule indicate that dietary supplement manufacturers

understood the provisions of the rule. Moreover, as noted in the Analysis of Impact in section VI.E of this document, most of the claims of which FDA has been notified are consistent with the final rule. Thus, based on what has been provided to FDA, most manufacturers would appear to be already in compliance with this final rule. If it becomes apparent that there are provisions that are being violated because of true confusion about their applicability, FDA will issue clarifying guidance. FDA agrees that its enforcement resources are limited, and is issuing this rule in part to avoid inefficient use of those resources on case-by-case enforcement. FDA believes that the dietary supplement industry will make good faith efforts to comply with this rule, once it becomes effective.

#### W. Other Comments

(92.) One comment said FDA should conduct an educational campaign to enhance public awareness of the differences between structure/function claims and disease claims and the meaning of individual claims.

FDA intends to conduct various outreach activities on dietary supplement matters.

(93.) One comment said FDA should amend the tentative final monograph on OTC laxatives to be consistent with the rule. The comment explained that the tentative final monograph should permit the words "help maintain regularity" on OTC labeling.

The agency disagrees with the comment. The fact that "helps maintain regularity" is an acceptable structure/function claim does not mean that it satisfies the requirements for inclusion in an OTC monograph, including the requirement of a finding of general recognition of safety and effectiveness.

(94.) Several comments addressed manufacturing or related issues. One comment said FDA should investigate effects of dissolution on product potency and efficacy, while other comments advocated using United States Pharmacopeia standards for all dietary supplements on matters pertaining to dissolution, disintegration, purity, and potency. One comment added that poor product quality would present a health threat to consumers and result in economic fraud.

Another comment said FDA should concentrate on standardization and quality control instead of regulating labeling statements, but offered no specific suggestions. Some comments, however, made specific recommendations. One comment said that product labels should contain lot numbers and expiration dates and that manufacturers should conduct stability tests to determine accurate expiration dates. Another comment said the public should be protected against poor manufacturing standards for herbal products. Other comments simply stated that there is substantial potential for public harm because there are: Multiple sources of dietary supplement ingredients; multiple

suppliers; a lack of regulatory production standards, or questions concerning product safety, efficacy, and manufacturing quality; vigorous product promotion; and a sizeable market. One comment simply asked for good manufacturing practice regulations for dietary supplements.

