

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 101**

[Docket No. 98N-0044]

RIN 0910-AB97

Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations defining the types of statements that can be made concerning the effect of a dietary supplement on the structure or function of the body. The regulations also establish criteria for determining when a statement about a dietary supplement is a claim to diagnose, cure, mitigate, treat, or prevent disease. This action is intended to clarify the types of claims that may be made for dietary supplements without prior review by FDA and the types of claims that require prior authorization as health claims or prior approval as drug claims.

DATES: The final rule will become effective February 7, 2000.

FOR FURTHER INFORMATION CONTACT: Ann Marlin Witt, Office of Policy, Planning, and Legislation (HF-11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0084.

SUPPLEMENTARY INFORMATION:**I. Introduction**

In the *Federal Register* of April 29, 1998 (63 FR 23624), FDA proposed regulations to identify the types of statements that may be made without prior FDA review about the effects of dietary supplements on the structure or function of the body ("structure/function claims"), and to distinguish these claims from claims that a product diagnoses, treats, prevents, cures, or mitigates disease (disease claims). FDA received over 235,000 submissions in response to the proposed rule. Many of these were form letters, but over 22,000 were individual letters from the dietary supplement industry, trade associations, health professional groups, and consumers. Almost all the comments from the dietary supplement industry and from individuals, which made up the vast majority of the comments, objected to all or part of the proposed rule, arguing that it inappropriately

restricted the structure/function claims that could be made for dietary supplements. Most of the comments from health professional groups and groups devoted to particular diseases supported the proposed rule, or believed it did not go far enough in limiting structure/function claims for dietary supplements.

After reviewing the comments, FDA concluded that the comments had raised significant questions about some of the key provisions of the proposal such that a public meeting was warranted. In the *Federal Register* of July 8, 1999 (64 FR 36824), FDA announced a public meeting to be held on August 4, 1999, at which representatives of the dietary supplement industry, consumer groups, and health professionals were asked to address three major issues raised by the comments. The three issues, described in the *Federal Register* notice, were: (1) Whether to finalize the proposed definition of "disease" or retain a 1993 definition of "disease or health-related condition" that was in effect at the time the Dietary Supplement Health and Education Act (DSHEA) was enacted; (2) whether to modify one of the proposed criteria for assessing disease claims to permit structure/function claims related to certain conditions associated with natural states, such as hot flashes associated with menopause and decreased sexual function associated with aging; and (3) whether to permit implied disease claims structure/function claims. The July 8, 1999, notice also reopened the comment period until August 4, 1999, to receive written comments on these three issues.

This document addresses the comments received on the proposed rule, as well as comments received in response to the July 8, 1999, *Federal Register* notice. A few comments raised issues that are beyond the scope of this rule and generally will not be addressed in this document.

A. Highlights of the Final Rule

Like the proposed rule, the final rule contains criteria to determine when a labeling statement made about a dietary supplement constitutes a structure/function claim for which no prior FDA review is required and when it constitutes a disease-related claim that requires either authorization of a health claim or review under the drug provisions of Federal Food, Drug, and Cosmetic Act (the act). FDA has, however, made several important changes in the final rule in response to comments.

First, the agency has deleted the proposed definition of "disease." Rather than creating a new definition of

disease, FDA will use the preexisting definition of "disease or health-related condition" in § 101.14(a)(5) (21 CFR 101.14(a)(5)) (formerly § 101.14(a)(6)), which was issued as part of the implementation of the health claims provisions of the Nutrition Labeling and Education Act (NLEA). This change has been made in response to the large number of comments that objected to the proposed definition and urged that FDA retain the NLEA definition.

Second, FDA has revised the criterion that applies to conditions associated with such natural states or processes as menopause, aging, adolescence, and pregnancy. The proposed rule stated that menopause, aging, and pregnancy are not themselves diseases but that certain conditions associated with them are diseases if they are recognizable to consumers or health professionals as abnormal. Many comments objected to classifying as diseases such common conditions as hot flashes, premenstrual syndrome (PMS), and decreased sexual function associated with aging. In response to these comments, FDA has revised proposed § 101.93(g)(2)(iii). Common conditions associated with natural states or processes that do not cause significant or permanent harm will not be treated as diseases under the final rule. For example, hot flashes, common symptoms associated with the menstrual cycle, ordinary morning sickness associated with pregnancy, mild memory problems associated with aging, hair loss associated with aging, and noncystic acne will not be treated as diseases under this provision. Uncommon or serious conditions like senile dementia, toxemia of pregnancy, severe depression associated with the menstrual cycle, and cystic acne will continue to be treated as diseases under the final rule.

Third, FDA has revised the criterion that relates to the use in labeling of the titles of publications that refer to diseases. In response to comments objecting that, as proposed, this criterion would hamper manufacturers from providing consumers with information substantiating their claims, FDA has revised this criterion. Under the revised criterion, the use in labeling of a publication title that refers to a disease will be considered a disease claim only if, in context, it implies that the product may be used to diagnose, treat, mitigate, cure, or prevent disease. Highlighting, bolding, using large type size, or prominent placement of a citation that refers to a disease in the title could suggest that the product has an effect on disease. Placing a citation to a scientific reference that refers to a disease in the title on the

immediate product label or packaging will be considered a disease claim for that product. The agency will also consider whether the cited article provides legitimate support for the express structure/function statement made for that 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.

B. Background

DSHEA created a new regime for the regulation of dietary supplements. These products were previously regulated either as foods or as drugs, depending upon whether they had the attributes of food and upon their intended uses. Before the passage of DSHEA, a dietary supplement for which a health-related claim was made was regulated either as a drug, which had to be shown to be safe and effective before marketing, or as a food, for which prior authorization to make a health claim was required if the claim concerned a disease or health-related condition. If the claim concerned a non-disease-related effect on the structure or function of the body and the claimed effect derived from a food attribute, such as nutritive value, the claim was considered a food claim, and prior authorization was not required. Under section 201(g)(1)(B) and (g)(1)(C) of the act (21 U.S.C. 321(g)(1)(B) and (g)(1)(C)), a drug is defined as "an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or "an article (other than food) intended to affect the structure or any function of the body." Section 505 of the act (21 U.S.C. 355) requires that new drugs (see section 201(p) of the act) be shown to be safe and effective for their intended uses before marketing. Under sections 403(r)(1)(B) and (r)(5)(D) of the act (21 U.S.C. 343(r)(1)(B) and (r)(5)(D)) and § 101.14, prior authorization is required to make a health claim for a dietary supplement. A health claim is a claim that "characterizes the relationship of any nutrient * * * in the food to a disease or health-related condition" (section 403(r)(1)(B) of the act; see § 101.14(a)(1)).

DSHEA specifically authorized certain types of claims about the uses of dietary supplements, including some claims that formerly would have required review by FDA before the claim is made. Section 403(r)(6) of the act, added by DSHEA, allows dietary supplement labeling to bear, among

other types of statements, a statement that "describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans" or that "characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function." Such statements are generally referred to as "structure/function claims." Because many of these claims would previously have been covered by the drug definition in section 201(g)(1)(C) of the act, section 201(g)(1) was amended by DSHEA to provide that a dietary supplement "for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement."

Although a dietary supplement manufacturer who wishes to make a statement permitted under section 403(r)(6) of the act need not obtain prior review of the statement, the manufacturer must possess substantiation that the statement is truthful and not misleading, and must include in the statement the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." DSHEA also requires the manufacturer of a dietary supplement bearing a statement under section 403(r)(6) of the act to notify FDA, no later than 30 days after the first marketing of the dietary supplement with the statement, that such a statement is being made for the product. Regulations implementing these requirements were published in the **Federal Register** of September 23, 1997, and are codified at § 101.93 (21 CFR 101.93) (62 FR 49883 at 49886, September 23, 1997).

DSHEA did not alter the statutory treatment of dietary supplement claims related to disease ("disease claims"). Section 403(r)(6) of the act, specifically provides that statements permitted under that section "may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases," except that such statements may claim a benefit related to a classical nutrient deficiency disease, provided that they also disclose the prevalence of the disease in the United States. Consistent with the quoted provision, Congress did not modify section 201(g)(1)(B) of the act to exclude disease claims for dietary supplements from use as evidence of intended use as a drug, as it had done for section 201(g)(1)(C) of the act. Thus, dietary supplements "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of

disease" remain within the definition of a "drug." In enacting DSHEA, Congress also maintained the requirement of prior authorization of a claim that characterizes the relationship of a nutrient in a dietary supplement to a disease (section 403(r)(1)(B) and (r)(5)(D) of the act). An interested person may submit a petition to FDA requesting the agency to issue a regulation authorizing the health claim (see § 101.70 (21 CFR 101.70)). The petitioner must demonstrate, among other things, that the use of the substance at levels necessary to justify the claim is safe and that there is "significant scientific agreement" among qualified experts that the claim is supported by the totality of publicly available scientific evidence (§ 101.14(b)(3)(ii) and (c)). The agency notes that for health claims to be used on conventional foods, an interested person may submit to FDA a notification of an authoritative statement by one of certain designated scientific bodies concerning the substance-disease relationship to which the claim refers (see section 403(r)(3)(C) of the act). Unless FDA issues a regulation modifying or prohibiting the claim, or a Federal district court finds that applicable statutory requirements have not been met, the claim may be used 120 days after the notification has been submitted (see section 403(r)(3)(C)(ii) and (r)(3)(D) of the act). This alternative authorization procedure does not apply to dietary supplements by statute, but FDA has proposed to extend it to dietary supplements by regulation (see 64 FR 3250, January 21, 1999).

Although FDA believes that dietary supplements have potential benefits for consumers, dietary supplements labeled with unproven disease claims, i.e., those that have not met the requirements for health claim authorization or new drug approval, can pose serious risks. Such claims may encourage consumers to self-treat for a serious disease without benefit of a medical diagnosis or treatment. They may also cause consumers to substitute potentially ineffective products for proven ones, foregoing or delaying effective treatment for serious and life-threatening illnesses. Reliance on disease prevention claims may encourage consumers to feel sufficiently protected from developing serious diseases (e.g., cancer or human immunodeficiency virus (HIV) infection) that they delay or forego regular screening, and forfeit the opportunity for early medical treatment that may be critical to survival. Finally, use of dietary supplements to treat

disease may increase the risk of adverse reactions due to the interaction of the dietary supplement with other compounds a consumer is taking for that disease or for other conditions, e.g., prescription medications.

This final rule is intended to apply only to structure/function claims and disease claims within the meaning of section 403(r)(6) of the act. DSHEA, generally, and section 403(r)(6) of the act, specifically, apply only to dietary supplements for human consumption and were enacted to provide a unique regulatory regime for these products. Thus, this rule is neither intended to apply to products other than dietary supplements for human consumption nor to interpret other provisions of the act.

The final rule establishes criteria for determining whether a statement made about a dietary supplement is acceptable as a structure/function claim under section 403(r)(6) of the act. The rule is neither intended to establish whether any particular structure/function claim is appropriate for any specific product, nor whether the claim would be permitted under other provisions of the act. Like the labeling of any other FDA-regulated product, the labeling of dietary supplements must comply with all applicable requirements of the act and regulations. For example, an otherwise acceptable structure/function claim might nevertheless be false or misleading for other reasons, causing the product to be misbranded under section 403(a)(1) of the act.

C. The Proposed Rule

The proposed rule defined criteria for determining when a statement about a dietary supplement is a claim to diagnose, cure, mitigate, treat, or prevent disease ("disease claim"), and thus requires prior approval as a drug or prior authorization as a health claim. The proposed rule included a definition of "disease," which was to replace a definition of "disease or health-related condition" issued for implementation of the health claims regulations, and 10 criteria for identifying express or implied disease claims. FDA proposed to treat a statement about a dietary supplement as a disease claim if the statement claimed, explicitly or implicitly, that the product: (1) Has an effect on a specific disease or class of diseases; (2) has an effect, using scientific or lay terminology, on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific disease or of a number of different specific diseases; (3) has an effect on a consequence of a natural

state that presents a characteristic set of signs or symptoms recognizable to health care professionals or consumers as constituting an abnormality of the body; (4) has an effect on disease through one or more of the following factors: (a) The name of the product; (b) a statement about the formulation of the product, including a claim that the product contains an ingredient that has been regulated by FDA as a drug and is well known to consumers for its use in preventing or treating a disease; (c) citation of a publication or reference, if the citation refers to a disease use; (d) use of the term "disease" or "diseased;" or (e) use of pictures, vignettes, symbols, or other means; (5) belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease; (6) is a substitute for a product that is a therapy for a disease; (7) augments a particular therapy or drug action; (8) has a role in the body's response to a disease or to a vector of disease; (9) treats, prevents, or mitigates adverse events associated with a therapy for a disease and manifested by a characteristic set of signs or symptoms; or (10) otherwise suggests an effect on a disease or diseases.

Claims that did not fall within the proposed criteria for disease claims and that otherwise complied with the notification and disclaimer provisions of § 101.93(a) through (e) were to be eligible for use as structure/function claims. The proposed rule also provided examples of claims that would be permitted as structure/function claims and those that would require prior review as disease claims under each of the 10 criteria.

The basis for the proposed rule was the agency's experience in implementing section 403(r)(6) of the act, and the final report (the report) of the President's Commission on Dietary Supplement Labels (Ref. 1), which included a number of recommendations for distinguishing structure/function and disease claims and suggested that FDA issue further guidance on acceptable structure/function claims.

II. Comments

A. General Comments

(1.) Many comments focused on the impact of the rule on consumers. Many comments opposing the proposed rule said that consumers should be able to receive truthful and non-misleading information and that the proposed rule would curtail or restrict such information or restrict the focus of dietary supplements to preventive care and wellness. Some comments added that DSHEA, through the dissemination

of truthful and non-misleading information on health and promotion and disease prevention, makes consumers responsible for their own health. Other comments said that FDA should let the public educate itself. Other comments suggested that FDA simply adopt a "truthful and non-misleading" standard. Some comments added that full disclosure of all pertinent information (such as the preliminary status of scientific studies substantiating the claim) would be sufficient. Another comment questioned whether consumers would, as the preamble to the proposed rule stated, benefit from not having to search for information and from getting appropriate information. The comment argued that consumers would receive less information under the rule and would have to search more extensively for information.

Many comments supporting the proposed rule, including comments from nutrition counselors and health professionals, said that the proposal would reduce confusion among patients, prevent consumers from being misled, diminish the number of inappropriate disease claims, and help consumers decide when to seek medical attention. One comment added that, while it supported the need for consumers to have choice regarding dietary supplements, the choice should be made based on accurate information that is supported by appropriate scientific investigations. One comment argued that in the absence of valid effectiveness data, which does not exist for most dietary supplements, it is not possible to provide "truthful" information about the effects of these products. Some comments said that the proposal would protect consumers from harmful or potentially harmful products and save consumers from needless suffering and financial loss; others expressed concern that inappropriate statements would expose consumers to potentially harmful drug-supplement interactions, create "false hopes," and lead consumers to stop complying with advice from health care professionals or to avoid proven treatments.

FDA agrees that DSHEA encourages the dissemination of truthful and non-misleading information about the uses of dietary supplements to affect the structure or function of the body, and encourages full disclosure of information about claims authorized by the statute. To the extent that truthful and non-misleading information is being withheld from consumers in the context of structure/function claims for dietary supplements, it is the statute that, in the first instance, precludes

certain information from being included in such claims. Section 403(r)(6) of the act permits dietary supplement labels to carry structure/function claims without meeting the requirements for drug approval or health claim authorization, but precludes them from carrying unreviewed claims that the product diagnoses, treats, mitigates, cures, or prevents disease. (The statute does not ultimately prevent dissemination of information about disease uses to the consumer in labeling claims or otherwise. Instead, it requires that claims about disease uses meet certain standards of substantiation and undergo agency review.) This final rule differentiates between structure/function claims authorized by section 403(r)(6) of the act and disease claims that may not be made in dietary supplement labeling under the authority of section 403(r)(6). The agency notes that, in response to comments, the final rule classifies many more claims as structure/function claims than would have been so classified under the proposed rule, thus increasing the amount of information available to the consumer without prior FDA review.

The agency also declines to adopt a "truthful and non-misleading" standard instead of the final rule. Section 403(a)(1) of the act already subjects all food claims, including structure/function claims on dietary supplements, to the "truthful and non-misleading" standard, so promulgating the same standard through regulations is unnecessary. In addition, section 403(r)(6)(B) of the act already requires dietary supplement manufacturers to have substantiation that their statements are truthful and non-misleading. Finally a fundamental problem with this approach is that a "truthful and non-misleading" standard, unlike the final rule, would not provide any criteria for differentiating between structure/function claims and disease claims.

(2.) Some comments focused on product safety. One comment said that regulation of claims is unnecessary because dietary supplements are safe. Similarly, another comment claimed that "one million peer-reviewed studies" showed that dietary supplements provide benefits, whereas a recent medical journal reported deaths and other injuries to patients who use prescription drugs. Other comments declared that dietary supplements are safer than most regularly-used drug products. In contrast, other comments argued that the safety of many dietary supplements is unknown, and that risks have been documented with some supplements. Some comments claimed that dietary supplements pose risks

because they can cause consumers to avoid or delay more effective treatment. One comment stated that there is a substantial potential for public harm because of the unknown or unregulated source materials for many dietary supplements, the variety of suppliers, and the lack of regulatory production standards and quality control.

Although this final rule may not appear to be a safety measure because it addresses the labeling of dietary supplements rather than their composition, protecting consumer health and safety is one of its major purposes. Because structure/function claims are not subject to the new drug approval standard or the health claim authorization standard and do not undergo FDA review before marketing, FDA believes it is important to ensure that such claims do not promote products for disease treatment or prevention claims. Disease treatment or prevention claims can pose serious risks to consumers if they induce consumers to substitute ineffective or less effective treatments for proven ones, especially if the disease involved is serious or life-threatening. Therefore, the agency believes that ensuring that such claims cannot be made without a demonstration of safety and effectiveness will protect and promote public health.

FDA also believes that the safety and the effectiveness of products intended to promote health, including both dietary supplements and drugs, cannot be viewed independently of each other. FDA agrees that prescription drugs can and do cause adverse reactions. It is important to remember, however, that "safety" is relative. Products that are capable of treating diseases have powerful effects on the body and frequently carry risks. Before prescription drugs are marketed, both their risks and their benefits must be carefully investigated and documented in adequately designed clinical trials. Prescription drugs are permitted to be marketed only when the agency concludes that their documented benefits outweigh their known and potential risks. Those with significant risks are approved for marketing only if the benefits warrant those risks. And they are marketed as "prescription" drugs to ensure that health professionals manage their risks. Even over-the-counter (OTC) drugs are evaluated for both benefits and risks and are permitted to be marketed only when their established benefits outweigh their risks. There is no comparable testing and approval process for dietary supplements marketed with structure/function claims. The manufacturer must

have substantiation of the structure/function claim, but this substantiation is not reviewed before the product is marketed with the claim. Contrary to the suggestion in the comment, few dietary supplements have been the subjects of adequately designed clinical trials.

This does not mean that dietary supplements are unsafe or that they do not have benefits. Some have already been shown to be safe and to have benefits, and the safety and effectiveness of others are likely to be shown in the future. At this time, however, many marketed supplements have not been the subjects of adequate studies to establish whether or not they are safe or effective, or the nature of the benefits they may provide.

(3.) Many comments asserted that FDA had no authority to issue the proposed rule because it was inconsistent with DSHEA and congressional intent, in that it restricted rather than increased the amount of information given to consumers. Some comments said that Congress enacted DSHEA to reverse FDA's "overly restrictive" approach towards health claims and to increase the dissemination of truthful and non-misleading health information and that Congress repeatedly expressed its displeasure with FDA's regulatory approach. One comment said FDA must determine whether a proposed action is consistent with its statutory authority before it takes any regulatory action. The comment cited excerpts from congressional documents "condemning the agency's repeated penchant" for restricting statements on dietary supplement labels and labeling, and said that, given congressional intent and the act's language, FDA has no authority to proceed with rulemaking without a grant of authority from Congress. One comment cited section 403B of the act (21 U.S.C. 343-2) as evidence that Congress, by exempting certain publications from the definition of labeling, barred FDA from restricting in "any way whatsoever" the dissemination of such publications and information.

FDA agrees that DSHEA was intended to authorize the dissemination of more truthful and non-misleading information in dietary supplement labeling without the need for prior agency review. In response to comments that the proposed rule was too restrictive, FDA has modified the final rule to incorporate many of the changes requested by the comments, including a return to the preexisting definition of "disease or health-related condition," and a less restrictive interpretation of the types of structure/function claims

that can be made about conditions associated with such natural states as aging, pregnancy, and the menstrual cycle. The final rule classifies many more claims as structure/function claims than the proposed rule would have.

The agency does not agree, however, that section 403(r)(6) of the act authorizes dissemination of any and all information about dietary supplements without prior review. That section authorizes statements about the effects of dietary supplements on the structure or function of the body, but not statements that claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases. Section 403B of the act exempts from being considered labeling certain balanced, third-party publications that are physically separate from product labeling and do not promote a particular brand or product. This provision does not authorize dietary supplement manufacturers to ignore the restrictions in section 403(r)(6) of the act on what structure/function claims may be made by a manufacturer about its product on the product label and in materials that are indisputably part of the product's labeling.

The agency also disagrees with the assertion that separate congressional authority is needed for this rulemaking. FDA issued the proposed rule, and this final rule, to implement section 403(r)(6) of the act. No independent authority to issue these regulations is necessary because section 701(a) of the act (21 U.S.C 371(a)) expressly gives FDA "the authority to promulgate regulations for the efficient enforcement of this Act, except as otherwise provided in (section 701 of the act) * * *." The proposed rule identified section 701(a) of the act as being part of the agency's legal authority (see 63 FR 23624 at 23628 and 23631), and there is no exception in the act that restricts or limits, either expressly or impliedly, the agency's ability to issue regulations to implement section 403(r)(6) of the act. Therefore, the rule is authorized by law and consistent with FDA's statutory authority.

(4.) Some comments contended that FDA did not provide a sufficient justification for issuing the rule. Two comments challenged FDA's assertion that the rule would reduce substantial confusion among manufacturers. The comments referred to statements in the preamble to the proposed rule which said FDA received approximately 2,300 notifications of structure/function claims and sent objection letters to approximately 150 notifications. One comment said the low objection rate did

not indicate "substantial confusion" among manufacturers, while the other comment hypothesized that, if FDA objected to a small number of claims in each notification, the number of objectionable claims was very small. Other comments contended that the Commission report did not support the proposed rule. These comments were divided in their reasons. Some comments argued that the Commission exceeded its statutory mandate under section 12 of DSHEA or failed to perform its statutory obligations. Thus, the comments stated, FDA cannot base any regulation on the Commission's findings, guidance, or recommendations and has no authority to proceed with the rulemaking. Other comments stated that FDA relied on statements from individual Commission members rather than the report itself, that the report did not suggest that FDA issue regulations, and that the report did not suggest that FDA issue a new definition of disease. One comment said that the Commission did not support a need for regulations. Another comment noted that the Commission did not recommend regulations and asserted that FDA had publicly said that DSHEA is self-implementing.

FDA does not agree that there is insufficient support for this rule. FDA's experience, the Commission report, and FDA's authority under section 701(a) of the act to issue regulations implementing statutory requirements provide more than adequate support for the rule. The preamble to the proposed rule referred to substantial confusion among manufacturers and consumers, rather than manufacturers alone. Comments received from other sources, particularly physicians, dieticians, and health professional organizations, agreed that consumers are confused and misled by claims. In addition, the number of objection letters is not the sole indicator of manufacturer confusion, for three reasons. First, manufacturers and consumers have asked FDA to provide clarification on structure/function and disease claims, and such requests for clarification would not necessarily have resulted in an objection letter from FDA. Second, the agency has repeatedly said that the absence of an objection letter does not necessarily indicate acceptance of the claim. Third, there are apparently a large number of marketed dietary supplement products making claims for which FDA has not received 30-day notification letters under section 403(r)(6) of the act. (In the proposed rule, FDA estimated that approximately 22,500 dietary supplement labels

carried structure/function claims. FDA had received 2,300 notifications at the time of the proposed rule. While some notifications contain more than one claim, they do not average 10 claims per notification.)

FDA also does not agree that the Commission report was necessary to provide support for this rule. The proposal was based not only on the Commission report, but also on the agency's experience in reviewing 30-day notification letters submitted under section 403(r)(6) of the act (63 FR 23624 at 23625). Although FDA believes the rule is consistent with the views expressed in the Commission report, the Commission report was not a necessary prerequisite for the agency to issue the rule. FDA issued the proposal under section 403(r)(6) of the act (section 6 of DSHEA) and the rulemaking authority of section 701(a) of the act, not under section 12 of DSHEA. FDA takes no view on whether the Commission met its statutory obligations in issuing its report. To the extent that the report is beyond the Commission's authority, FDA's experience and section 701(a) of the act provide adequate support for the rule. Thus, whether or not the Commission exceeded its mandate is irrelevant to the validity of the rule.

With regard to the issues raised about the consistency of the agency's approach with the Commission report, it is true that the Commission did not specifically recommend regulations, but the Commission did express the view that FDA guidance on claims under section 403(r)(6) of the act would be "appropriate and helpful in clarifying the appropriate scope" of such claims (the report, p. 38).

As to the agency's public statements that DSHEA is self-implementing, the comment took those statements out of context. When DSHEA was passed, there was confusion in the industry about whether the types of statements permitted by section 403(r)(6) of the act could be made under the authority of the statute alone, in the absence of implementing regulations. To clear up this confusion, at least one agency official publicly said that DSHEA was "self-implementing." Agency statements to this effect were intended to clarify that manufacturers were not required to wait for FDA to issue implementing regulations before making claims under section 403(r)(6) of the act; however, they were in no way intended to imply that the agency lacked authority to issue implementing regulations.

Contrary to the suggestion in one of the comments, FDA did not rely on the views of individual Commission members, but on the official 7-point

“guidance” developed by the Commission “as to what constitutes an acceptable statement of nutritional support of the structure/function type” (the report at pp. 38 and 39). The criteria developed by FDA are highly consistent with the Commission’s guidance. FDA also agrees that the Commission did not make any findings or recommendations on the definition of disease. As described elsewhere in this rule, the final rule does not modify the existing definition of disease found in FDA’s health claims regulations.

(5.) One comment said that FDA should have admitted that there is and will be some overlap between disease and structure/function claims and that the agency should have drafted a rule to prevent extreme overlap between structure/function claims and drug or health claims.

FDA disagrees with this comment. In the proposed rule, FDA recognized that section 403(r)(6) of the act leaves open questions concerning the distinction between structure/function claims and disease claims. Diseases cause, and can be characterized as, abnormalities in the structure or function of the body. It would therefore be possible to describe almost all products intended to treat or prevent disease in terms of their effects on the structure or function of the body, without mentioning the disease itself.

The language of DSHEA, however, does not support treating those structure/function claims that are also disease claims as statements permitted under section 403(r)(6) of the act. As noted above, section 403(r)(6) of the act contains two passages that indicate Congress’ intent to exclude from the scope of structure/function claims any claim that is also a disease claim. Section 403(r)(6) of the act provides that structure/function statements “may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases.” It also requires structure/function claims to be accompanied by a disclaimer stating that the product “is not intended to diagnose, treat, cure, or prevent any disease.”

In light of the statutory framework, FDA concluded in the preamble to the proposed rule that section 403(r)(6) of the act authorizes claims related to the effect of a product on the structure or function of the body only if they are not also disease claims. FDA’s conclusion was consistent with the policy guidance offered by the President’s Commission on Dietary Supplement Labels. In the report the Commission offered general guidance on structure/function claims, including the following:

3. Statements indicating the role of a nutrient or dietary ingredient in affecting the

structure or function of humans may be made when the statements do not suggest disease prevention or treatment.

(The report, p. 38)

Accordingly, FDA believes that it is appropriate to define the universe of permitted structure/function claims by first identifying those claims that should be considered disease claims.

Remaining claims about the effect of a dietary supplement on the structure or function of the body may be acceptable structure/function claims under section 403(r)(6) of the act, provided that they are consistent with the requirement in section 201(ff)(1) of the act that a dietary supplement be “intended to supplement the diet.”

(6.) Some comments, particularly those received at the public hearing or during the reopened comment period, argued that it is difficult or impossible to draw principled distinctions between structure/function claims and disease claims. Some of these comments said that section 403(r)(6) of the act, which is premised on such a distinction, is not scientifically based. Other comments argued that it is not necessary or practical to draw clear lines between disease claims and structure/function claims, and that dietary supplement labeling should instead focus on educating consumers about the conditions for which a product may be used. According to these comments, if there are disease conditions that might be implied by a particular claim, the labeling should, for example, inform consumers of the symptoms of such conditions, the importance of seeking medical attention for them, and their health-related consequences. Other comments argued that consumers reading the labels of dietary supplements will incorrectly assume that the information provided therein has been reviewed by the government and that the claims, express or implied, are supported by the kind of scientific evidence that supports drugs with similar claims.

FDA agrees that it may be very difficult to draw clear lines between structure/function claims and disease claims. Despite the difficulty, implementing section 403(r)(6) of the act requires the agency to draw these lines. FDA would not be carrying out its statutory obligations if it abdicated responsibility for distinguishing between the two types of claims, and instead permitted dietary supplements to disseminate information about specific disease states. FDA agrees that scientifically valid information about diseases is helpful to consumers, if it is delivered consistently and accurately, but does not agree that section 403(r)(6)

of the act authorizes such dissemination. FDA strongly believes that the dissemination of such information on dietary supplement labels increases the likelihood that consumers will believe that the supplements are intended to treat or prevent the diseases described in the labeling. Therefore, it is important that any disease claims in dietary supplement labeling continue to be subject to prior FDA review to evaluate the safety and effectiveness of the product for the use described or suggested by the claim.

The agency also notes that there may be important health-related consequences associated with taking a dietary supplement, even if the product does not bear disease claims. For the labeling of a dietary supplement to be considered truthful and non-misleading (see sections 403(a) and (r)(6) and 201(g)(1) of the act), it must include all information that is material in light of the claims made for the product and the consequences that may result from its use (see section 201(m)) of the act.

(7.) Many comments discussed the rule’s effect on scientific research. Some comments argued that the proposal would discourage scientific research on dietary supplements. One comment contended that such research might prompt FDA to consider a dietary supplement to be a drug. Another comment said the proposal would “chill” the availability of third-party information on dietary supplements.

The agency disagrees with the comments. The comments provided no evidence, and the agency is aware of none, that establishing criteria for distinguishing structure/function claims and disease claims will adversely affect the conduct or use of scientific research. In the agency’s experience, establishing regulatory standards has generated more research rather than less. As described below, some comments from pharmaceutical companies and from patient organizations expressed the contrary concern that allowing dietary supplements to make disease claims without FDA review would undermine incentives for rigorous scientific research. The agency also notes that nothing in this rule would treat scientific research or the publication of research results in a scientific journal as evidence that a product is marketed as a dietary supplement or is a drug.

(8.) Several comments addressed the relationship between dietary supplements and drug products, and the effects of this regulation on drug products and drug development. Some comments suggested that the proposal represented an attempt by FDA to

regulate dietary supplements in a manner that benefits pharmaceutical interests or to regulate dietary supplements in a manner that is similar to European regulatory systems that apply drug requirements to such products.

In contrast, other comments expressed concern over the negative effects of DSHEA and the proposed rule on incentives for pharmaceutical drug development. One comment asked FDA to provide an "unambiguous demarcation" that would preserve research and development incentives for drug products and permit evaluation of opportunities in the dietary supplement marketplace. According to this comment, section 403(r)(6) of the act, and DSHEA generally, were intended to create "parity" between the dietary supplement and food industries without undermining research and development incentives for the pharmaceutical industry and to address a perceived failure by FDA to implement the health claims provision for dietary supplements in section 403(r)(5)(D) of the act. The comment contended that section 403(r)(6) of the act is intended to provide a limited statutory safe harbor for certain dietary supplements that might otherwise be subject to regulation under the health claim rules for food or as unapproved new drugs, but it does not permit any and all structure/function statements for dietary supplements. Thus, the comment said FDA should have "parallel interpretations" of sections 201(g)(1)(C) and 403(r)(6) of the act. The comment suggested that FDA enforce the requirement of a "documented mechanism" imposed in section 403(r)(6)(A) of the act, which permits claims that "characterize the documented mechanism by which a nutrient or dietary supplement acts to maintain" structure or function and that FDA limit claims to "maintaining," rather than "promoting" or "improving" structure or function.

FDA does not agree that this rule was designed to benefit the pharmaceutical industry or to establish rules that are consistent with European regulation of dietary supplements. As noted above, some pharmaceutical companies believe that the rule will harm them by permitting competition by products that have not had to undergo rigorous testing or review. Other pharmaceutical companies already produce dietary supplements and expressed the same reservations about the rule as other dietary supplement manufacturers. There was also no attempt to model this rule after European regulation of dietary supplements.

FDA recognizes the importance of maintaining incentives for research and product innovation. By establishing criteria for determining when a statement may be a disease claim, the final rule indirectly contributes towards preserving the incentives for pharmaceutical research and development by ensuring that products marketed for treatment or prevention of diseases must all meet the same regulatory standards. As stated below, FDA believes that if the rule were to permit dietary supplements to carry implied disease claims, the incentives for new drug development could be significantly undermined.

FDA agrees with the comment that the structure/function provisions of sections 403(r)(6) and 201(g)(1)(C) of the act are similar in scope. FDA also agrees that to make a statement about the mechanism by which a dietary supplement maintains structure or function, the mechanism of action must be "documented." FDA does not agree, however, that this is the only provision under which a dietary supplement may claim to maintain healthy structure or function. Maintenance claims also can be made under the provision that authorizes statements that "describe the role" of a supplement "intended to affect the structure or function" of the body (section 403(r)(6)(A) of the act).

In response to the comment asking FDA to limit claims to "maintaining," rather than "promoting" or "improving," structure/function, the agency agrees that "improving" often suggests some abnormality or deficiency that can be treated, so a claim to "improve" a structure or function of the body would be more likely to be a disease claim. On the other hand, a claim to improve memory or strength would be a permitted structure/function claim, unless disease treatment were implied. Use of the term "promote" may be acceptable under the portion of section 403(r)(6)(A) of the act which authorizes claims that "describe[] the role of a * * * dietary ingredient intended to affect the structure or function." Whether a claim for "promoting" structure or function is a disease claim will depend on the context and nature of the claim. For example, a claim that a product "helps promote digestion" would be a structure/function claim because it does not refer explicitly or implicitly to an effect on a disease state, but a claim that a product promotes low blood pressure would be considered a disease claim. Both the preamble to the proposed rule and the Commission recognized that statements using the word "promote" can be appropriate when the statements

do not suggest disease prevention or treatment or use for a serious health condition that consumers cannot evaluate (see 63 FR 23624 at 23626).

(9.) A few comments objected to the statement that a dietary supplement bearing an appropriate structure/function claim may be subject to regulation as a drug if there is other evidence that it is intended for the diagnosis, cure, mitigation, treatment, or prevention of disease. One comment argued that many dietary supplements are used for medicinal purposes and it would be "easy" for FDA to find evidence that they were intended for this purpose based on consumer use of the product.

Although FDA's longstanding interpretation of section 201(g)(1)(B) of the act authorizes the agency to rely on evidence outside the labeling and advertising of a product to establish its intended use, FDA does not rely on such evidence alone except in unusual circumstances. For example, the courts have suggested that if the agency seeks to rely solely on evidence that consumers use a product for a particular purpose to support a finding of intended use for that purpose, consumers must use the product predominantly or nearly exclusively for that purpose. (See, e.g., *Action on Smoking and Health (ASH) v. Harris*, 655 F.2d 236, 239-240 (D.C. Cir. 1980); *National Nutritional Foods (NNFA) v. Weinberger*, 512 F.2d 688, 702 (2d Cir. 1975), cert. denied, 423 U.S. 827 (1975).) The fact that some consumers used a dietary supplement for medicinal purposes would not by itself be sufficient to establish intended use as a drug, if use for medicinal purposes was not the predominant use.

FDA reiterates, however, that in appropriate circumstances, FDA may find that a dietary supplement for which only structure/function claims are made in labeling may nevertheless be a drug if there is other evidence of intended use to prevent or treat disease.

(10.) Some comments discussed the "disclaimer" statement required by section 403(r)(6)(C) of the act. The disclaimer reads as follows: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." One comment said the disclaimer resolves any consumer confusion between dietary supplement claims and drug claims. Another comment said the proposed rule showed that FDA was implicitly rejecting the disclaimer's meaning because the proposed rule would restrict the amount of information flowing to consumers. One comment said the disclaimer reflects

Congress' understanding of a tension between structure/function and disease claims, while another comment asserted that the disclaimers required on a label are an attempt to decrease the amount of space on a label for a structure/function claim.

Section 403(r)(6) of the act requires dietary supplement manufacturers who wish to make a structure/function statement to include the disclaimer, and, since 1997, FDA regulations regarding the disclaimer have been codified at § 101.93. However, the disclaimer's role does not eliminate the need for this final rule to establish criteria for determining whether a statement is a disease claim. Section 403(r)(6) of the act provides that a statement for a dietary supplement that is made under section 403(r)(6) "may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases." Had Congress thought the disclaimer, alone, was sufficient to distinguish between structure/function claims and disease claims, it would not have enacted the restriction against disease claims in section 403(r)(6) of the act.