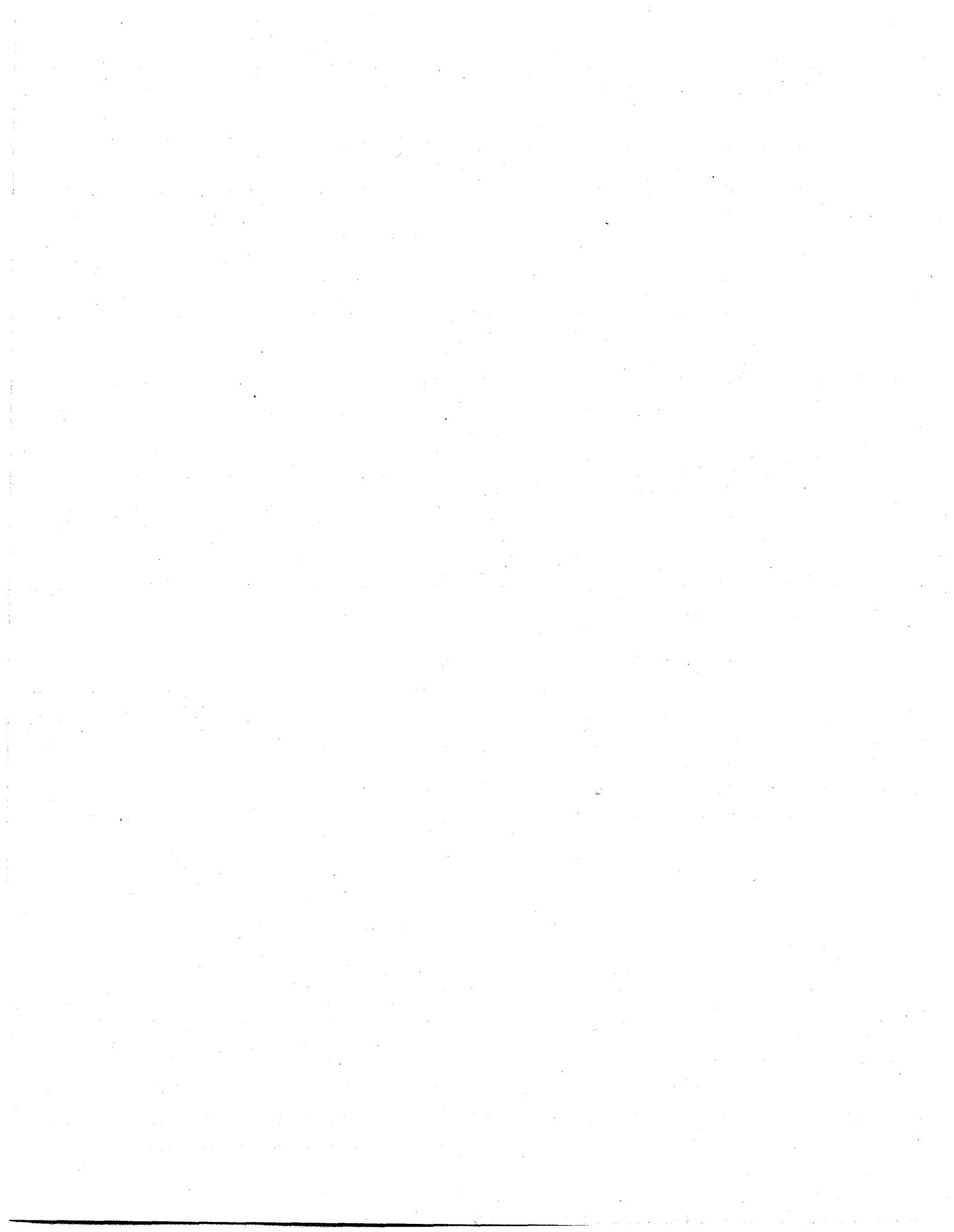
Manufacturing issues are outside the scope of this rule. FDA intends to issue a separate proposed rule on current good manufacturing practice (CGMP) for dietary supplements, and that proposed CGMP rule may address some of the issues raised by the comments.

### III. Legal Authority

#### A. Scope of Section 403(r)(6) of the Act

##### 1. Relationship Between Sections 403(r)(6) and 201(g)(1)(C) of the Act

(95.) Several comments stated that the proposal mistakenly suggests that there is only one type of structure/function claim that may be used for dietary supplements. Some of these comments said that if a structure/function claim does not trigger drug status for the product and is not a health claim, then such a claim may be made in labeling for a dietary supplement so long as it is truthful and not misleading. These comments asserted that such a claim is not subject to the notice, labeling, or disclaimer requirements in section 403(r)(6) of the act. As an example, the comments said the claim that "calcium helps build



strong bones" is not a health claim because it does not characterize a relationship between the substance and a disease, damage, or dysfunction of the body. The comments added that FDA recognized this in the final rule that it published in the FEDERAL REGISTER on September 23, 1997 (62 FR 49859, 49860, 49863, and 49864), when it stated in the preamble that claims that cranberry juice cocktail helps maintain urinary tract health or that calcium builds strong bones and teeth are not health claims because no disease is mentioned explicitly or implicitly. Some comments added that FDA cannot say that only those claims falling under section 406(r)(6) of the act are structure/function claims because such a result would be contrary to the act and would mean that the proposed rule must be withdrawn.

FDA agrees with these comments in part and disagrees in part. The agency agrees that statements such as "calcium helps build strong bones" are not health claims because they do not characterize the relationship between a substance and a disease or health-related condition. Rather, such statements are structure/function claims authorized by section 403(r)(6) of the act.

FDA does not agree with the comment's statement that dietary supplements may bear structure/function claims without complying with the notice, disclaimer, and other requirements of section 403(r)(6) of the act. Section 403(r)(6) of the act, by its

terms, applies to dietary supplements. The other possible source of authority to make structure/function claims on dietary supplements is section 201(g)(1)(C) of the act, which provides that "articles (other than food) intended to affect the structure or any function of the body of man or other animals" are drugs. Under this provision, foods may make claims to affect the structure or function of the body without being regulated as drugs. By its terms, however, section 201(g)(1)(C) of the act exempts a dietary supplement that bears a structure/function claim from drug regulation only if it is also a food. The last sentence of section 201(ff) of the act provides, "Except for purposes of section 201(g), a dietary supplement shall be deemed to be a food within the meaning of this Act." The clear import of this language is that dietary supplements are not foods under section 201(g) of the act and therefore cannot qualify for the "(other than food)" exception to the drug definition in section 201(g)(1)(C). As a result, dietary supplements that use structure/function claims may do so only under section 403(r)(6) of the act and are therefore subject to the disclaimer, notification, and other requirements in that section and in FDA's implementing regulation.

The agency acknowledges that it took a contrary position in the September 1997 final rule preamble referred to in the comment. In that preamble, FDA said that a dietary supplement

could bear a structure/function claim under the "(other than food)" exception to the definition of "drug" in section 201(g)(1)(C) of the act, provided that the claim was truthful, non-misleading, and derived from nutritive value (see 62 FR 49859 at 49860, 49863, and 49864). However, the agency has now reconsidered in light of the plain language of section 201(ff) of the act and is revoking its statements on this subject in the September 1997 preamble (i.e., the statements at 62 FR 49859 at 49860, 49863, and 49864 concerning structure/function claims for dietary supplements under section 201(g)(1)(C)). It should be noted, however, that the agency is not revoking its statements in that preamble concerning structure/function claims for conventional foods under section 201(g)(1)(C) of the act. As explained in the September 1997 preamble (62 FR 49859 at 49860), conventional foods may make structure/function claims under section 201(g)(1)(C) of the act as long as such claims are truthful, non-misleading, and derive from the nutritive value of the food.

For a limited transition period, FDA does not intend to take enforcement action against firms who have relied on the agency's September 1997 final rule preamble statements to make a structure/function claim for a dietary supplement under section 201(g)(1)(C) of the act. To allow a reasonable time for the necessary label changes, the transition period will last until

the applicable compliance date for the rest of the rule; i.e., small businesses will have 18 months from publication to comply, and other firms will have 12 months. As of the applicable compliance date, firms that have been making structure/function claims under section 201(g)(1)(C) of the act must either remove the claim or comply with the requirements of section 403(r)(6) of the act and § 101.93, including notifying FDA of the claim and relabeling to add the required disclaimer. New structure/function claims are not subject to this transition period; any firm that makes a structure/function claim in the labeling of a dietary supplement after the effective date of this rule must comply with section 403(r)(6) of the act and § 101.93.

(96.) One comment objected to a sentence in the introductory paragraph in the preamble to the proposed rule. The sentence stated that, before DSHEA, certain claims could have rendered a product a "drug" under the act. The comment argued that even before DSHEA, dietary supplements could make structure/function claims and not be considered drugs. The comment said that section 201(g)(1)(C) of the act expressly excluded food from the definition of drug and that dietary supplements fell within the "food" exception. The comment characterized DSHEA as limiting and restricting "what had been the unconditional right of dietary supplement marketers to make structure/function claims."

The agency agrees that before DSHEA, dietary supplements that were also foods could make structure/function claims under section 201(g)(1)(C) of the act without being considered drugs. However, the passage of DSHEA changed the regulatory framework for structure/function claims on dietary supplements by adding sections 201(ff) and 403(r)(6) to the act. As explained in the response to the preceding set of comments, section 201(ff) of the act provides that dietary supplements are not considered food for purposes of section 201(g). Therefore, dietary supplements may no longer make structure/function claims under the "food" exception to the drug definition in section 201(g)(1)(C) of the act. FDA therefore agrees with the comment that in one respect, DSHEA limited the ability of dietary supplement marketers to make structure/function claims.

The sentence in the introductory paragraph of the preamble to the proposed rule correctly stated that "certain claims"--structure/function claims for dietary supplements that were not also foods--could have rendered the product a drug before the passage of DSHEA (63 FR 23624). Post-DSHEA, however, dietary supplements may make structure/function claims under section 403(r)(6) of the act regardless of whether they are also foods. Thus, although in one way DSHEA did limit the ability of dietary supplement marketers to make structure/function claims, it also significantly expanded the opportunity to make structure/function

claims in another way by removing the limitation that dietary supplements must be foods to make structure/function claims. Under section 403(r)(6) of the act, claims may be made for nondisease effects of a dietary supplement on the structure or function of the body, regardless of whether those effects are nutritive, as long as the product is intended to supplement the diet as provided in section 201(ff)(1) of the act.