FDA does not agree with the assertion that the disclaimer, which is expressly required by the act, is a scheme to decrease the space for structure/function claims on a label. FDA believes that the disclaimer is intended to make sure that consumers understand that structure/function claims, unlike health claims and claims that appear on the labels of drugs, are not reviewed by FDA prior to marketing, and to caution consumers that dietary supplements bearing such claims are not for therapeutic uses.

(11.) Several comments sought additional statements or language on product labels. One comment supported the marketing of dietary supplements and other substances whose effectiveness has not been established and that have no appreciable toxicity as long as the product's label stated that effectiveness had not been proven. Another comment said precautions, such as adverse reactions and contraindications to certain diseases and medications, are important information for labels. The comment also sought a description of a dietary supplement product's contents as a percentage of a person's recommended daily intake (RDI) and in actual units.

FDA declines to revise the rule as suggested by the comments. With regard to the marketing of dietary supplements with a label statement that the product's effectiveness has not been proven, the agency advises that dietary supplements that do not do what they claim to do are

misbranded. The act forbids false and misleading labeling and advertising claims and requires businesses to have substantiation for any structure/function claims they make for dietary supplements in labeling (see section 403(a) and (r)(6)(B)) of the act. The presence of a disclaimer indicating that effectiveness has not been established cannot vitiate these statutory obligations. Therefore, it would be inappropriate for FDA to sanction the use of effectiveness disclaimers.

Although the act does not prescribe any specific statements concerning adverse reactions or contraindications that dietary supplements must carry, the agency notes that dietary supplement labeling, like the labeling of all other FDA-regulated products, is required to include all information that is material in light of consequences that may result from the use of the product or representations made about it (see sections 403(a)(1) and 201(n) of the act).

As for requiring information on the percentage of RDI and actual units for dietary ingredients in dietary supplements, FDA agrees that such information is useful. In fact, FDA's nutrition labeling regulations for dietary supplements generally require the percentage of the RDI or daily reference value (DRV) that a dietary supplement contains to be given for dietary ingredients that have an RDI or DRV (see § 101.36(b)(2)(iii) (21 CFR 101.36(b)(2)(iii))). In addition, the amount in units must be given, regardless of whether an RDI or DRV has been established (see § 101.36(b)(2) and (b)(3) (21 CFR 101.36(b)(2) and (b)(3))). This information can be found on the Supplement Facts panel of dietary supplements.

(12.) One comment objected to referring to structure/function statements as "claims." The comment said that, under section 403(r)(6) of the act, such statements must be truthful and non-misleading, so they should be called "statements" instead of "claims."

FDA has traditionally used the term "claim" to refer to any statement made by a manufacturer that recommends or suggests a particular use of a product. This term is used for all products regulated by FDA, including drugs, foods, devices, and dietary supplements. Use of the term "claim" is not intended to suggest that a statement is untrue or misleading in any way.

(13.) One comment said that any substance used with "pharmacologic intent" should be classified as a drug or biologic in order to ensure the efficacy, potency, and purity of medicines. The comment explained that such substances have a potential for

therapeutic benefit as well as harm, and suggested that existing and new dietary supplements that are marketed with health-related claims be required to provide scientific evidence of their safety and efficacy as a condition of their being marketed as a drug or biologic.

FDA declines to adopt the comment's suggestion. Section 403(r)(6) of the act expressly authorizes certain structure/function claims for dietary supplements. Many of these claims may be said to be "health-related." (The agency is uncertain what is meant by "pharmacologic intent.") Thus, the act does not require all substances with health-related claims to be classified as a drug or biologic.

Regarding safety and effectiveness evidence for dietary supplements that bear health-related claims, FDA agrees that such evidence should continue to be required where the claim is a health claim within the meaning of § 101.14(a)(1) or a claim that subjects the product to regulation as a drug under section 201(g)(1)(B) of the act. With regard to health-related claims that are authorized by section 403(r)(6) of the act, section 403(r)(6)(B) does require manufacturers to have substantiation for their claims. However, the act does not generally require dietary supplement manufacturers that make claims for their products under section 403(r)(6) of the act to provide a premarket demonstration of safety and effectiveness to FDA.

(14.) One comment recommended that FDA not finalize the proposed rule because it claimed that the proposal's criteria were based on a subjective evaluation of claims and not on objective information from market research studies to determine whether consumers are confused by the claim. The comment also argued that FDA did not provide data and information regarding consumer confusion, and that all interested parties should be able to evaluate and comment on any data before FDA finalizes the proposal. The comment asserted that a significantly revised and limited final rule could provide a basic regulatory definition of disease and a "construct" for structure/function claims so that detailed regulatory criteria would be unnecessary.

The act does not require market research studies to determine whether a particular statement is a structure/function claim or disease claim, and it would be both impractical and inefficient to require such studies to decide the status of every possible claim that could be made under section 403(r)(6) of the act. FDA also does not

believe that market research studies are necessary to provide a reasonable basis for the agency's determinations concerning the meaning of labeling claims. The agency has extensive experience in interpreting such claims. The agency has, however, modified the second criterion in § 101.93(g)(2)(ii) to eliminate reference to recognition of signs and symptoms by consumers or health professionals because many comments objected that this standard would appear to require consumer testing. FDA has replaced the recognition standard with an objective standard.

(15.) One comment said that it would be inappropriate for FDA to issue any regulation that restricted the scope of statements of nutritional support related to a nutrient content claim or claims pertaining to a classical nutrient deficiency-related disease. The comment said that claims such as "calcium builds strong bones" are acceptable and that FDA should clarify this fact in the final rule.

FDA agrees that dietary supplements may carry structure/function statements concerning the relationship of nutrients and the structure or function of the body, such as "calcium builds strong bones." The preamble to the proposed rule also specifically acknowledged that although statements under section 403(r)(6) of the act generally may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases, "such statements may claim a benefit related to a classical nutrient deficiency disease, provided that they also disclose the prevalence of the disease in the United States" (63 FR 23624). The final rule codifies this exception at § 101.93(g)(2), which states that "FDA will find that a statement about a product claims to diagnose, mitigate, treat, cure, or otherwise prevent disease (*other than a classical nutrient deficiency disease*) * * *" (emphasis added). Classical nutrient diseases are also specifically excluded from the definition of disease in § 101.93(g)(1). Thus, because the final rule already contains the exception, no change to the rule is necessary.

(16.) Many comments suggested that FDA issue a guidance document instead of regulations. Some of the comments stated that regulations are neither desirable nor necessary. Others stated that a guidance document would be appropriate because it would permit new information to support new structure/function claims or because it would enable FDA to conduct consumer research and industry outreach programs before imposing new rules. Some comments also requested separate

guidance documents for specific claims or recommended that FDA create or use advisory committees to help draft guidance documents. Two comments said that the Commission report only provided guidance and suggestions, so FDA did not have to issue the proposed rule. Another comment said that publishing a guidance document would consume fewer agency resources and that a rule is unnecessary because the industry already knows the permissible scope of statements for dietary supplements.

FDA disagrees with the comments. The final rule creates uniform, enforceable requirements for structure/function claims. By doing so, the final rule establishes a "level playing field" for all members of the dietary supplement industry, and permits rational use of FDA's limited enforcement resources. In contrast, guidance documents, although they represent FDA's best advice on a particular matter, are not binding on any party. Relying solely on guidance documents would not be as effective in achieving consistency in the regulation of structure/function claims on dietary supplements and would lead to case-by-case enforcement.

FDA does, however, intend to issue a guidance document to provide additional information regarding structure/function and disease claims. The guidance document would complement, rather than substitute for, the final rule.

As for those comments stating that a guidance document would permit new information to support new structure/function claims or that outreach programs are necessary, FDA notes that interested persons may generate such information regardless of the rule. FDA may also conduct research or other programs or consult advisory committees or other persons if such actions would be helpful. In short, gathering more information or conducting research and other programs is not dependent on whether FDA issues a guidance document instead of a rule.

(17.) A few comments stated that FDA should enforce existing laws and regulations, remove unsafe products from the market, take action against dietary supplements that make "extravagant, unsubstantiated" claims, or promote educational activities instead of issuing regulations. One comment suggested that FDA resources would be better spent reviewing notices sent to the agency instead of issuing regulations. Another comment suggested that FDA continue to clarify issues on a case-by-case basis.

FDA disagrees with the comments. Regulations offer several important advantages that case-by-case clarification, individual enforcement actions, and educational activities generally cannot. For example, when FDA develops a regulation, it provides notice, obtains public comment, considers alternatives, and evaluates the rule's potential impacts, costs, and benefits. Individual enforcement actions and educational activities are not subject to these considerations.

Regulations also establish uniform, industry-wide requirements in a single administrative proceeding (rulemaking). In contrast, individual enforcement actions focus on distinct facts that may not lend themselves to uniform application to an entire industry. Moreover, enforcement actions are resource-intensive and require multiple steps, such as inspections, warning letters, and sometimes litigation, before they are completed. Educational activities may deal with general topics and provide valuable opportunities for discussing issues with FDA, but they do not create uniform requirements.

Regulations are also easier to locate because they are published in the **Federal Register** when they are issued, are codified and published in the Code of Federal Regulations (CFR) and can be found in libraries and on government Internet sites (such as the Government Printing Office's website at www.gpo.gov). In contrast, agency correspondence and results of individual enforcement actions are not as widely available and may be difficult for some regulated entities and consumers to obtain.

Thus, when it comes to establishing uniform, industry-wide requirements, conserving agency resources, and providing public notice and an opportunity to comment, regulations are preferable to individual enforcement actions and educational activities.

(18.) A comment suggested that FDA adopt an approach like hazard analysis critical control point (HACCP) instead of issuing the rule.

FDA disagrees with the comment. HACCP is best suited for issues relating to how a product is manufactured. Here, the principal issue is the claims made for a product rather than how the product is made.

(19.) A comment stated that FDA lacks the expertise to determine whether a botanical is a drug or a dietary supplement. The comment explained that botanicals can be used for medicinal purposes, but that they can also be used for promoting general well being and supporting the structure or function of the body. According to the

comment, FDA declared Yellowdock, an herb, to have medicinal purposes only, when the herb also had a long history of use as a food source.

The comment may have misinterpreted the rule. The focus of this rule is not on whether a substance has a history of use as a food but on claims made in the product's labeling. The rule defines the types of statements that may be made concerning a dietary supplement's effect on the structure or function of the body. FDA has many years of experience in regulating and interpreting health-related product claims.

(20.) One comment said other countries (naming several European nations) and the World Health Organization have established lists of ingredients and botanical products that are safe and permitted for therapeutic purposes. The comment suggested that FDA consider assembling a committee to establish a similar list for the United States.

A list of dietary ingredients and botanical products and their therapeutic uses might provide valuable information. Nevertheless, section 403(r)(6) of the act permits only structure/function claims for dietary supplements that are not also disease claims, and so such a list would not be relevant to this rulemaking.

(21.) Two comments suggested that FDA list examples of structure/function claims in order to reduce confusion. Another comment would have FDA describe both disease claims and structure/function claims.

FDA intends to issue a guidance document that will provide examples of claims that would and would not be considered disease claims. This final rule also includes many examples of structure/function and disease claims.

B. Permitted Structure/Function Statements (§ 101.93(f))

Proposed § 101.93(f) stated that dietary supplement labels and labeling may bear structure/function statements that are not disease claims within the meaning of proposed § 101.93(g) and that otherwise comply with the notification and disclaimer provisions of § 101.93(a) through (e). FDA is revising § 101.93(f) on its own initiative to make it clear that a dietary supplement may bear a disease claim if it is the subject of an authorized health claim, but that otherwise disease claims will subject the product to regulation as a drug.

C. Definition of Disease (§ 101.93(g)(1))

To assist in describing what constitutes a disease claim, the

proposed rule contained a definition of "disease." The proposed definition was based on standard medical and legal definitions of the term (Refs. 2, 3, 4, and 5). Proposed § 101.93(g)(1) defined "disease" as:

any deviation from, impairment of, or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of one or more signs or symptoms, including laboratory or clinical measurements that are characteristic of a disease.

The proposed definition would have replaced an earlier definition issued in 1993 as part of the regulations implementing the health claims provisions of NLEA. The implementing regulations require dietary supplement manufacturers to obtain prior authorization of any labeling statement that characterizes the relationship between a substance in the supplement to a "disease or a health-related condition" (section 403(r)(1)(B) of the act; § 101.14(a)(1)). The phrase "disease or health-related condition" was defined in those regulations as:

damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition * * *. Section 101.14(a)(5) (formerly § 101.14(a)(6)). The definition was redesignated as § 101.14(a)(5) effective March 23, 1999 (see 62 FR 49859, 49867).

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

In the July 8, 1999, **Federal Register** notice announcing a public meeting and reopening the comment period, FDA requested additional comment on the definition of disease. The notice listed four questions on which it sought specific comment: (1) What are the consequences, with respect to the range of acceptable structure/function claims, of adopting: (a) The 1993 definition in § 101.14(a)(5), or (b) the definition in the proposed rule? (2) If FDA were to retain the 1993 definition, does the reference to "damage" exclude any conditions that are medically understood to be diseases? Please provide examples. (3) If

it does not exclude any such conditions, is the 1993 definition otherwise consistent with current medical definitions of disease? (4) If it does exclude conditions that are medically understood to be diseases, could it be revised in a way that would include such conditions?

(22.) Almost all of the comments from the dietary supplement industry and from individuals objected to the new definition of disease. Most of these comments argued that the new definition is too broad, sweeping in many minor deviations or abnormalities that are not diseases. (Many of these comments did not appear to have understood that the definition required not only a deviation, but one that "is manifested by a characteristic set of one or more signs or symptoms.") One comment said that under the new definition wrinkles and gray hair would qualify as diseases. Some comments objected to the fact that the proposed definition was not limited to adverse deviations from normal structure or function. Other comments argued that the breadth of the proposed definition is inconsistent with the intent of DSHEA. Some comments objected to the distinction between normal and abnormal functions, and argued that Congress did not intend to limit structure/function claims to normal structure or function. Some comments contended that the definition of disease should not include the phrase "structure or function." Other comments said that Congress should be presumed to have been aware of the 1993 definition of "disease or health-related condition" and to have intended FDA to use that definition. Several comments argued that the new definition of "disease or health-related condition" for health claims would inappropriately broaden the scope of health claims for conventional foods and concomitantly narrow the scope of acceptable structure/function claims for foods. One comment said that redefining "disease or health-related condition" in § 101.14(a)(5) would undermine the existing definition of "statement of nutritional support," and would violate DSHEA and the First Amendment. Most of the comments from the dietary supplement industry and from individuals recommended that FDA return to the 1993 definition.

Most of the comments from health professional groups and groups devoted to specific diseases, including those who participated in the August 4, 1999, public meeting, supported the new definition of disease as more consistent with a medical understanding of disease than the NLEA definition. Some of these

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

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

A disease is any adverse deviation from, or impairment of, or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of one or more signs or symptoms that are not characteristic of a natural state or process. According to this comment, the addition of the word "adverse" appropriately narrows the nature of the deviation, "laboratory or clinical measurements" are appropriately deleted because they are already included under the concept of "signs," and the exclusion of natural states "encompasses Congress' intent to allow health promotion/maintenance claims." One comment suggested that, if FDA were to retain the 1993 definition, it add the word "impairment" after "damage" to cover those recognized disease conditions for which evidence of damage is missing. A pharmaceutical trade association urged FDA to convene a small workshop of physicians, patients, and other stakeholders to develop a consensus on the distinction between disease claims and structure/function claims.

In response to the comments, FDA has reconsidered the proposed definition of disease in § 101.93(g)(1), and has concluded that it is not necessary to change the 1993 health claims definition, because it can be construed in a manner that covers conditions that are medically understood to be diseases. In light of Congress' desire to increase

the number of claims that could be made for dietary supplements without subjecting them to drug regulation, FDA is persuaded that it is therefore appropriate to retain a narrower definition of disease at this time.

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

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

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

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

to a specific disease (e.g., 'helps prevent tumors')."

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

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

FDA does not agree that DSHEA was intended to permit structure/function claims about diseases that can normally be treated without a physician's care. Nothing in the statute or its legislative history suggests that Congress intended to accord different treatment to this subset of diseases. Diseases that do not ordinarily require a physician's care are generally those for which drugs may be sold over OTC. (OTC drug claims include both disease claims and structure/function claims.) Drugs carrying OTC claims are already regulated under rules different from those applicable to prescription drugs. FDA has undertaken a comprehensive review of OTC drug claims and published monographs on these claims. Had Congress intended to permit dietary supplements to make all OTC claims (both disease claims and structure/function claims) without prior review, it could easily have so indicated. Because Congress did not do so, FDA does not believe that there is support for treating this subset of diseases differently from other diseases. As discussed elsewhere in this document, the structure/function claims made for OTC drugs also may be made, in appropriate circumstances, for dietary supplements under section 403(r)(6) of the act.

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

FDA does not agree that its interpretation of a medical term like "disease" should ignore medical definitions of the term, unless there is

clear guidance from Congress that it intended a nonmedical definition of the term. In any case, the comment provided no argument or evidence that the 1993 definition was based on, or reflects, consumer understanding of the term "disease."

D. Disease Claims (§ 101.93(g)(2))

(26.) Many comments agreed with the statement in proposed § 101.93(g)(2) that, in determining whether a statement is a disease claim, it is appropriate to consider the context in which the claim is presented. One comment argued, however, that language of the regulation and preamble showed that FDA was biased because the agency would only consider the context of a claim to convert a dietary supplement to a drug.

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

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

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

(28.) Several comments from medical and consumer groups supported the establishment of criteria for structure/function claims, but were concerned that the criteria in the proposed rule were too vague and would fail to protect consumers from misleading claims. A major medical association contended that some of the structure/function claims listed as acceptable in the proposal were debatable and expressed doubt that the public health would be adequately protected. Some of these comments expressed the view that some of the structure/function claims listed in

the proposal in fact imply disease prevention. For example, some of these comments argued that health maintenance claims imply disease prevention. On the other hand, a comment from a major dietary supplement trade association argued that the overall impact of the criteria restricts the value of structure/function claims in providing consumers with useful information about dietary supplements.

FDA agrees that consumers should have access to, and be allowed to evaluate for themselves, as much truthful information about dietary supplements as is possible, consistent with the statutory restrictions on disease treatment and prevention claims. FDA believes that the criteria in this rule strike a reasonable balance between these competing goals. Undoubtedly, the criteria will not satisfy everyone. For example, some of the claims considered to be structure/function claims may imply specific disease prevention to some consumers. Because of the importance of the context in which a claim is presented, it will not always be possible to draw a line between structure/function and disease claims in this rule with great specificity. FDA believes that, within these constraints, the criteria, as finalized, adequately distinguish between structure/function claims and disease claims. In developing final criteria, the agency has tried to pay particularly close attention to claims that might relate to serious health conditions that patients cannot safely evaluate on their own. The question of whether health maintenance claims necessarily imply disease prevention is discussed in more detail below.