## 2. Structure/Function Claims for Conventional Foods

(97.) Several comments sought consistency in the treatment of conventional foods and dietary supplements with respect to structure/function claims and health claims. Some of these comments contended that this rule would permit dietary supplements to carry claims that would be health claims if made for a conventional food. One comment stated that differential treatment of foods and dietary supplements was inconsistent with the Commission's recommendations. This comment suggested that differential treatment would cause consumers to perceive dietary supplements as better sources for safeguarding health than conventional foods. One comment expressed the view that the rule should apply to claims for conventional foods as well as dietary supplements and requested FDA to clarify the rule's scope. Other comments said that any structure/function claims that may be made for dietary supplements may also be made for conventional foods. The comments explained that the history of the act shows that

claims that food affect the structure or function of the body do not result in the food being classified as a drug, citing the district court and appellate decisions in American Health Products Co. v. Hayes, 574 F. Supp. 1498, 1501 (S.D.N.Y. 1983), aff'd, 744 F.2d 912 (2d Cir. 1984). Another comment stated that established case law shows that an article may be a food if it is used primarily for taste, aroma, or nutritional value, but that nutritional value is not required in all instances. One comment further noted that FDA, when it implemented the labeling requirements for DSHEA (62 FR 49859, 49860, and 49861) said that it was committed to "as much parity between dietary supplements and conventional foods as is possible within the statute" and that FDA has recognized that a dietary supplement may lawfully be in conventional food form, but must be represented as a dietary supplement (citing 62 FR 49826 at 49837, September 23, 1997).

Given this background, the comments argued that FDA cannot take the position that a structure/function claim may be made for a conventional food only if the effect derives from the food's nutritional value. One comment added that the act does not distinguish foods based on their nutritional value and that DSHEA considers structure/function claims for all dietary ingredients to be "statements of nutritional support." The comment said FDA, therefore, should recognize that structure/function claims that can be made for dietary ingredients when those ingredients are in

dietary supplements can also be made when those ingredients are in conventional food, but added that the disclaimer statement and notification to FDA, as required by section 403(r)(6)(C) of the act, apply only to dietary supplements and not to conventional food. One comment said that requiring structure/function claims for conventional foods to be derived from the food's nutritional value would create a marketing disparity and put conventional foods at a competitive disadvantage.

This rule applies to claims for dietary supplements only. Its purpose is to implement section 403(r)(6) of the act, which applies to dietary supplements only. Therefore, a detailed discussion of the regulatory framework applicable to structure/function claims for conventional foods, which are made under section 201(g)(1)(C) of the act, is beyond the scope of the rule. FDA advises, however, that for consistency, the agency is likely to interpret the dividing line between structure/function claims and disease claims in a similar manner for conventional foods as for dietary supplements. The agency also notes that as discussed in the response to comment 1 in section II.A of this document, FDA reaffirms the statements about structure/function claims for conventional foods in the September 23, 1997 (62 FR 49859), final rule entitled "Food Labeling: Nutrient Content Claims, Health Claims, and Statements of Nutritional Support for Dietary Supplements." As explained in that rule (62 FR 49859 at

49860, 49861, and 49864), the fact that structure/function claims for conventional foods are limited to effects derived from nutritional value, while structure/function claims for dietary supplements are not, is a result of differences in the language of the exemption for foods in section 201(g)(1)(C) of the act, as interpreted by the courts (see Nutrilab, Inc. v. Schweiker, 713 F.2d 335, 338 (7th Cir. 1983)), and the language of section 403(r)(6) of the act.

(98.) One comment suggested revising the definition of "disease or health-related condition" in proposed § 101.14(a)(6) to include a reference to § 101.93, and also recommended revising the definition of "health claim" at § 101.14(a)(1) to be consistent with § 101.93. Currently, § 101.14(a)(1) reads as follows:

Health claim means any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication, including "third party" references, written statements (e.g., a brand name including a term such as "heart"), symbols (e.g., a heart symbol), or vignettes, characterizes the

relationship of any substance to a disease or health-related condition. Implied 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.