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

cup of tea." While the preamble to the proposed rule considered the claim of "improves absentmindedness" to be a structure/function claim, the comment viewed the same claim as a disease claim "because of the association of absentmindedness with Alzheimer's disease." The comment continued, "That claim should not be permissible for the same reason that a claim that a dietary supplement is an 'oral contraceptive' is not permissible—the claim is simply not one for the effects of a dietary ingredient."

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

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

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

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

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

from the scope of acceptable structure/function claims OTC monograph claims or other approved claims for products classified as drugs under section 201(g)(1)(C) of the act.

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

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

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

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

methods of substantiation may be more straightforward. Such an approach would turn section 403(r)(6) of the act on its head.

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

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

Under proposed § 101.93(g)(2)(i), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect on a specific disease or class of diseases. FDA included the following examples of such disease claims: "Protective against the development of cancer," "reduces the pain and stiffness associated with arthritis," "decreases the effects of alcohol intoxication," or "alleviates constipation." FDA included the following examples of claims that do not refer explicitly or implicitly to an effect on a specific disease state: "Helps promote urinary tract health," "helps maintain cardiovascular function and a healthy circulatory system," "helps maintain intestinal flora," and "promotes relaxation." FDA proposed to treat both express and implied disease claims as disease claims that could not be made for dietary supplements without prior review either as health claims or as drug claims. Implied disease claims do not mention the name of a specific disease, but refer to identifiable characteristics of a disease from which the disease itself may be inferred. There are many possible ways to imply treatment or prevention of disease, from listing the characteristic signs and symptoms of the disease to providing images of people suffering from the disease. Nine of the 10 criteria proposed by FDA for identifying disease claims could be considered methods of implying disease treatment or prevention.

In the July 8, 1999, **Federal Register** notice announcing a public meeting and reopening the comment period, FDA sought additional comment on the applicability of the rule to implied disease claims. The discussion in the notice offered three examples of possible implied disease claims: (1) "shrinks tumors of the lung" or "prevents development of malignant tumors" ("treats cancer" would be the corresponding express claim); (2) "prevention of seizures" ("treatment of

epilepsy" would be the corresponding express claim); (3) "relief of sneezing, runny nose, and itchy watery eyes caused by exposure to pollen or other allergens" ("treatment of hayfever" would be the corresponding express claim). The notice listed four questions related to implied disease claims on which the agency sought specific comments: (1) If implied disease claims should be permitted, has FDA correctly drawn the line between what constitutes an express disease claim and what constitutes a permitted implied claim? (2) If such claims should be permitted, what are representative examples of the types of implied disease claims that should be permitted without prior review? (3) Are the examples of implied claims mentioned in the July 8 notice appropriate structure/function claims? (4) Is a claim that a product "maintains healthy function" an implied disease claim in all cases? If not, under what circumstances is such a claim not an implied disease claim?

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

Many other comments objected to treating implied disease claims as disease claims, arguing that dietary supplements should be allowed to carry any truthful claim that does not explicitly refer to a specific disease. Some comments argued that Congress intended consumers to have access to as much information about supplements as possible. Other comments contended that barring implied disease claims eliminates any meaningful claims for dietary supplements. Other comments argued that treating implied claims as disease claims gives FDA "unlimited discretion" to treat structure/function

claims as disease claims. Some comments, however, agreed that disease claims may be implied as well as express, and said that it is appropriate to consider a structure/function statement in context to determine whether it conveys a disease claim.

FDA continues to believe that structure/function claims should not imply disease treatment or prevention. Most disease treatment or prevention claims, including claims about serious and life-threatening diseases, can be described in a manner that will be easily understood by consumers without express reference to a specific disease. The following examples of implied disease claims demonstrate that it is not difficult to convey prevention or treatment of a specific disease or class of diseases without actually mentioning the name of the disease, which are given in parentheses: "Relieves crushing chest pain" (angina or heart attack), "prevents bone fragility in post-menopausal women" (osteoporosis), "improves joint mobility and reduces joint inflammation and pain" (rheumatoid arthritis), "heals stomach or duodenal lesions and bleeding" (ulcers), "anticonvulsant" (epilepsy), "relief of bronchospasm" (asthma), "prevents wasting in persons with weakened immune systems" (AIDS) (acquired immune deficiency syndrome), "prevents irregular heartbeat" (arrhythmias), "controls blood sugar in persons with insufficient insulin" (diabetes), "prevents the spread of neoplastic cells" (prevention of cancer metastases); "antibiotic" (infections), "herbal Prozac" (depression). The distinction between implied and express disease claims is thus, in many cases, a semantic one that has little, if any, practical meaning to consumers. The argument that Congress intended to encourage the free flow of information about dietary supplements and therefore intended to permit implied disease claims is illogical. If Congress wanted to ensure that consumers receive information about how these products can treat or prevent diseases, it is difficult to imagine why it would have specifically denied the right to make such claims expressly, and allowed manufacturers to make the claims only by implication.

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

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

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

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

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

Second, section 403(r)(6) of the act states that structure/function statements may not "claim" to treat or prevent disease, and, according to the comments, this term should be read to refer only to express claims. Some comments noted that section 403(r)(6) of the act does not use the word "implied" to qualify the term "claims," and contrasted the language of the drug definition in section 201(g)(1)(B) of the act ("articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease") with the

language of section 403(r)(6)(C) of the act, which states that a structure/function statement may not "claim" to diagnose, cure, mitigate, treat, or prevent disease. One comment agreed with the proposal's statement that while DSHEA authorizes structure/function claims that are not also disease claims, but nevertheless asserted that the statute authorizes structure/function claims that imply "some protection against disease." This comment reasoned that the act, as amended by DSHEA, allows dietary supplements to be "intended" to affect the structure or function of the body, provided that the product does not "expressly claim to prevent, etc. disease" (emphasis in original) and the product bears "an express, formal disclaimer of an intent to prevent, etc. disease." The comment also said that the Commission report only referred to express claims.

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

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

As described above, Congress created a partial exemption for dietary supplements from the definition of drug in section 201(g)(1)(C) of the act by providing that truthful and non-misleading claims under section

403(r)(6) of the act do not in themselves trigger drug regulation. Congress did not, however, create any exemption from section 201(g)(1)(B) of the act for dietary supplements. Thus, dietary supplements that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" are subject to regulation as drugs under the act. It has been FDA's longstanding interpretation of section 201(g)(1)(B) of the act that the phrase "intended for use" refers to the objective intent of the manufacturer, which is not limited to a manufacturer's express representations. See § 201.128 (21 CFR 201.128); *NNFA v. Weinberger*, 557 F.2d 325, 334 (2d Cir. 1977) ("the FDA is not bound by the manufacturer's subjective claims of intent," but may establish intent "on the basis of objective evidence"). Evidence of objective intent can come from a variety of sources, and may include both implied and express claims (*United States v. Undetermined Quantities* * * * *Pets Smellfree*, 22 F.3d 235 (10th Cir. 1994); *United States v. Storage Spaces Designated Nos. "8" and "49"*, 777 F.2d 1363, 1366 (9th Cir. 1985) ("intent may be derived or inferred from labeling, promotional material, advertising, or any other relevant source"), *cert. denied*, 479 U.S. 1086 (1987); *United States v. Kasz Enterprises, Inc.* 855 F. Supp. 534, 539, 543-44 (D.R.I. 1994), *modified on other grounds*, 862 F. Supp. 717 (D.R.I. 1994); *United States v. Articles of Drug* * * * *Neptune*, 568 F. Supp. 1182 (N.D. Ca. 1983); *United States v. Vitasafe*, 226 F. Supp. 266 (D.N.J. 1964); *United States v. 14 105 Pound Bags* * * * *Mineral Compound*, 118 F. Supp. 837 (D.C. Idaho 1953); *United States v. 43 1/2 Gross Rubber Prophylactics*, 65 F. Supp. 534, 535 (D. Minn. 1946), *aff'd sub nom. Gellman v. United States*, 159 F.2d 881 (8th Cir. 1947); 59 FR 6084, 6088 (February 9, 1994) (terms "antibacterial," "antimicrobial," "antiseptic," or "kills germs" constitute implied drug claims that cause products carrying them to be drugs); 58 FR 47611, 47612 (September 9, 1993) (labeling indicating that "hormones" are present in a product constitutes implied drug claim); 58 FR 28194, 28204 (May 12, 1993) (products carrying term "sunscreen" are drugs because "sunscreen" implies disease prevention, even if not expressly promoted for prevention of skin cancer)).

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

Permitting implied disease claims as structure/function claims would also conflict with the health claims scheme established in section 403(r)(1) through (r)(1)(5) of the act, which requires food and dietary supplement manufacturers to obtain health claim authorization before making a claim "which expressly or by implication" characterizes the relationship of a nutrient to a disease or health-related condition. Under this provision, a claim that characterized, by implication, the relationship between a dietary supplement ingredient and a disease would require authorization as a health claim. Interpreting section 403(r)(6) of the act as permitting the same implied claim without authorization of a health claim directly conflicts with 403(r)(1) through (r)(1)(5) of the act.

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

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

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

prevention of disease." FDA has interpreted section 201(g)(1)(B) of the act to cover both express and implied claims for more than 50 years. Had Congress intended 403(r)(6) of the act to permit any claims covered by section 201(g)(1)(B) of the act, it would have had to provide an exemption from the latter section.

Further, FDA does not agree that the Commission report referred only to express claims. In its guidance on statements under section 403(r)(6) of the act, the Commission specifically said that such statements "should be distinct from NLEA health claims in that they do not state or imply a link between a supplement and prevention of a specific disease or health-related condition" (the report, p. 38) (emphasis added). In addition, the Commission cautioned that claims using terms such as, e.g., "support," "maintain," or "promote" are appropriate only if they do not "suggest disease prevention or treatment or use for a serious health condition that is beyond the ability of the consumer to evaluate" (the report, p. 38) (emphasis added). Clearly, the Commission was concerned about implied claims as well as express claims.

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

(36.) A few comments addressed the examples of implied claims listed in the July 8, 1999, **Federal Register** notice. Some comments said that all of the examples were appropriate structure/function claims. Two comments suggested that “shrinks tumors,” “prevents development of malignant tumors,” and “prevents seizures” are express disease claims because they employ “synonyms” for specific diseases. According to these comments, “tumor” is a synonym for cancer, and “seizure” is a synonym for epilepsy. Another comment said that FDA should treat as implied disease claims only those claims “where there is a direct causal relationship between the structure/function parameter identified in the claim and a specific known disease.” According to this comment, a tumor is a “direct manifestation of cancer” and therefore reference to a tumor is a disease claim. In contrast, risk factors for disease, in which the comment includes elevated cholesterol, are not direct manifestations of a disease, and therefore may be the subject of structure/function claims. Another comment contended that disease claims should be limited to express claims and to terms or measurements that are “surrogates for the disease itself.” According to this comment, tumors are a surrogate for cancer, but elevated cholesterol is not a surrogate for heart disease. One comment argued that “relief of sneezing, runny nose, and itchy watery eyes caused by exposure to pollen or other allergens” is an acceptable structure/function claim, but did not explain why.

FDA has considered these comments, but does not believe that any of them have provided a principle that distinguishes between claims that consumers will understand as disease claims and those that will not be understood as disease claims. According to the comments, some of the claims that FDA offered as examples of implied disease claims should not be allowed as structure/function claims. FDA agrees that claims that refer to synonyms for disease, direct manifestations of disease, and surrogates for disease are disease claims. Each of these principles, however, would permit many types of implied disease claims that would be clearly understood by consumers as disease claims, e.g., “Herbal Prozac” and “antibiotic.”

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

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

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

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

FDA has considered the comments on constipation and agrees that certain constipation claims should not be treated as disease claims. Constipation has a variety of causes, many of them unrelated to disease. For example, constipation can be caused by changes in diet and schedule, and by travel. Constipation can also, however, be a symptom of such serious diseases as bowel obstruction and irritable bowel syndrome. FDA is aware that there may be differences of opinion about whether occasional constipation, alone, constitutes a disease, but believes that treating it as a disease would not be consistent with the intent of DSHEA. “For relief of occasional constipation” would therefore not be considered a disease claim under the rule. The labeling of a product that claimed to treat occasional constipation should make clear, however, that the product is not intended to be used to treat chronic constipation, which may be a symptom of a serious disease.

(39.) One comment questioned whether a claim that begins, “According

to the National Cancer Institute” would be a disease claim because it used the word “cancer.”

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

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

Under proposed § 101.93(g)(2)(ii), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect (using scientific or lay terminology) on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific disease or of a number of diseases. FDA provided as examples of such disease claims: “Improves urine flow in men over 50 years old,” “lowers cholesterol,” “reduces joint pain,” and “relieves headache.” Stating that claims of an effect on symptoms that are not recognizable as characteristic of a specific disease or diseases would not constitute disease claims, FDA provided the following examples of acceptable structure/function claims: “Reduces stress and frustration,” “inhibits platelet aggregation,” and “improves absentmindedness.” The agency also stated that if the context did not suggest treatment or prevention of a disease, a claim that a substance helps maintain normal function would not ordinarily be a disease claim. Examples included: “Helps maintain a healthy cholesterol level,” or “helps maintain regularity.”

FDA specifically requested comment on the distinction between maintaining normal function, which is potentially the basis for an acceptable structure/function claim, and preventing or treating abnormal function, which is potentially a disease claim. FDA noted that the members of the Commission were divided on this issue, but that the final report concluded that “statements that mention a body system, organ, or function affected by the supplement using terms such as ‘stimulate,’ ‘maintain,’ ‘support,’ ‘regulate,’ or ‘promote’ can be appropriate when the statements do not suggest disease prevention or treatment or use for a serious health condition that is beyond the ability of the consumer to evaluate” (the report, p. 38). Recognizing that

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

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

FDA agrees with these comments that the proposal’s focus on recognition of signs and symptoms by consumers or health professionals might have made the provision difficult to apply, both for manufacturers and for the agency. Accordingly, the agency has substituted a more objective criterion. The final rule eliminates the reference to recognition, and focuses simply on whether the labeling suggests that the product will produce a change in the characteristic signs or symptoms of a specific disease or class of diseases. FDA believes that it will be easier for manufacturers to verify whether symptoms are in fact characteristic of a disease. FDA and manufacturers may look to medical texts and other objective sources of information about disease to determine whether a label implies treatment or prevention of disease by listing the characteristic signs and symptoms of a disease or class of diseases.

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

FDA does not agree with the comment that objected to the recognition standard because it would prohibit a claim “as soon as consumers understood that certain signs and symptoms are characteristic of a disease—that is, as soon as consumers understood why they should take a particular supplement * * *.” This comment assumes that the only reason people take dietary supplements is to treat or prevent disease and that it is appropriate to market supplements by implying that they can do so. Many people take dietary supplements for health-related reasons that do not involve treatment or prevention of specific diseases. As discussed elsewhere in this document, FDA does not believe that the act permits structure/function claims to imply treatment or prevention of specific diseases.

(41.) Several comments contended that the recognition standard was too restrictive because all signs or symptoms relating to the structure or function of the body are potentially recognizable to health care professionals and educated consumers as characteristic of some specific disease. Another comment argued that the proposal to treat references to signs and symptoms as disease claims was arbitrary and artificial. The comment said that specific examples of disease claims used in the proposal could as easily refer to nondisease states, e.g., “reduces joint pain” could refer to over-exercise. Conversely, “stress and frustration” could refer to anxiety and depression. Another comment contended that “reduces joint pain” is an acceptable structure/function claim if other language or graphics in the labeling clearly communicated treatment of conditions unrelated to arthritis. One comment asked whether “helps support cartilage and joint function” would constitute a permissible structure/function claim. Some comments said that references to signs and symptoms should not be evidence of a disease claim because signs and symptoms can be associated with a number of varying conditions. One comment claimed that “inhibits platelet aggregation” does not mean anything to most consumers. On the other hand, some medical groups, groups devoted to specific diseases, and others expressed concern that the examples of structure/function claims provided by FDA permitted references to signs or symptoms that imply disease treatment or prevention. According to one comment, “inhibits platelet aggregation” could be interpreted to mean “prevents heart attack,” and

“improves absentmindedness” could be interpreted as a treatment for Alzheimer’s disease.

FDA believes that removing the reference to recognition by consumers or health professionals from § 101.93(g)(2)(ii) will permit a clearer distinction between those signs and symptoms that imply a disease and those that do not. The focus will be on whether specific signs or symptoms are characteristic of a disease, based on objective sources. FDA does not believe that “improves absentmindedness” or “relieves stress and frustration” are characteristic of the specific diseases mentioned in the comments. FDA agrees that some signs and symptoms are associated with such a wide variety of diseases and nondisease states that they may not imply a specific disease or class of diseases. For example, FDA would not interpret “improves absentmindedness” as implying treatment of Alzheimer’s disease because absentmindedness is not as serious as the type of memory loss characteristically suffered by Alzheimer’s patients; absentmindedness is, in fact, suffered predominantly by people who do not have Alzheimer’s disease or any other disease. Stress and frustration, while associated with some anxiety disorders, are not the characteristic symptoms of those disorders; in addition, these symptoms are equally associated with many other nondisease states.

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

FDA also believes that “joint pain” is characteristic of arthritis. According to the Merck Manual, joint tenderness is the most sensitive physical sign of rheumatoid arthritis (Ref. 6). The claim “helps support cartilage and joint

function,” on the other hand, would be a permissible structure/function claim, because it relates to maintaining normal function rather than treating joint pain.

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

FDA agrees in part and disagrees in part with this comment. The agency agrees that references in dietary supplement labeling to physiologic markers or symptoms of a disease that are quantifiably linked to that disease in an official government health agency summary statement or consensus report would be appropriately treated as implied disease claims. Indeed, in the cases described, elevated blood pressure (hypertension) and elevated cholesterol (hypercholesterolemia) are diseases themselves, with subsequent events (heart attack, stroke) the late consequences of those diseases.

Although FDA agrees that fever and elevated white cell counts are almost always evidence of a disease, FDA does not agree that the second criterion appropriately describes the remaining circumstances in which references to signs or symptoms should be treated as disease claims. The appropriate test is whether: (1) The condition to be treated or prevented is a disease and (2) the signs and symptoms referred to in the labeling, in context, are characteristic of a disease and thus permit the inference that the product is intended to treat or prevent the disease. The second criterion offered by the comment does not provide information on either of these elements.