The comment would revise the definition to read as follows:

Health claim means any claim made on the label or in labeling of a food, including a dietary supplement, that expressly or by implication, including "third party" references, written statements (e.g., a brand name that includes or implies a disease, such as "Raynaudin"), symbols, or vignettes, characterizes the relationship of any substance to a

disease or health-related condition (e.g., disease-indicating electrocardiogram tracings, pictures of organs that suggest prevention or treatment of a disease state, the prescription symbol, or any reference to prescription use). Implied 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.

As stated in response to comment 51 of section II.I of this document, FDA does not believe that §§ 101.14(a)(1) and 101.93(g) are inconsistent. As a result of the special regime for dietary supplements under DSHEA, there may be some differences in the treatment of dietary supplements and conventional foods under § 101.14(a)(1).

### 3. Relationship Between Structure/Function Claims and Health Claims

(99.) One comment stated that the proposed rule "improperly distinguishes between other health-related claims and structure/function claims." Relying in part on the introduction to section 403(r)(6) of the act ("For purposes of paragraph (r)(1)(B) \* \* \*"), the comment asserted that structure/function claims are a subset of the claims authorized by section 403(r)(1)(B) of the act (health claims). Consequently, because claims under section 403(r)(1)(B) of the act may characterize the relationship of a nutrient to a disease, the comment stated that FDA cannot preclude structure/function claims from making any contextual references to diseases.

FDA disagrees with this comment. Structure/function claims are not a subset of health claims because, clearly, there are claims about the effect of a product on the structure or function of the body that are not also health claims. To be a health claim, a claim must refer to the relationship between a food substance and a disease or health-related condition. FDA interprets "health-related condition" to mean a state of health leading to disease. Claims such as "calcium builds strong bones" are not health claims because they do not refer explicitly or implicitly to any disease or health-related condition. Therefore, the comment is based on an invalid premise.

(100.) One comment requested that FDA revise § 101.93(f) to state that the requirements of section 403(r)(6) of the act, e.g., use of the disclaimer and substantiation, apply only to structure/function claims that fall within the definition of a "health claim" in § 101.14(a)(1) and (a)(5). According to this comment, the introduction to section 403(r)(6) of the act ("For purposes of paragraph (r)(1)(B) \* \* \*") establishes that structure/function claims that do not fall within the definition of health claims are not subject to section 403(r)(6), and may be made without complying with any of its requirements.

FDA does not agree and, in fact, believes that the opposite is true. As explained elsewhere in this document and in the proposed rule, structure/function claims that fall within the definition of health claims, or that otherwise constitute disease claims, do not fall within the scope of claims authorized under section 403(r)(6) of the act, but other structure/function claims do fall within the scope of section 403(r)(6) and are subject to its requirements. Adopting the interpretation advocated by the comment would bring about illogical results for dietary supplement labeling claims in two ways. First, structure/function claims that are also health claims would not be subject to the health claims prior authorization requirements, but instead could be made simply by meeting the requirements of section 403(r)(6) of the act and FDA's implementing regulations.

The language in section 403(r)(6) of the act excluding claims to affect disease from the coverage of that section demonstrates that Congress made a public health judgment that claims promoting dietary supplements for disease uses should continue to require premarket authorization. It would not make sense for Congress to exclude labeling claims pertaining to disease uses in one part of section 403(r)(6) of the act, while permitting such claims in another paragraph of the same section. Moreover, the interpretation advocated by the comment would lead to confusing and contradictory labeling. A dietary supplement that bears a health claim--a claim that, by definition, is a claim that a substance in the supplement in some way has an effect on a disease--would also have to bear a contradictory disclaimer that it is not intended to treat, mitigate, or prevent any disease. Second, structure/function claims that are not also health claims would not be authorized under section 403(r)(6) of the act at all. In fact, a structure/function claim on a dietary supplement would subject it to drug regulation because, as explained in the response to comment 1 in section II.A of this document, section 403(r)(6) of the act is the only provision that authorizes the use of structure/function claims on dietary supplements.