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

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

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

The basis for determining whether such a reference to signs or symptoms constitutes an implied disease claim is not whether the definition of disease includes mention of signs or symptoms. Rather, FDA looks at whether the objective evidence shows that the product is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” within the meaning of section 201(g)(1)(B) of the act and § 201.128, or the claim constitutes a health claim within the meaning of section 403(r)(1)(B) of the act and § 101.14(a)(1). For example, § 201.128 provides that the objective intent of those responsible for the labeling of drugs “is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article.” Section 101.14(a)(1) provides that “[i]mplied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition.” Both of these provisions permit FDA to look at whether a reference to the characteristic signs or symptoms of a disease constitute an implied disease claim.

(44.) Many comments argued that the distinction between claims that a product maintains healthy function and that it prevents or treats abnormal function is artificial, and that consumers understand both types of claims as disease treatment or prevention claims.

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

One comment said that the proposed rule would frustrate the “orphan drug” process. The comment contended that if dietary supplement labeling may claim to promote or maintain “healthy” endpoints that are related to signs and symptoms of specific diseases, then incentives to conduct research on orphan drugs would be undermined. The comment explained that dietary supplements do not require the same financial investment as drugs do (because drugs must be approved as safe and effective for their intended uses and meet quality controls), and could undercut sales of a more heavily regulated and more expensive approved drug. The comment said that a dietary supplement manufacturer’s ability to make a disease prevention claim by characterizing the product as promoting good health “cannot become a license to sell an active ingredient in a product

that is functionally a drug but is labeled as a dietary supplement.”

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

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

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

For the reasons described elsewhere in this document, however, FDA does not believe that DSHEA permits claims concerning treatment or prevention of abnormal function, where such abnormal function implies a specific disease or class of diseases. Accordingly, FDA believes that the statutory scheme is consistent with treating many health maintenance statements as structure/function claims, while treating as health claims or new drug claims statements that imply disease treatment or prevention by reference to an effect on abnormal structure or function.

The Commission report also supports the distinction drawn by FDA between maintaining healthy function and

preventing or treating abnormal function. The report’s Guidance states:

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

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

(Report at pp. 38 and 39.)

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

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

(45.) Many comments responded to FDA’s specific request for comment on whether it is appropriate to treat “maintains healthy cholesterol levels” as a permissible structure/function claim, while treating “lowers cholesterol” as a disease claim. A few comments supported the distinction drawn in the proposed rule. Many did not, however. One comment from a major trade association claimed that the distinction between lowering and maintaining cholesterol levels is ambiguous, asking “What is a healthy

cholesterol level, but a lower cholesterol level?” Another comment from a food industry group contended that “cholesterol” itself is a sign or symptom, and thus that both types of claims refer to a sign or symptom of disease. Several comments argued that lowering cholesterol is inextricably linked to cardiovascular disease. Some comments argued that the distinction between maintaining normal cholesterol and lowering cholesterol is arbitrary because both have as their purpose preventing heart disease, and consumers link cholesterol levels with disease prevention. Other comments, however, argued that cholesterol claims do not imply disease prevention. A comment from an organization devoted to prevention and treatment of heart disease argued that if any cholesterol claims were to be permitted, a claim like “promotes cholesterol clearance” would be a more accurate structure/function statement than “maintains healthy cholesterol” and less likely to imply disease prevention. 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(g)(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 of 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.

(69.) 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.

O. 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 Phen-fen," 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 of 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 indigestion" 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 *Nutrilib, 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 labeling, promotional material, advertising, and 'any other

relevant source'" (557 F.2d at 334 (citations omitted)). See also § 201.128 (listing evidence FDA will consider in determining the intended use of a drug).

(104.) One comment said that the proposal must be withdrawn because, contrary to section 403(r)(6) of the act, it gives manufacturers the burden to prove that a claim is not a drug claim when, in fact, FDA has the burden, by a preponderance of relevant evidence, to establish that a dietary supplement is misbranded. The comment cited two court opinions, *United States v. 29 Cartons * * * an Article of Food (Oakmont)*, 987 F.2d 33 (1st Cir. 1993) and *United States v. An Article of Food * * * Viponte Ltd. Black Currant Oil*, 984 F.2d 814 (7th Cir. 1993), for the proposition that, before DSHEA was enacted, courts had invalidated an FDA enforcement theory that shifted the burden of proof to manufacturers.

FDA disagrees with this comment. Although the comment is correct that FDA has the burden of proving that a dietary supplement—or, in fact, any food—is misbranded, the rule does not give manufacturers the burden of proving that a claim is not a drug claim. The rule does not shift the burden of proof in an enforcement action but rather sets forth criteria for what claims are disease claims that may subject a product marketed as a dietary supplement to regulation as a drug.

The two cases cited in the comment are inapposite. They concern FDA's efforts to regulate certain dietary ingredients as food additives and do not have any relevance to claims issues.

(105.) One comment said that the proposed rule is inconsistent with the act and congressional intent, arguing that, by enacting DSHEA, Congress had taken steps to reverse FDA's "overly restrictive" approach towards claims and had commanded the agency to expand, rather than restrict, the amount of health information permitted on dietary supplement labels and labeling. According to the comment, the proposal "directly and substantially violates the overall statutory scheme and the expressed legislative intent" and FDA "has no authority to proceed with the rulemaking without a grant of authority from Congress in light of the Act's language and Congressional intent."

The agency disagrees with this comment and believes that the rule is consistent with the act and congressional intent. Although Congress, in enacting DSHEA, did expand the scope of information in dietary supplement labeling by providing for claims to affect the structure or function of the body and the other types of claims authorized by

section 403(r)(6) of the act, Congress also explicitly limited statements under section 403(r)(6) to those that do not claim to “diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases.” This rule does not create new restrictions but merely implements the provisions of section 403(r)(6) of the act. FDA has authority to issue implementing regulations under section 701(a) of the act, which authorizes the agency to issue regulations for the efficient enforcement of the act.

(106.) One comment declared that FDA has no legal basis to include a broad variety of implied claims.

FDA disagrees with this comment. The agency has regulated implied claims in labeling for many years, in many contexts. (See, e.g., 21 CFR 104.5(b) and (d) (prohibiting certain implied claims relating to compliance with nutritional quality guidelines); 21 CFR 101.13(a) (classifying implied claims to characterize the level of a nutrient in food as nutrient content claims subject to the same requirements as express claims); 21 CFR 101.95 (prescribing conditions under which implied claims of freshness may be made for foods); 21 CFR 201.10(c)(3) (prohibiting use in ingredient statement of fanciful drug or ingredient names that falsely imply that the drug or ingredient has some unique effectiveness or composition); 21 CFR 201.302(c) (prohibiting implied claims that drugs for internal use that contain mineral oil are for administration to infants). The agency has also regulated implied claims in prescription drug advertising. (See, e.g., § 202.1(a)(3) (21 CFR 202.1(a)(3)) (prohibiting use in advertising of fanciful product or ingredient names that falsely imply that the drug or ingredient has some unique effectiveness or composition); § 202.1(e)(6)(v) (prohibiting implied claims that a study represents more widespread experience with the drug than it actually does).) More specifically, the agency has repeatedly taken the position that implied disease claims in labeling subject a product to regulation as a drug. In the animal drug context, § 500.52 (21 CFR 500.52) provides that the use of certain terms in the labeling of products intended for use in or on animals implies that the product is capable of a therapeutic effect and causes the product to be a drug within the meaning of section 201(g) of the act. In the human drug context, § 201.56(c) (21 CFR 201.56(c)) prohibits “implied claims or suggestions of drug use” in prescription drug labeling unless the product has been shown to be safe and effective for the implied or suggested use. (See also § 310.530 (21

CFR 310.530) (use of the word “hormone” in labeling is an implied drug claim.) Moreover, courts have upheld FDA’s authority to regulate implied drug claims. (See, e.g., *United States v. Storage Spaces Designated Nos. “8” and “49”*, 777 F.2d 1363, 1366 & n. 5 (9th Cir. 1985), *cert. denied*, 479 U.S. 1086 (1987); *Pasadena Research Labs., Inc. v. United States*, 169 F.2d 375, 383 (9th Cir.), *cert. denied*, 335 U.S. 853 (1948); *United States v. Six Dozen Bottles * * ** “*Dr. Peter’s Kuriko*”, 158 F.2d 667, 669 (7th Cir. 1947); *United States v. John J. Fulton Co.*, 33 F.2d 506, 507 (9th Cir. 1929); *Bradley v. United States*, 264 F. 79, 81–82 (5th Cir. 1920); *United States v. Kasz Enterprises, Inc.*, 855 F. Supp. 534, 539, 543–44 (D.R.I. 1994), *modified on other grounds*, 862 F. Supp. 717 (D.R.I.1994); *United States v. 43 1/2 Gross Rubber Prophylactics*, 65 F. Supp. 534, 535 (D. Minn. 1946), *aff’d sub nom. Gellman v. United States*, 159 F.2d 881 (8th Cir. 1947).)

(107.) Many comments argued that the proposed rule ignored the Supreme Court decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993).

FDA disagrees with these comments. The comments did not explain how the rule was contrary to or even affected by the decision. *Daubert* involved the admissibility of scientific evidence in a judicial proceeding under the Federal Rules of Evidence. This rulemaking does not present issues regarding the admissibility of evidence in any proceeding, judicial or administrative, nor does it address expert testimony (which was at issue in *Daubert*). Thus, FDA does not agree that the rule “ignores” or is contrary to the *Daubert* decision.

C. Constitutional Issues

1. First Amendment

(108.) Several comments focused on the First Amendment. One comment argued that the rule violates the First Amendment because it is more restrictive than is necessary to advance FDA’s interests. The comment conceded that the government may regulate or prohibit commercial speech if the speech is inherently false, deceptive, or misleading, but argued that the government can only restrict commercial speech that is not false, deceptive, or misleading if the government shows that the restriction directly and materially advances a substantial state interest in a manner that is no more extensive than necessary to serve that interest (citing *Ibanez v. Florida Dept. Of Bus. & Prof’l Regulation*, 512 U.S. 136, 142 (1994);

Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n, 447 U.S. 557, 566 (1980)). The comment argued that not all structure/function claims prohibited under the proposed rule are inherently false or misleading and that if FDA does not review the evidence for a claim, the claim does not become false or misleading. Although the comment admitted that FDA has a substantial interest in regulating the safety, efficacy, and labeling of dietary supplements in order to protect the public health, the comment claimed that the regulation was more extensive than necessary. The comment argued that a disclaimer is “the constitutionally mandated method of regulating commercial speech.”

Other comments said the proposed rule violates the First Amendment because, using the analysis in *Central Hudson Gas & Electric Corp. v. Public Service Commission*, 447 U.S. 557 (1980), it is not narrowly tailored to meet FDA’s interests and does not directly and materially advance the agency’s interests. In general, these comments offered various reasons why the proposed rule did not survive scrutiny under *Central Hudson*. For example, under *Central Hudson*, the government may regulate commercial speech that concerns unlawful activity or is misleading if, among other things, the government asserts a substantial interest in support of its regulation. In brief, the comments said FDA failed to assert a substantial interest or construed the government’s interest to be Congress’ interest in increasing the amount of information to consumers. Others said that, contrary to *Central Hudson*, the proposed rule was not narrowly tailored and suppressed more speech than necessary to protect a possible government interest in protecting consumers from fraud and protecting public health and either suggested alternatives or said FDA should consider less restrictive alternatives. Some comments said the proposal also did not advance the asserted government interest because it blurred, instead of clarified, the line between drug and dietary supplement claims.

One comment also asserted that there is no substantial government interest involved, because FDA has not shown a concern for consumer safety or a danger to public health; according to this comment, the proposed rule was a response to confusion by manufacturers and consumers about what claims are permitted.

Some comments also argued that FDA has not shown that the claims are misleading or that the commercial speech covered by the proposed rule is

inherently misleading. One comment asserted that, if statements were untruthful or misleading, DSHEA would have prohibited them.

Another comment said the proposal "trenches on" the First Amendment because consumers have the right to receive, and manufacturers have the right to express, non-misleading information. The comment cited *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998) for this proposition. Another comment cited the *Washington Legal Foundation* decision to argue that the proposed rule would "impermissibly curtail" the flow of information to consumers. The comment suggested that less restrictive alternatives, such as "allowing implicit, but not explicit, claims," establishing "categories of diseases that clearly denoted drug claims" or identifying terms that connote "treatment," "cure," or "mitigation" exist.

A few comments simply claimed that the proposal violates the First Amendment because it would decrease the amount of scientific information on labels and labeling or because it represents a "prior restraint" on health claims. Other comments objected to particular provisions of the proposed rule on First Amendment grounds, notably proposed § 101.93(g)(2)(iv)(C), which provided that citation of the title of a scientific reference in dietary supplement labeling would be a disease claim if the title referred to a disease use of the product. Several comments said that this provision of the proposed rule would violate the First Amendment as an unlawful restraint on commercial speech. Others characterized the proposed provision as simply a restriction on freedom of speech, whether the restriction was on the right of companies to provide the information or on the right of consumers to receive the information. One comment said that references to publication titles could be prohibited if they were misleading, but that the rule should not contain a blanket prohibition. Some comments added that the agency should reconsider its position on this provision in light of *Washington Legal Foundation v. Friedman*.

Finally, a comment said that the proposal was contrary to the decision of the U.S. Court of Appeals for the District of Columbia Circuit in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999). According to the comment, the court of appeals' First Amendment ruling in *Pearson* requires the agency to permit health claims that do not satisfy the "significant scientific agreement" standard as long as the claim can be

rendered non-misleading by requiring a disclaimer. According to the comment, the court's decision also requires FDA to further define the "significant scientific agreement" standard for authorizing dietary supplement health claims. The comment said that the proposed rule was premature in light of the need to amend the health claims regulations to conform to the *Pearson* decision. The comment also argued that, in light of *Pearson*, FDA may not issue a final rule that prohibits disease claims but rather must choose the less restrictive alternative of permitting such claims provided that they are accompanied with disclaimers.

FDA does not believe that the rule violates the First Amendment. The rule does not prohibit any speech; rather, it clarifies the circumstances under which FDA will consider a certain type of speech—labeling claims—to be evidence of intended use as a drug, absent health claim authorization. Thus, the rule does not regulate speech as such, but rather as evidence of intended use. The use of speech as evidence of a company's intended use for its products is constitutional because "[t]he First Amendment * * * does not prohibit the evidentiary use of speech * * * to prove motive or intent" (*Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993)). (See also *Village of Hoffman Estates v. Flipside*, 455 U.S. 489, 495–96 (1982) (upholding village ordinance treating the proximity of drug-oriented literature as evidence that items were marketed for use with illegal drugs). Because it is the intent and not the speech that triggers a regulatory burden on the speaker, there is no First Amendment violation. (See *Wisconsin v. Mitchell*, 508 U.S. at 489; *United States v. Articles of Drug * * * B-Complex Cholinol Capsules*, 362 F.2d 923, 927 (3d Cir. 1966) (no impingement on free speech for FDA to use statements made by a lecturer employed by a manufacturer as evidence of the manufacturer's intent that its products be used for therapeutic purposes).)

Even if the rule were viewed as a direct restriction on speech, it would not violate the First Amendment. The marketing in interstate commerce of a drug that has not been determined by FDA to be safe and effective is illegal (see section 301(a) and (d) of the act (21 U.S.C. 331(a) and (d)) and 505 of the act. Thus, labeling claims that promote a dietary supplement for disease uses promote the product for use as an unapproved new drug, which is illegal. Speech promoting an illegal activity may be restricted without violating the First Amendment (*Central Hudson*, 447 U.S. at 563–564). In *Pittsburgh Press Co.*

v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376 (1973), the Supreme Court held that an advertisement could be prohibited where it indicated that the advertiser was likely to have an illegal intent while engaging in the proposed transaction (*id.* at 389). There, as here, "the restriction * * * is incidental to a valid limitation on economic activity" (*id.*).

Nor does the rule create an unconstitutional prior restraint. FDA does not believe that the regulations in § 101.93(f) and (g) are properly analyzed as a prior restraint at all. As explained previously, the regulations do not restrict speech but rather treat it as evidence of a product's intended use. Using speech to infer intent does not violate the First Amendment (*Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993)). Thus, the regulations do not prevent speech from happening, but, as evidence of intended use, they determine the consequences that result from certain types of speech. (See *Village of Hoffman Estates v. Flipside*, 455 U.S. at 495–96 (rejecting head shop's "exorbitant" claim that village ordinance treating the proximity of drug-oriented literature as evidence of intended use was a prior restraint).)

Although the regulations cannot themselves be considered as a direct prior restraint, it is true that claims classified as disease claims under the regulations are subject to prior authorization requirements that could be considered prior restraints—namely, the prior authorization requirement for dietary supplement health claims and the new drug approval requirements that are triggered in the absence of health claim authorization. In both cases, a disease claim cannot be made until FDA has evaluated the safety of the product and the evidence supporting the claim. However, labeling claims are commercial speech, and the Supreme Court has indicated that the prior restraint doctrine may not apply to commercial speech. (See *Central Hudson*, 447 U.S. at 571 n.13 ("[C]ommercial speech is such a sturdy brand of expression that traditional prior restraint doctrine may not apply to it."; *Virginia State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 771–72 n.24 (1976) (greater objectivity and hardness of commercial speech may make prior restraint doctrine inapplicable). Commercial speech is "sturdy" because of its profit motive. "[S]ince advertising is the *sine qua non* of commercial profits, there is little likelihood of its being chilled by proper regulation and forgone entirely" (*Virginia State Bd. of Pharmacy*, 425 U.S. at 771–72 n.24). The same is true

of labeling. The Supreme Court has expressed approval of prior review requirements in commercial speech cases. (See *Shapiro v. Kentucky Bar Ass'n*, 486 U.S. 466, 476 (1988) (lawyer may be required to file solicitation letter with State in advance, to give it "ample opportunity to supervise mailings and penalize actual abuses"); *Central Hudson*, 447 U.S. at 571 n.13 (State may require "a system of previewing advertising campaigns").)

If the prior authorization requirement for dietary supplement health claims and the approval requirement for new drugs were to be considered prior restraints, they would be constitutional prior restraints. The only court of appeals to address the issue in the health claims context ruled that the health claims authorization process is not an unconstitutional prior restraint. In a recent case challenging the NLEA and FDA's health claim regulations for dietary supplements, the U.S. Court of Appeals for the Second Circuit held that the prior restraint doctrine did apply, but it went on to uphold the statute and regulations based on consideration of the *Central Hudson* factors. *Nutritional Health Alliance v. Shalala*, 144 F.3d 220, 227–28 (2d Cir.), cert. denied, 119 S. Ct. 589 (1998). In *Nutritional Health Alliance*, the Second Circuit held that the health claims authorization process is "sufficiently narrowly tailored" and has adequate procedural safeguards—including a deadline for final agency action, a decision making standard to constrain the agency's discretion, and provision for development of a record for judicial review—to render it constitutionally valid (144 F.3d at 228; see § 101.70 (procedures for petitioning for a health claim)). In upholding the regulatory scheme, the court also stressed that matters of public health and safety were involved (144 F.3d at 228). The same considerations that the court in *Nutritional Health Alliance* relied on also operate in the new drug approval context: Matters of public health and safety are involved, and the act and implementing regulations provide many procedural safeguards, including a deadline, a decision making standard, and the development of a record for judicial review (see section 505(c)(1), (d), and (h) of the act and; 21 CFR 314.200.) Moreover, as far as FDA is aware, the constitutionality of the new drug approval process has never been challenged on First Amendment grounds. Therefore, FDA does not believe that the prior restraint argument in the comments has merit.

Many of the comments assumed that the test for restrictions on commercial speech set forth by the Supreme Court

in *Central Hudson* applies. FDA believes that it is not necessary to reach the *Central Hudson* test because the rule is constitutional under *Wisconsin v. Mitchell*, *Pittsburgh Press*, and *Village of Hoffman Estates*; however, the rule also easily passes muster under the four-part test in *Central Hudson*. Under that test, the first question is whether the commercial speech at issue is false, misleading, or concerns unlawful activity, because such speech is beyond the First Amendment's protection and may be prohibited. If the speech is truthful, non-misleading, and concerns lawful activity, the government may nonetheless regulate it if the government interest asserted to justify the regulation is substantial; the regulation directly advances the asserted governmental interest; and the regulation is no more extensive than necessary to serve the government interest (*Central Hudson*, 447 U.S. at 566). The Supreme Court has explained that the last element of the test is not a "least restrictive means" requirement, but rather requires narrow tailoring—"a fit that is not necessarily perfect, but reasonable" between means and ends (*Board of Trustees of the State Univ. of N.Y. v. Fox*, 109 S. Ct. 3028, 3032–35 (1989)). In subsequent decisions, the Court has also clarified that "misleading" in the first element of the test refers to speech that is inherently or actually misleading. Thus, if the speech to be regulated is not inherently or actually misleading, the remainder of the test applies. (See *In re R.M.J.*, 455 U.S. 191, 203 (1982).)

As previously discussed, FDA believes that claims for disease uses that have not been found to be safe and effective are speech related to an unlawful activity, and therefore there is no need to reach the remaining elements of the *Central Hudson* test. The agency also considers such claims inherently misleading because, when accompanied by a disclaimer that directly contradicts the claim by stating that the product is not intended to have an effect on disease, they are inherently likely to confuse consumers rather than provide them with useable information. Speech that is "more likely to deceive the public than to inform it" is not protected by the First Amendment (*Central Hudson*, 447 U.S. at 563). If not inherently misleading, claims for disease uses that have not been found to be safe and effective are at least potentially misleading because of the confusion caused by the disclaimer. Such claims also may lead consumers to believe that the product has benefits in

treating or preventing disease, even if that is not the case.

Even if the remaining elements of the *Central Hudson* test are reached, the rule and the statutory provisions that it implements are constitutional. As previously noted, this rule restricts no speech directly. Rather, it determines what types of speech in dietary supplement labeling will trigger other statutory provisions and regulations that may be considered restrictions on speech. To the extent that this rule, the statute, and the drug and health claim regulations restrict speech by requiring either health claim authorization or new drug approval before a business may make a disease claim for a dietary supplement, that restriction directly advances the substantial government interest in protecting and promoting the public health by helping to ensure that products intended to have an effect on a disease are safe and effective for that intended use. That interest is an interest both in preventing direct harm from such products—i.e., protecting the public from adverse events that such products might cause—and in preventing the indirect harm to health that is caused when an ill person foregoes medical care in favor of ineffective self-treatment.

Requiring prior FDA review and authorization of disease claims ensures that such claims will be evaluated by a public health agency that has scientific and medical expertise so that only products that are safe and effective will be permitted to be sold for therapeutic purposes. As a government agency with no financial stake in either permitting or denying claims, FDA is in a position to evaluate the strength of the safety and efficacy evidence objectively.

The rule and the other components of the regulatory framework for drugs and health claims also advance the related substantial government interest in protecting consumers from fraud. If products are marketed for disease uses only after they have been demonstrated to be safe and effective for such uses, consumers will not suffer economic harm from spending money on worthless remedies.

Moreover, the rule is not more extensive than necessary. The agency does not believe that the alternatives mentioned in the comments, or any other alternative, would adequately further its substantial interest in protecting and promoting public health by ensuring the safety and efficacy of products intended to have an effect on disease. For example, allowing implicit disease claims, but not explicit ones, would merely allow companies to do indirectly what they cannot do

directly—to market products for disease uses without demonstrating their safety and efficacy. Likewise, identifying specific terms that connote treatment, cure, or mitigation would not accomplish the goal of requiring proof of the safety and effectiveness of products marketed for disease uses. Merely regulating synonyms for those terms would leave unregulated those claims that achieve the same effect without using such a synonym, such as the claims “herbal Prozac” and “for cancer.” The suggestion in one comment that FDA establish “categories of diseases that clearly denote drug claims” is not a workable alternative either. Section 403(r)(6) of the act provides that the category of structure/function claims excludes claims to affect any category of disease, not just certain categories.

Permitting disease claims under section 403(r)(6) of the act as long as they are accompanied with a disclaimer, as suggested by the comment that cited the Pearson decision, would be an untenable alternative. If companies could avoid the time and expense of complying with the new drug provisions of the act merely by attaching a disclaimer to a disease treatment or prevention claim, the longstanding system of drug regulation in this country would be eviscerated, with serious public health consequences. Nothing in *Pearson* requires such a result. Indeed, the *Pearson* court recognized that its ruling did not apply to drugs (164 F.3d at 656 n. 6). Because the act classifies products on the basis of intended use, dietary supplements that make disease claims are drugs, unless the disease claim is also an authorized health claim for which the product qualifies (see section 201(g)(1) of the act).

The *Washington Legal Foundation* decision is not to the contrary. That case involved the dissemination of information on “off-label” (unapproved) uses for approved drugs and devices to physicians by means of scientific and educational symposia, reprints, and textbooks. The U.S. District Court for the District of Columbia held certain FDA guidance documents that described acceptable ways of disseminating such information unconstitutional under the *Central Hudson* test. While recognizing the substantial government interest in having off-label uses for drugs and devices found to be safe and effective by FDA, the court held that the guidance documents violated the First Amendment because it believed that they “restricted” speech in a manner that was more extensive than necessary to further that interest. (See 13 F. Supp.

2d at 73.) (Subsequent to the 1998 decision cited by the comments, the court rendered another decision adverse to FDA (*Washington Legal Foundation v. Henney*, 1999 WL 557679 (D.D.C. July 28, 1999)). That decision concerned the constitutionality of certain provisions of the FDA Modernization Act of 1997 involving the same subject matter as the guidance documents, and the court’s First Amendment rationale was similar to its rationale in the 1998 decision pertaining to the guidance documents.)

FDA disagrees with the district court decision in *Washington Legal Foundation* and has appealed. In any event, however, the outcome in *Washington Legal Foundation* does not determine the outcome here for several reasons. First, in *Washington Legal Foundation* the court found a less restrictive alternative that it concluded would more precisely address the government’s regulatory concerns: Requiring manufacturers who disseminate information about off-label uses to physicians through scientific reprints or educational symposia to disclose: (1) Their interest in drugs or devices that are the subject of such activities, and (2) the fact that the use discussed has not been approved by FDA. Here, as explained previously, there are no less restrictive alternatives to this rule that would further the government’s substantial public health interest. Second, in *Washington Legal Foundation* physicians were the intended audience of the commercial speech at issue. In contrast, consumers are the primary audience for dietary supplement labeling. Although the marketplace includes consumers of varying levels of sophistication, the average consumer does not possess the medical and scientific expertise necessary to evaluate claims about the effect of a product on disease. (See *American Home Products Corp. v. FTC*, 695 F.2d 681, 698 (3d Cir. 1983); *Association of Nat’l Advertisers, Inc. v. Lungren*, 44 F.3d 726, 733–34 (9th Cir. 1994), cert. denied, 516 U.S. 812 (1995).) Finally, in *Washington Legal Foundation*, it was undisputed that the products involved were drugs (or, in some cases, devices) to be used in treating or preventing disease. In contrast, the purpose of this rule is to distinguish between products that are intended to affect disease and products that are not.

The agency does not believe this rule is premature in light of the need to reassess the regulatory regime for health claims under *Pearson*. Since health claims and structure/function claims are regulated separately, there is no need to wait for any post-Pearson changes for

health claims to be complete before proceeding with this rulemaking on structure/function claims. Moreover, since the agency has decided not to amend the health claims regulations as part of this rulemaking, there is no potential conflict between the two.

The First Amendment issues raised in comments on § 101.93(g)(4)(iii) (proposed § 101.93(g)(2)(iv)(C)), concerning citations to scientific references in labeling, are not different from those raised by comments on the rule as a whole and are addressed in the preceding analysis. FDA also notes that, as discussed elsewhere in this document, § 101.93(g)(4)(iii) has been revised to narrow the circumstances under which the agency will consider citations to scientific references in labeling to be disease claims.

(109.) Another comment further asserted that the prohibition against implied disease claims violates the First Amendment because it does not advance the safety of dietary supplements. The comment acknowledged that some dietary supplements “may present serious safety risks,” but said “these risks will not be lessened by prohibiting truthful, non-misleading structure/function claims * * *.” The comment suggested that other provisions in DSHEA address the safety of dietary supplements and that FDA can bring an enforcement action if it has safety concerns.

FDA agrees with this comment in part and disagrees in part. The agency agrees that prohibiting truthful, non-misleading structure/function claims would not lessen the safety risks posed by some dietary supplements. The rule is aimed at the safety risks posed by unapproved drug claims and unauthorized health claims on dietary supplements. Unproven disease claims on a product marketed as a dietary supplement may induce consumers to treat themselves with the supplement instead of seeking treatments that are known to be effective. Such claims may also dissuade consumers from seeing a doctor. These are very real safety risks. To the extent that safety risks are caused by the composition of a dietary supplement rather than by claims made for it, the agency agrees that other provisions in DSHEA and the act are the appropriate remedy.

2. Equal Protection

(110.) One comment claimed the rule violates the equal protection clause of the Fourteenth Amendment because it supposedly gives more protection to the “labeling rights and speech” of pharmaceutical manufacturers than to dietary supplement manufacturers.

First, it should be noted that the equal protection clause of the Fourteenth Amendment applies only to the States, not to the Federal Government.

However, the due process clause of the Fifth Amendment contains an equal protection component that is equivalent to the equal protection clause of the Fourteenth Amendment (*Schweiker v. Wilson*, 450 U.S. 221, 226 & n. 6 (1981)). Even if the comment is interpreted to refer to equal protection under the Fifth Amendment, FDA disagrees with it. First, the comment does not explain in what manner the rule gives more protection to the labeling rights and speech of pharmaceutical manufacturers than to those of dietary supplement manufacturers. Second, even if the rule does treat these two classes of manufacturers differently, treating different regulated groups differently does not in itself violate the equal protection clause. Unless a regulatory classification jeopardizes the exercise of a fundamental right or classifies upon inherently suspect grounds such as race or religion, it is subject to the least exacting form of equal protection review: Whether the classification it draws bears a rational relationship to a legitimate government interest. (See *Nordlinger v. Hahn*, 505 U.S. 1, 10 (1992).)

This rule neither jeopardizes the exercise of a fundamental right nor creates a suspect classification. The purpose of the rule is to clarify the statutory distinction between products that are intended for use in treating or preventing disease and products that are intended for use in affecting the structure or function of the body. Products intended to treat or prevent disease are subject to regulation as drugs, unless they qualify for an authorized health claim. Products intended to affect the structure or function of the body may be regulated as dietary supplements, subject to certain conditions. Products regulated as drugs must meet strict requirements for a premarket demonstration of safety and efficacy (see sections 201(p) and 505 of the act); these requirements do not apply to dietary supplements. The distinction that the statute and this rule draw between products that are intended to have an effect on disease and those that are intended only to affect the structure or function of the body is clearly rationally related to the legitimate government interest of ensuring that products intended to have an effect on a disease are safe and effective for that intended use.

3. Takings Under the Fifth Amendment (111.) Several comments claimed that the proposal violates the Takings Clause

of the Fifth Amendment because it would prohibit the use of specific terms that now appear in product names, trademarks, trade names, symbols, and company logos, or would harm companies that use such terms in their corporate names. One comment said FDA must provide compensation for each taking, but that the proposal failed to do so.

FDA disagrees with these comments. The Takings Clause forbids the government from taking private property for public use without just compensation. However, FDA believes that no taking will occur as a result of this rule.

The first issue to be considered is whether the categories of names, words, and symbols identified in the comments on this issue are property within the meaning of the Takings Clause. The Constitution itself does not define what qualifies as property. Rather, "existing rules or understandings derived from an independent source," such as State or Federal law, define the interests that qualify for protection as property under the Fifth Amendment (*Lucas v. South Carolina Coastal Council*, 505 U.S. 1003, 1030 (1992)).

The categories of names, words, and symbols mentioned by the comments are intangible property interests. As discussed below, trademarks and trade names are property to the extent that they are associated with business goodwill. A trademark is a word, name, symbol, device, or combination thereof that a person uses, or intends to use and has applied to register, to identify and distinguish his or her goods from others on the market and to indicate their source (15 U.S.C. 1127). A trade name is the name a person uses to identify his or her business (15 U.S.C. 1127) and may include corporate, partnership, and other names. Symbols and logos, when used to identify a product or company, may be property insofar as they are trademarks or trade names. Likewise, product names may be property if they are protected by a trademark or trade name. For brevity, in the remainder of this discussion the categories of names, words, and symbols mentioned by the comments on the takings issue will be referred to collectively as "trademarks and trade names."

Trademarks and trade names are property, but only insofar as they are associated with the goodwill of an ongoing business. (See *American Steel Foundries v. Robertson*, 269 U.S. 372, 380 (1926).) They have no intrinsic value. The purpose of a trademark or trade name is to prevent confusion with the products of another manufacturer. (See *United Drug Co. v. Theodore*

Rectanus Co., 248 U.S. 90, 97 (1918).) Trademarks and trade names are given legal protection to prevent one manufacturer from passing off its goods as the goods of another and thus taking advantage of the latter's goodwill (*American Steel Foundries*, 269 U.S. at 380; *United Drug*, 248 U.S. at 97).

The Supreme Court has declined to prescribe a "set formula" for identifying takings and instead has characterized takings analysis as an "essentially ad hoc, factual" inquiry (*Penn Central Transp. Co. v. City of New York*, 438 U.S. 104, 124 (1978)). Nonetheless, the Court has identified three factors for consideration in assessing whether a regulatory taking has occurred: The character of the governmental action; the regulation's economic impact; and the extent to which the regulation interferes with reasonable investment-backed expectations (*Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1005 (1984)). The force of any one of these factors may be "so overwhelming * * * that it disposes of the taking question" (*Monsanto*, 467 U.S. at 1005). When examined in light of these three factors, the rule does not effect a compensable taking under the Fifth Amendment.

a. *The character of the government action.* With respect to the first factor, the character of the government action, courts are more likely to find a taking when the interference with property can be characterized as a physical invasion by government than when the interference is caused by a regulatory program that "adjust[s] the benefits and burdens of economic life to promote the common good" (*Penn Central*, 438 U.S. at 124). The Supreme Court has held that, when a governmental action is taken in order to protect the public interest in health, safety, and welfare, this factor weighs heavily against finding a taking. (See *Keystone Bituminous Coal Ass'n v. DeBenedictis*, 480 U.S. 470, 488 (1987).) Regulatory actions taken to protect the public health are rarely, if ever, held to constitute takings. (See *Porter v. DiBlasio*, 93 F.3d 301, 310 (7th Cir. 1996) (action taken to protect public health falls within class of property deprivations for which Fifth Amendment does not require compensation); *Jarboe-Lackey Feedlots, Inc. v. United States*, 7 Cl. Ct. 329 (1985) (seizure of adulterated meat not a taking).)

Although these regulations will restrict the use of certain terms, including terms that appear in some trademarks and trade names, this restriction does not rise to the level of a taking. Governmental restrictions on the uses individuals can make of their

property are “properly treated as part of the burden of common citizenship” (*Keystone*, 480 U.S. at 491 (citation omitted)). These burdens are “borne to secure ‘the advantage of living and doing business in a civilized community’” (*Andrus v. Allard*, 444 U.S. 51, 67 (1979) (quoting *Pennsylvania Coal Co. v. Mahon*, 260 U.S. 393, 422 (1922) (Brandeis, J., dissenting))). Moreover, these regulations are not without benefit to manufacturers. (See *Keystone*, 480 U.S. at 491 (“While each of us is burdened somewhat by such restrictions, we, in turn, benefit greatly from the restrictions that are placed on others.”).) The regulations will help ensure a level playing field in the dietary supplement market because no manufacturer will be able to make an implied disease claim without prior FDA review under the health claim or new drug standard. Previously, unreviewed implied disease claims on dietary supplements proliferated, in part because of uncertainty about the line between structure/function claims and disease claims.

These regulations are rationally related to, and substantially advance, FDA’s legitimate interest in promoting and protecting the public health by ensuring the safety and efficacy of products promoted for use in treating or preventing disease. (See *Keystone*, 480 U.S. 470 at 485; *Monsanto*, 467 U.S. at 1007.) By clarifying that such products may not be marketed under the structure/function claim regime, FDA is seeking to ensure that they are regulated through the drug approval or health claims authorization process, as appropriate.

The effect of the regulations cannot be characterized as a taking of property. Dietary supplement companies will not be precluded from using terms that imply a disease claim in their trademarks and trade names. If they wish to continue using trademarks and trade names that imply a disease claim, they may do so, provided that they first meet the safety and efficacy standards and other regulatory requirements applicable to drugs or, in appropriate cases, provided that they obtain authorization to make a health claim. (As discussed below, only non-misleading trademarks and trade names may be used.)

Even if these regulations could be said to prevent a business from using a trademark or trade name on its dietary supplements, such a result still would not constitute a taking of the trademark or trade name. The purpose of giving trademarks and trade names legal protection is to prevent one

manufacturer from passing off its goods as the goods of another (*American Steel Foundries*, 269 U.S. at 380). This regulation will not allow one manufacturer to use another’s trademark or trade name; rather, all manufacturers will be precluded from using trademarks and trade names that contain an implied disease claim unless they have obtained new drug approval or health claim authorization. Thus, manufacturers will not suffer any competitive injury.