The introductory language in section 403(r)(6) ("For purposes of [section 403](r)(1)(B) \* \* \*") does not support the interpretation advocated in the comment. If Congress had wanted

to subject only structure/function claims that are also health claims to section 403(r)(6) of the act, it could have done so much more directly by using language such as "A statement for a dietary supplement may be made if \* \* \* and the statement is a statement of the type governed by paragraph (r)(1)(B)." The ambiguity of the "For purposes of (r)(1)(B)" language is well demonstrated by the diametrically opposed interpretations adopted by this comment and the preceding comment. FDA interprets this language as a caution that the category of claims covered by section 403(r)(6) of the act is not to be interpreted as coextensive with health claims, the category covered by section 403(r)(1)(B) of the act. Congress may have been concerned that the health claims category would swallow the category of claims under section 403(r)(6) of the act because all claims under section 403(r)(6) could be characterized as referring to a "health-related condition" if that term were defined broadly as "a state of health." The result would have been that all structure/function claims, as claims about the relationship between a substance and a health-related condition, would also have been health claims and would have required premarket authorization. By including the introductory language, Congress effectively forestalled such an interpretation.

(101.) Another comment said the proposed rule does not distinguish between structure/function statements that assert

health claims and those that do not, and said the failure to make this distinction would mean that more products would be subject to the rule than necessary.

FDA does not agree that the rule fails to distinguish between structure/function claims that do and do not assert health claims. On the contrary, the rule makes clear that only structure/function claims that do not assert health claims may be made under section 403(r)(6) of the act. To the extent that the comment may be suggesting that structure/function claims that are also health claims should be exempt from the health claims authorization requirements, the agency disagrees for the reasons given in the response to the previous comment.

B. Miscellaneous Legal Issues

(102.) Two comments said the proposed rule violated the Administrative Procedure Act because it was arbitrary and capricious, on two grounds. One comment asserted that FDA failed to consider an important aspect of the problem of distinguishing between drug claims and dietary supplement claims: The application of the "general well-being" provision of section 403(r)(6) of the act. The comment argued that FDA should have considered whether claims relating to normal body functions might qualify as "general well-being" claims under section 403(r)(6) of the act before deciding to regulate them as disease claims. The comment also argued that FDA's explanation of the need for the

proposed rule ran counter to the evidence before the agency, in that the agency's actions on notifications of claims under section 403(r)(6) of the act did not support a need for further regulation.

The "general well-being" provision of section 403(r)(6) of the act authorizes statements in dietary supplement labeling that describe "general well-being from consumption of a nutrient or dietary ingredient" (section 403(r)(6)(A) of the act). FDA did not consider whether statements were authorized under this provision in developing the proposed rule because the purpose of the rule was to implement the structure/function provisions of section 403(r)(6)(A) of the act, not other provisions. However, consideration of this provision as applied to normal body functions would not have led to a different result. The criteria in the rule were developed to identify claims that refer directly or indirectly to an effect on disease and do not encompass claims that refer only to general well-being. Claims relating to normal body functions are authorized under the rule.

The comment's argument about the use of FDA's actions on notifications of claims under section 403(r)(6) of the act to justify the rule is addressed in comment 4 of section II.A of this document.

(103.) One comment claimed that the proposal does not require FDA to show any evidence of a manufacturer's intent to find that

a dietary supplement claim constitutes an illegal drug claim. The comment argued that proposed § 101.93(g)(2)(ii), (g)(2)(iii), (g)(2)(viii), and (g)(2)(x) run afoul of the recent appellate decision in Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155 (4th Cir. 1998), contending that "a product is not a drug merely because a consumer uses it as one" and that "there must be proof as to the manufacturer's intent." The comment also cited National Nutritional Foods Ass'n v. Mathews, 557 F.2d 325 (2d Cir. 1977), to support its position that a manufacturer's intent, as determined from labeling or advertising, is the primary factor in determining whether a product is intended to treat a disease.

Although FDA disagrees with the Brown & Williamson decision and is awaiting the outcome of Supreme Court review, this rule does not depend on the resolution of the legal issues in that case. The focus of the rule is on express and implied claims made by the vendor in labeling. None of the provisions of the rule, including those mentioned in the comment, rely on consumer use as a standard for determining whether the product is intended to treat or prevent disease.

The rule is consistent with the decision in National Nutritional Foods Ass'n v. Mathews, in which the court said, "FDA is not bound by the manufacturer's subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence. Such intent also may be derived or inferred from