Moreover, deprivation of a trademark alone is not a deprivation of property. Because the trademark is “merely a protection for the good will” (*Hanover Star Milling Co. v. Metcalf*, 240 U.S. 403, 414 (1916)), only if a regulation takes the owner’s goodwill as well would the regulation be a taking. It is not apparent, however, that these regulations will deprive manufacturers of any goodwill. Manufacturers will be faced with a choice as to whether to change their trademark or trade name or to seek approval for their products as drugs. In some cases, they will also have a third option: Seeking authorization to make a health claim. If they are able to obtain drug approval for the intended use suggested by the trademark or trade name, they will not have to change the trademark or trade name, provided that the name is not confusingly similar to the name of another drug or otherwise misleading (see section 502(a)(1) of the act (21 U.S.C. 352(a)(1)); and § 201.10(c)(3) and (c)(5)). Similarly, if they are able to obtain authorization to make a health claim for the intended use suggested by the trademark or trade name, they will not have to change the trademark or trade name unless it is misleading. (See section 403(a)(1) of the act.) Even if a manufacturer chooses to change its trade name or trademark, it will not be deprived of the goodwill underlying them but only of that particular symbol of the goodwill. The manufacturer will still be able to transfer the goodwill associated with its products to another trade name or trademark.

Case law on the treatment of goodwill under the Takings Clause supports the view that no taking will occur as a result of these regulations. The general rule is that the owner of a place of business to which the government takes title is not entitled to compensation for loss of goodwill (*United States v. General Motors Corp.*, 323 U.S. 373, 379 (1945)). The reason for the rule is that the business may reopen at another location to which the goodwill may be transferred (*Kimball Laundry Co. v. United States*, 338 U.S. 1, 11–12 (1949)). Only where the government operates the

business, thereby depriving the owner of its “going-concern value,” is there a compensable taking of goodwill. In *Kimball*, the Supreme Court held that the government owed compensation for the loss of goodwill associated with the temporary taking of a laundry during World War II. This action was held to be a taking of goodwill because the government not only physically took but also operated the laundry during the war (*Kimball*, 338 U.S. at 12–13). Thus, during the period that the government operated the laundry, there was no business to whose benefit the goodwill associated with the private laundry business could inure. Here, the government is not taking any trademark or trade name for its own use, nor is it shutting down the businesses that own them. Therefore, the goodwill symbolized by the trademark or trade name will remain with these businesses.

Finally, although trademarks and trade names can be property when they symbolize and protect the goodwill associated with a business, there can be no property interest in an illegal product. Dietary supplements that bear claims to treat or prevent disease are misbranded and are also unapproved new drugs (unless the claim is an authorized health claim). As such, they may not legally be sold in interstate commerce (see section 301 (a) and (d) of the act. There can be no taking of an illegal article. (See *Meserey v. United States*, 447 F. Supp. 548, 554 (D. Nev. 1977) (“Plaintiff has not been denied his property. He is denied the right to introduce his goods into commerce unless they are in compliance with the [Federal Food, Drug, and Cosmetic] Act.”).) Moreover, it has always been illegal to market dietary supplements or other foods with disease claims, except that since 1990 the act has permitted authorized health claims. These regulations merely clarify the line between acceptable structure/function claims and prohibited disease claims. (See *Lucas*, 505 U.S. at 1030 (“The use of [property] for what are now expressly prohibited purposes was *always* unlawful, and * * * it was open to the State at any point to make the implication of those background principles of * * * law explicit” without paying compensation) (emphasis in original).) For this reason and the other reasons previously discussed, the first factor of the takings analysis indicates that these regulations effect no takings.

b. *The economic impact of the government action.* The second factor to consider is the economic impact of the government action. This impact is not to be considered piecemeal by dividing a property interest “into discrete

segments and attempt[ing] to determine whether rights in a particular segment have been entirely abrogated” (*Penn Central*, 438 U.S. at 130). The analysis involves looking not just at what has been lost, but at the nature and extent of the interference with rights in the property as a whole. (See *Penn Central*, 438 U.S. at 130–31; *Andrus v. Allard*, 444 U.S. at 65–66.) Thus, here the total impact of the regulations on property rights should be considered, rather than only whether a business can or cannot continue to use a particular trademark or trade name. It is clear that a regulation’s economic impact may be great without rising to the level of a taking. (See *Pace Resources, Inc. v. Shrewsbury Township*, 808 F.2d 1023, 1031 (3d Cir.), cert. denied, 482 U.S. 906 (1987) (citing *Hadacheck v. Sebastian*, 239 U.S. 394 (1915) (reduction in value from \$800,000 to \$60,000); *Euclid v. Ambler Realty Co.*, 272 U.S. 365 (1926) (75 percent diminution in value)).

In assessing whether a regulation effects a taking, the Supreme Court has considered whether the regulation denies an owner the “economically viable” use of its property. (See, e.g., *Keystone*, 480 U.S. at 499.) Although it is undeniable that compliance with these regulations will cost money and may mean that certain trademarks and trade names must be altered, companies will not be denied the economically viable use of their property. As previously discussed, some firms may be able to obtain new drug approval or health claim authorization for those products that bear trademarks or trade names that include disease claims. If approved as new drugs or authorized to bear a health claim, in many cases these products could continue to bear the original trademark or trade name. This approach would, however, require the company involved to make significant expenditures of time and money to submit a new drug application (NDA) or health claim petition to FDA. The financial burden required to comply with such requirements is not a taking under these circumstances, however, just as it is not a taking to require other companies to comply with applicable requirements before marketing a new drug or a food bearing a health claim. Obtaining new drug approval or authorization to make a health claim may be costly, but it is not the kind of economic impact that leads to a taking. “Requiring money to be spent is not a taking of property” (*Atlas Corp.*) v. *United States*, 895 F.2d 745, 756 (Fed. Cir.), cert. denied, 498 U.S. 811 (1990)).

As previously noted in the discussion of the first factor of the takings analysis, case law indicates that the regulations

will cause no loss of goodwill even in cases where a trademark or trade name must be changed because new drug approval or health claim authorization cannot be obtained. Even if the regulations do cause a loss of goodwill, however, FDA believes that the economic impact of that loss of goodwill is outweighed in the takings analysis by lack of reasonable investment-backed expectations in being able to make disease claims in trademarks and trade names.

c. *Interference with reasonable investment-backed expectations.* The final factor to consider is whether a company has a reasonable investment-backed expectation in continuing to use a trademark or trade name. To be reasonable, expectations must take into account the power of the state to regulate in the public interest (*Pace Resources*, 808 F.2d at 1033). Reasonable expectations must also take into account the regulatory environment, including the foreseeability of changes in the regulatory scheme. “In an industry that long has been the focus of great public concern and significant government regulation,” *Monsanto*, 467 U.S. at 1008, the possibility is substantial that there will be modifications of the regulatory requirements. “Those who do business in the regulated field cannot object” if the regulatory scheme is “buttressed * * * to achieve the legislative end” (*Connolly v. Pension Benefit Guar. Corp.*, 475 U.S. 211, 227 (1986) (citation omitted)). The lack of a reasonable investment-backed expectation can outweigh the other takings factors and be determinative in whether a taking has occurred (*Monsanto*, 467 U.S. at 1005).

Companies that use trademarks or trade names that include disease claims lack a reasonable investment-backed expectation that they will be able to continue to use those trademarks and trade names. First, the Supreme Court has said that it is unreasonable to have high expectations in personal property (i.e., property other than land): “[I]n the case of personal property, by reason of the State’s traditionally high degree of control over commercial dealings, [the property owner] ought to be aware of the possibility that new regulation might even render his property economically worthless * * *.” (*Lucas v. South Carolina Coastal Council*, 505 U.S. at 1027–28). Second, the dietary supplement and drug industries are a “focus of great public concern and significant government regulation” (*Monsanto*, 467 U.S. at 1008). A product that bears a disease claim, whether that claim appears in a trademark, trade

name, or elsewhere, has been subject to regulation as a drug since 1906, except that since 1990 the act has permitted conventional foods and dietary supplements to bear authorized health claims without drug approval. Since 1938, drugs (with certain narrow exceptions) have been subject to a premarket approval requirement. Given this longstanding history of close regulation, it cannot be reasonable for a manufacturer or distributor to expect to be able to make disease claims without prior authorization from FDA.

Moreover, it has always been illegal to market dietary supplements or other foods with disease claims, except that since 1990 authorized health claims have been permitted. These regulations merely clarify the line between acceptable structure/function claims and prohibited disease claims. (See *Lucas*, 505 U.S. at 1030 (“The use of [property] for what are now expressly prohibited purposes was *always* unlawful, and * * * it was open to the State at any point to make the implication of those background principles of * * * law explicit.”).) Companies in the dietary supplement industry should have been aware that FDA was likely to issue such a clarification, not only because of the regulatory environment generally but also for several specific reasons. First, the passage of DSHEA, which added section 403(r)(6) to the act, created a likelihood that FDA would issue regulations “to achieve the legislative end” of permitting structure/function claims without premarket review, while continuing to prohibit disease claims lacking FDA authorization (see *Connolly*, 475 U.S. at 227 (citation omitted)). Second, the Commission on Dietary Supplement Labels specifically encouraged FDA to clarify the appropriate scope of structure/function statements (Ref. to Commission report, p. 38). Third, the rapidly expanding dietary supplement market and the proliferation of implied disease claims in labeling should have put the industry on notice that FDA might take action.

For all these reasons, there can be no reasonable investment-backed expectations with respect to trademarks and trade names that include disease claims. Thus, the third factor of the takings analysis weighs strongly against finding a taking of property that requires compensation under the Fifth Amendment. Moreover, the three factors, taken together, show that these regulations do not effect such a taking. Therefore, FDA concludes that the comments arguing the contrary are unpersuasive.

IV. Implementation Plan

The preamble to the proposed rule discussed FDA's tentative conclusions regarding the effective date of a final rule and the agency's implementation plan. In general, the preamble to the proposed rule stated that a final rule would become effective 30 days after the date of the final rule's publication in the **Federal Register**. Any product that is marketed for the first time after publication of the final rule, and any new claims made for an existing product for the first time after the publication of the final rule, will be expected to be in compliance beginning 30 days after publication of the final rule. However, small businesses that marketed a product as of the date of publication of a final rule would have had an additional 17 months to bring existing claims (i.e., claims already in the products's labeling on January 6, 2000 for those products into compliance, provided that the small business had notified FDA of the claim as required by section 403(r)(6) of the act and § 101.93(a) and that FDA had not objected to the claim. For all other products that were on the market as of the date of publication of a final rule, FDA would have allowed an additional 11 months beyond the effective date to bring existing claims for those products into compliance, provided that the firm had notified FDA of the claim as required by section 403(r)(6) of the act and § 101.93(a) and that FDA had not objected to the claim. Any product marketed for the first time after the date of publication of the final rule, and any new claim made for an existing product for the first time after publication of the final rule, would have been expected to be in compliance beginning 30 days after the date of publication of a final rule.

(112.) Two comments suggested extending the compliance period to 6 months after the date of publication of a final rule. The comments also advocated that there be no distinction between large and small businesses for compliance dates. The comments further suggested that FDA give businesses whose products were on the market as of the date of publication of a final rule 15 months (instead of 11 or 17 months) to comply. Another comment suggested that the final rule become effective 12 months, rather than 30 days, after its publication date.

FDA believes that the proposed compliance periods of 11 and 17 months following the effective date of the final rule are reasonable and fair, and that the distinction between large and small businesses is appropriate.

FDA has decided, however, that it will not treat manufacturers who have not notified the agency of their claims differently from other manufacturers. At least some of those manufacturers who did not submit 30-day notifications to the agency may have failed to do so believing that notification was not necessary under section 201(g)(1)(C) of the act. Therefore, all manufacturers will have 11 months after the effective date of the final rule to come into compliance, and small businesses will have 17 months after the effective date of the final rule. The agency believes that these compliance periods, uniformly applied, are sufficiently long that it is not necessary to extend the effective date to 6 months after publication in the **Federal Register**.

For a limited transition period, FDA does not intend to take enforcement action against firms who have relied on the agency's September 1997 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) 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.

V. Environmental Impact

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

VI. Analysis of Impacts

A. Background

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies

to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to examine the economic impact of a rule on small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any one year by State, local and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

FDA concludes that this final rule is consistent with the principles set forth in the Executive Order and in these two statutes. The agency has determined that the rule is a significant regulatory action as defined by the Executive Order, because it raises novel policy issues. FDA has further determined that the final rule may have a significant economic impact on a substantial number of small entities. This section constitutes the agency's final regulatory flexibility analysis as required under the Regulatory Flexibility Act. Because this rule imposes no mandates on government entities and will not result in private expenditures of \$100 million in any one year, the Unfunded Mandates Reform Act does not require the agency to prepare a cost-benefit analysis.

B. Benefits of the Labeling Requirements

The primary purpose of the rule is to provide a consistent standard for distinguishing between claims that may be made in labeling without prior review by FDA and claims that require prior authorization as health claims or prior review as drug claims. The larger goal is to ensure that information about non-disease-related effects of a dietary supplement on the body may be freely disseminated in labeling, while at the same time guaranteeing that claims for use of a dietary supplement to treat or prevent disease are not made without prior review to ensure that the supplement is safe and effective for that use.

Although dietary supplements can play a valuable role in consumer health, the agency recognizes that, when inappropriately labeled, they can pose unnecessary risks. Such risks arise when the product labeling: (1) Encourages consumers to self-treat for a serious disease without the benefit of a medical diagnosis, or to self-treat for a

serious disease by substituting a dietary product of uncertain value for a medical therapy that has been shown to be safe and effective; (2) encourages consumers to feel sufficiently protected from a serious disease (e.g., cancer) that they delay, or possibly forego, regular screening or early medical attention that may be critical to improved odds of patient survival; or (3) increases the risk of adverse reactions due to interactions with other chemical compounds (e.g., prescription medications) taken by the patient. As consumer spending on dietary supplements continues to rise, the need for an information standard that minimizes these risks becomes more acute.

The rule may also benefit consumers by encouraging manufacturers of dietary supplements to develop the safety and effectiveness data needed to support a health or drug claim. Where disease claims can be made without this demonstration of safety and effectiveness, product manufacturers have less incentive to develop the substantial documentation needed to receive this agency authorization. The availability of additional products with authorized health or drug claims would be extremely useful to the many consumers who have difficulty distinguishing among the variety of products now marketed for particular health concerns.

The dietary supplement industry has grown rapidly, with estimated sales in 1996 of \$10.4 billion for all dietary supplements, including \$4.9 billion for vitamins and \$3.0 billion for nonprescription herbal products (Ref. 8). FDA has limited information on the number of products and quantities sold, or on the age, gender, and disease status of persons currently using dietary supplements. However, a 1997 survey of 43,000 households, conducted by the Hartman and New Hope research organization, indicates that approximately 70 percent of all households reported using vitamins, minerals, or herbal supplements in the past 6 months (Ref. 9). Among survey respondents, those under age 30 accounted for only 8 percent of all households with a member using dietary supplements; ages 30 to 39 accounted for 21 percent, ages 40 to 49 accounted for 22 percent, ages 50 to 59 accounted for 18 percent, and ages 60 or older accounted for 30 percent (Ref. 10). Although the oldest group of survey respondents were, on the whole, less knowledgeable about individual products, they reported more regular product use and more use for specific conditions than younger respondents.

FDA anticipates, therefore, that the final rule will clarify the dividing line between acceptable structure/function claims and disease claims, and thereby reduce the number of inappropriate disease claims in dietary supplement labeling. The defined standard for structure/function claims under section 403(r)(6) of the act will help to avoid instances of inappropriate substitution of dietary products for timely disease screening or medical treatment, and of adverse interactions or contraindications of drug-supplement combinations. In addition, the rule may promote the development of data and information for the support of new health or drug claims. Although FDA cannot quantify these regulatory benefits, the agency expects that this standard will positively support the effective integration of dietary supplements into consumers' overall programs of wellness and self-care.

C. Costs of Compliance

The costs to industry are the direct costs of compliance, which are primarily the costs of the needed product relabeling; and the indirect costs of compliance, which include the potential loss of product sales due to the elimination of disease claims. The following section details the agency's calculation of the direct costs of compliance. FDA has been unable, however, to estimate the extent of the indirect costs of this rule. As explained below, the agency estimates that over 800 dietary supplement products will need to be relabeled due to this rule. The substitution of a valid structure/function claim for a disease claim may, in fact, lead to a decrease in the sale of certain products. The magnitude of this impact, however, is unknown, as most firms will replace the disease claim with a structure/function claim that appeals to many of the same consumers. It is also possible that some firms will avoid a potential drop in sales by developing the safety and effectiveness data needed to obtain either a new drug approval or authorization from FDA to make a health claim. The agency cannot quantify the probability of these occurrences, however, and no industry comment includes such data.

1. Proposed Rule

In the preamble to the proposed rule (63 FR 23624), FDA had projected that the direct costs of compliance would range from \$0.1 million to \$8.5 million. This figure largely reflected agency estimates of the average cost of relabeling a typical dietary supplement product multiplied by the number of dietary supplement products that would

need to be relabeled to conform with the proposed criteria for structure/function claims. The cost categories included administrative, analytical, and inventory disposal activities.

FDA acknowledged that estimates of the number of dietary supplement products were approximate, but projected that the proposed rule would cover about 29,000 products, with about 75,000 distinct labels, or stock keeping units (SKU's). The agency also explained that the rule would directly affect from 500 to 850 manufacturers of dietary supplement products.

To estimate the lower-bound costs of the proposed rule, FDA assumed that the 2,300 notifications initially received from dietary supplement manufacturers adequately represented the number of products with structure/function claims. The agency had already objected to 150 notifications because they contained obvious disease claims, but identified an additional 60 notifications containing one or more claims that might not have met the newly proposed criteria for structure/function claims. Consequently, FDA's lower-bound direct cost estimate included label changes for 60 dietary supplement products. The estimated administrative, redesign, and inventory losses associated with these 60 label changes totaled between \$91,400 and \$123,400.

FDA also presented an upper-bound \$8.5 million estimate of the direct costs of the proposed rule, based on the likelihood that many additional dietary supplements are marketed with structure/function claims. For this estimate, the agency concluded that about 30 percent, or 22,500, of the estimated universe of 75,000 dietary supplement labels contain structure-function claims. Assuming that the proportion of disease claims on all labels containing structure/function claims equals the proportion of disease claims in the 2,300 notifications containing structure/function claims, the agency calculated that up to 585 labels ($60/2,300 \times 22,500$) could need to be changed if the proposed rule became final. The higher costs of the upper-bound estimate resulted both from the substantially increased assumed number of affected labels and from the impact of the significantly shorter compliance period (30 days) for manufacturers that had not notified FDA of their structure/function claim by the publication date of the final rule.

2. Final Rule

A number of the comments submitted in response to the proposed rule specifically addressed FDA's analysis of compliance costs. As a result, the

agency has altered several of its cost assumptions. In addition, FDA has adjusted its analysis to reflect the modified provisions of the final rule. As described below, the agency estimates the total direct costs of the final rule to be about \$3.73 million, but presents sensitivity analysis to indicate that the costs could rise to as much as \$10.35 million under certain worst-case assumptions.

Although several industry comments suggested that FDA had underestimated the costs of relabeling, no comments objected to the specific elements that were considered, i.e., administrative, redesign, and inventory disposal activities. In response, FDA has retained this format for its analysis of the final rule. One comment claimed that FDA had underestimated the number of products that would be affected, but provided no evidence or basis for determining a more accurate count. Another comment stated that the agency's cost estimates were not well explained and that all assumptions were not disclosed. Consequently, FDA has revised its analysis to: (1) Simplify the cost-estimating methodology, (2) clearly present and describe each assumption, (3) fully explain the derivation of the estimated direct costs of compliance, and (4) conduct sensitivity analysis for the remaining areas of significant uncertainty.

a. Cost of designing new labels.

Dietary supplements will no longer be able to make claims whose status was previously unclear, but which now have been defined as disease claims. Firms may comply either by obtaining new drug approval, by receiving authorization from FDA to make a health claim, or by revising their product labeling to eliminate disease claims. Because the cost of submitting adequate documentation to obtain new drug approval or health claim authorization far exceeds the cost of modifying a label, this analysis assumes that the direct costs of the rule will be the costs of modifying labels with disease claims. As explained above, FDA recognizes that some firms may choose to obtain health claim authorization or new drug approval as an alternative means of compliance, or to improve the marketability of their products. The agency believes, however, that it is unlikely that the rule would be the determining factor in a large number of instances.

No public comments provided alternative estimates of the number of affected dietary supplement products. As noted above, FDA had estimated that the industry markets approximately 29,000 covered products with about

75,000 distinct labels. The agency has used this estimate for its analyses of dietary supplement rules over the past several years (e.g., 60 FR 67211 December 28, 1995) and has received no indication from industry that better estimates were available. Although the agency's preliminary analysis reported that an estimated 30 percent of the products (8,700) carry structure/function claims, more recent data from a random survey conducted for FDA by RTI of about 3,000 dietary supplement products indicates that this percentage may have been too low (Ref. 11). Although RTI notes that the surveyed sample is too small to support quantitative inferences for the population of dietary supplements, FDA finds the data to be the best available. The RTI report actually shows that 69 percent of the products in its sample have claims, but this percentage includes "diet supplementation" claims. When adjusted to exclude "diet supplementation" only 62 percent of the products in the RTI data base include relevant claims. Even this 62 percent figure is too high, however, because RTI over-sampled herbal products, which have a higher probability of claims and would not exceed 60 percent and has used this figure as its final estimate.

Of the first 2,300 notifications of structure/function claims reviewed by FDA, no more than 60, or 2.6 percent of the products with claims, would have needed labeling changes due to the criteria described in the proposed rule. Since that time, the total number of notifications with structure/function claims submitted to the agency has increased to about 5,200. A subsequent review of all of the submitted claims indicates that the final rule could require about 1.9 times as many label modifications as the proposed rule, owing largely to the revised criteria for cholesterol claims in the final rule. FDA estimates that the final rule may require revised labels for about 4.81 percent of the 17,400 dietary supplement products (29,000 x 60 percent currently estimated as marketed with structure/function claims (Refs. 15 and 16). (Excluding cholesterol claims would reduce this figure to 1.74 percent of the products with claims.)

The resulting label cost calculations are straightforward. First, the agency found that revised labels (for all claims including cholesterol) may be needed for approximately 837 products (17,400 products with claims x 4.81 percent). Because each product may contain roughly 2.6 distinct SKU's (75,000 SKU's ÷ 29,000 products), labels for an estimated 2,164 SKU's may need to be modified (837 products x 2.6 SKU's/

product). As described in its earlier analysis, based on an average of the estimates provided in comments to earlier rules, FDA determined that the average label redesign cost is about \$1,700 per dietary supplement SKU for a 12-month compliance period, and \$1,300 for an 18-month compliance period. No industry comment questioned the reasonableness of these unit cost estimates.

The final rule sets compliance periods of 1 year for large firms (revenues above \$20 million) and 18 months for small firms (revenues below \$20 million), except that new claims (i.e., claims not made before the publication of the final rule) must be in compliance as of the effective date. Such claims will not necessitate relabeling, however. FDA does not know the size of the firms that will need to make label changes. RTI (Ref. 12) reports that 95 percent of the firms in the industry are small, but that the 5 percent that are large account for 80 percent of industry sales. The RTI product data base also indicates that approximately 25 percent of the sample products were manufactured by just 5 percent of the companies. Thus, FDA has assumed that approximately one-quarter of the affected products will come from large firms and three-quarters from small firms. Consequently, the total estimated label redesign costs equal about \$3.03 million (i.e., \$1,700 x 0.25 x 2,164 SKU's + \$1,300 x 0.75 x 2,164 SKU's).

b. Administrative costs. One industry comment contended that FDA had not adequately explained the basis for its company-specific administrative costs, estimated at \$425 and \$320 respectively, for 12-month and 18-month compliance periods. These figures were derived from data presented in a 1991 RTI report on the cost of FDA's food labeling regulations (Ref. 13). They included costs associated with interpreting a regulation, determining the manner of compliance and managing the compliance method. RTI had estimated that, on average, small firms would bear administrative costs of \$850 to comply with the new food labeling rules for a 1-year compliance period, and \$650 for a 2-year compliance period. For its analysis of the proposed rule, FDA reduced this figure by fifty percent, based on the smaller administrative effort that would be needed to comply with the proposed rule, compared to the conventional food labeling regulations evaluated by RTI in 1991. The regulations that were the subject of the 1991 RTI evaluation involved a broader range of administrative options and tasks, such as nutritional testing and

product reformulation. (The \$320 estimate for the 18-month compliance period was determined by interpolating between the estimates for 12 and 24 months.) The agency has raised these costs by about 27 percent to \$540 and \$407, respectively, to account for salary inflation since 1991 (Ref. 14).

FDA had initially estimated that 500 to 850 firms manufacture dietary supplements. The recent RTI study, however, has identified 1,050 manufacturers (Ref. 12). This higher number probably overestimates the size of the industry covered by this rule, because it includes homeopathic products, which are drugs by statutory definition, and "functional foods" and sports nutrition products, which may be either conventional foods or dietary supplements depending on how they are marketed and used. For this final analysis, FDA has assumed that 1,000 companies manufacture the dietary supplement products covered by this rule. Although only a small fraction of these establishments will need to implement changes in labeling due to this rule, the agency anticipates most firms will review the final rule to assess whether their labeling will be affected.

The administrative costs of the final rule would likely be higher for those firms that will need to revise labels and lower for those firms that do not. Nevertheless, FDA assumes that, on average, all large dietary supplement manufacturers would incur costs of \$540 and all small dietary supplement manufacturers would incur costs of \$407. As noted above, RTI found that about 95 percent of the firms in this industry are small. Thus, the agency calculated administrative costs to equal about \$413,000 (i.e., 950 small firms x \$407 + 50 large firms x \$540). FDA notes that these estimates may overstate the incremental administrative costs of this final rule, because dietary supplement firms must already comply with DSHEA and this rule is meant to clarify the meaning of that act, rather than to add new requirements. Nevertheless, the agency's sensitivity analysis, presented below, doubles the above cost estimates.

c. Costs of inventory losses. The final cost component involves the value of lost inventory. FDA's preliminary analysis relied on information from an earlier nutrition labeling rule that affected the entire dietary supplement industry. That information indicated that inventory disposal costs for the entire industry would be about \$8 million for an 18-month compliance period and \$15 million for a 12-month compliance period. As explained above, FDA estimated that about 2.89 percent

of the dietary supplement products will require new labels as a result of this rule (837 ÷ 29,000) and that about three quarters of the affected products are manufactured by small firms. Thus, total inventory disposal costs are calculated at \$281,000 (i.e., \$8 million x 2.89 percent x 0.75 + \$15 million x 2.89 percent x 0.25).

d. Total direct compliance costs. As described above, FDA has assumed the direct compliance costs of this rule to be the costs associated with relabeling those dietary supplements whose labeling claims are considered disease claims under the newly defined criteria. Redesign costs are estimated at \$3.03 million, administrative costs at \$413,000, and inventory disposal costs at \$281,000. In sum, therefore, the total estimated direct compliance costs equal almost \$3.73 million.

In addition, there may be costs associated with the discussion in the final rule concerning structure/function claims made under section 201(g)(1)(C) of the act. (See response to comment 95 in section III.A.1 of this document.) The agency believes that some firms have been making structure/function claims for dietary supplements without including a disclaimer statement or notifying FDA, based on FDA's statements in a 1997 preamble (62 FR 49859 at 49860, 49863, and 49864). Because the agency has not repudiated these statements, any firm that has relied on them to make a claim for a dietary supplement will need to add the disclaimer to all applicable labels, as well as to notify FDA, according to the requirements of this section 403(r)(6) of the act and § 101.93. Because firms making such claims have not identified themselves to FDA, the agency does not have a reliable database on which to base a cost estimate of the number of firms and products that may incur costs to comply with this new provision.

The costs to industry of the final rule are substantially different from the costs of the proposed rule, because of two important changes to the proposed requirements. First, the final rule requires more product labels to be changed, because it includes more specific parameters for acceptable structure/function claims about cholesterol. This change increases the direct compliance costs of the final rule. Second, the proposed rule required needed label modifications to be completed within 30 days after publication of the final rule, for those products without a properly submitted claim notification. Roughly 70 percent of all products with claims may have fallen into this group (1–5,200 products without notifications ÷ 17,400 products

with claims). Because relabeling costs are reported to double for each halving of the compliance period, compliance costs would have been eight times greater for those products. For the final rule, all large firms will be expected to comply within 12 months, and all small firms within 18 months, regardless of whether the firm has notified FDA of the structure/function claims on its products. This change significantly reduces the direct compliance costs of the final rule.

e. Sensitivity analysis. Due to uncertainty with respect to several factors in the agency's direct cost model, FDA has prepared a sensitivity analysis of other possible cost scenarios. First, FDA tripled the percentage of product notifications assumed to be out of compliance with the new criteria for structure/function claims. This change results in almost tripling the total direct compliance costs of the regulation, raising the estimate from about 3.73 million to about 10.35 to about \$5.93 million. Second, FDA doubled its estimate of administrative costs. This change raises the initial cost estimate to about \$4.14 million. Changing both assumptions simultaneously raises the total estimated costs to about \$11 million. Finally, under the initial scenario, if all of the needed label changes were assumed to affect only small businesses, the total cost estimate rises to about \$3.46 million. This sensitivity analysis indicates that the total direct costs of this rule would not impose a major burden on this industry even if the most uncertain cost factors are doubled or tripled from FDA's best estimates.

D. Other Industry Comments

Several comments insisted that FDA had not conducted a comprehensive cost-benefit analysis of the proposed rule, as required under Executive Order 12866. These comments stated that FDA's economic analysis ignored both the potential savings in consumer health care expenditures that would be lost by restricting important labeling information, as well as the likely negative effect of the proposal on the growth of the dietary supplement industry. One industry comment, for example, declared that a substantive cost-benefit analysis "must identify the potential health benefits that are lost as a consequence of reduced consumer access to useful information about the health-related properties of dietary supplements and ingredients." It noted that FDA's analysis "fails to consider the public health benefits associated with ingesting dietary supplements as

well as the losses to public health that could result from consumers failing to take appropriate dietary supplements due to uninformative structure/function claims." That comment also maintains that "FDA's failure to assess and consider such benefits (and costs) stands in contrast with the specific finding of DSHEA that 'appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures'." The comment also points out that FDA has performed such analyses in other rulemakings, e.g., tobacco, nutrition labeling, and ephedra regulations.

FDA disagrees. Although Executive Order 12866 directs agencies to assess the costs and benefits of economically significant rules, the quantification of these expected costs and benefits is required only "to the extent feasible" (58 FR 51735 at 51741, October 14, 1993). As described above, FDA believes that its final rule strikes the appropriate balance with respect to health-related claims in dietary supplement labeling. The rule classifies certain claims as acceptable structure/function claims that may be made without prior FDA review. Although the provision of structure/function information to consumers may reduce health care expenditures, no health organization, industry association, or any other interested public or private group has presented information or data that would allow the agency to develop a quantifiable estimate of the health care benefits. The rule classifies other claims as disease claims that are subject to existing requirements for new drug approval or health claim authorization before a product may be marketed with the claim. FDA believes that classifying claims into a category that requires FDA review of safety and efficacy evidence, where appropriate, will similarly reduce long-term health care expenditures. Again, however, the agency has no means of quantifying the probable health outcomes of this aspect of the rule and therefore has no means of quantifying its impact on health care expenditures. Because this analysis discusses the types of benefits and costs reasonably expected, and quantifies those that can be "feasibly" quantified, the agency has, in fact, complied with the direction of Executive Order 12866.

FDA has attempted to quantify the benefits of some of its previous regulations. The agency's estimated benefits of the tobacco rule relied on a widely established risk assessment published by the American Cancer Society. Estimated benefits of the proposed ephedra rule were based on

incidents identified in the agency's adverse event database. Estimated benefits of the nutrition labeling rule were derived from epidemiological studies of the consequences of dietary fat. In each case, the agency believed that it had a reasonably reliable data base upon which to base conclusions, and each risk assessment dealt with the risks of a single substance (tobacco, ephedra, and dietary fat). In contrast, this structure/function rule governs structure/function claims in the labeling for all dietary supplements. Although the agency could conceivably analyze a few of the claims covered by the rule, adequate data on the benefits and risks of most of these products are not available. Consequently, the agency believes that this rule will improve the nation's health, but concludes that it cannot feasibly quantify the effects of the rule on the nation's health expenditures.

One industry comment suggested that the regulatory system could impede firms from conducting research to substantiate structure/function claims, if DSHEA is construed so narrowly that it excludes meaningful health-related benefits. This comment noted, however, that the absence of an enforceable legal standard for substantiation would discriminate against companies that do research to support their claims and would deter science-based companies from entering the market. Similarly, a patient organization and several pharmaceutical companies expressed concern that the rule would permit some products to escape regulation as drugs and therefore diminish incentives for the costly clinical research conducted by pharmaceutical companies and academic scientists.

As stated previously in the document, FDA is not aware of any evidence that would indicate that the establishment of criteria for distinguishing structure/function claims from disease claims will adversely affect the conduct of scientific research. In fact, FDA believes that the final rule accords with the intent of DSHEA in promoting the enhancements to consumer health expected from the broad dissemination of structure/function information, while reducing the risks to consumer health associated with the promotion of disease treatment and/or prevention uses for products whose safety and efficacy have not been demonstrated.

E. Regulatory Alternatives

FDA has considered several major alternatives to the proposed rule as part of the rulemaking process. These include: (1) Taking no new regulatory action; (2) treating a statement about a

dietary supplement as a disease claim only if the statement included an express reference to a specific disease; and (3) treating a statement about a dietary supplement as a disease claim if the statement mentions an abnormality of the structure or function of the body, even if the abnormality was not characterized by a set of signs or symptoms recognized as the disease. These alternatives are fully discussed in the preamble to the proposed rule (63 FR 23624 at 23630) and alternative (2) is also discussed extensively in section II.E of this document. In brief, FDA finds that the public comment does not include evidence or arguments sufficient to persuade the agency to support these alternatives.

Within the broad framework of the final rule, FDA weighed other policy changes that could affect the compliance costs. One option would have set the compliance period for all firms at 6 months and another at 12 months from the publication date of the final rule. Other options would have extended the compliance period beyond 18 months for small businesses, or completely exempted small businesses from the rule. Finally, the proposed rule would have permitted firms 12 or 18 months to comply, depending on whether they were large or small firms; but only if they had submitted timely notifications of their structure/function claims to FDA and FDA had not objected to the claims. Other firms had only a 30-day compliance period.

Based on its model of food labeling costs, FDA assumes that compliance costs double for each halving of the compliance period (Ref. 13). Thus, the first option, which set a 6-month compliance date for all firms, results in average relabeling costs twice as high as that of the 12-month compliance period. FDA decided that this additional burden was not warranted. The option of a 12-month compliance period for small as well as large firms was rejected because of the additional burden to small firms, which may find it more difficult to effect rapid shifts in labeling procedures. The final rule provides small firms with an additional 6 months to introduce these labeling changes. Extending the compliance date for small firms beyond 18 months was rejected, because the agency did not believe that the delayed consumer benefits would be balanced by the relatively modest additional cost saving. Exempting all small firms was not acceptable, because most firms covered by this rule are small. The final option, which was to include the compliance periods specified in the proposed rule, required label changes within 30 days for

products bearing claims of which FDA had not been notified or claims to which FDA had already objected. This option was rejected because it could have increased costs per label for many small firms by a factor of eight.

F. Small Business Impacts

As stated above, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities, unless the rule is not expected to have a significant economic impact on a substantial number of small entities. With this final rule, FDA is defining the types of statements that can be made concerning the effect of a dietary supplement on the structure or function of the body. It also establishes criteria for determining when a statement represents a claim to diagnose, cure, mitigate, treat, or prevent disease and thus is not acceptable as a structure/function claim. The regulation was prepared in response to the dietary supplement industry's request for clarification from FDA with respect to the distinction between structure/function and disease claims, and to guidance in the Commission report suggesting that FDA provide such clarification to industry.

For its analysis of the proposed rule, FDA had estimated that between 500 and 850 firms were involved in dietary supplement manufacturing. A more recent industry survey reports that 1,050 companies manufacture dietary supplements; although as explained above, some of these companies may

manufacture products not covered by this rule. FDA has projected the industry size for this rule at about 1,000 firms. The Small Business Administration (SBA) has determined that dietary supplement manufacturers with fewer than 500 employees are small businesses. Because most data sources characterize firms in this industry by sales revenues rather than employment size, and because company revenues of less than \$20 million correlate reasonably well with a 500 employee threshold, FDA has received approval from the SBA to use a less-than-\$20 million sales revenue standard to represent small dietary supplement manufacturers. Table 1 displays the reported size distribution of the dietary supplement manufacturing industry.

As described above, FDA assumes that all small manufacturers of dietary supplements will incur administrative costs of about \$407 per firm. In addition, a number of small manufacturers of dietary supplements will need to alter some product labels, at an average redesign cost of about \$1,300 per SKU, and an average inventory cost of about \$107 per SKU. FDA further analyzed the dietary supplement product data base described in the October 1999 RTI report (Ref. 11) to determine how these products may be distributed among small businesses. As noted earlier, FDA estimates that about 628 of the 837 products (75 percent) needing revised labels due to this rule are manufactured by small firms. If these 628 products were randomly distributed among the 950 small

businesses, less than 0.1 percent of the small firms (1 firm) would be likely to have more than 4 of these products and only about 3 percent (30 firms) to have more than 2 of these products.

A small firm that needs to redesign labels for three products (about eight SKU's) due to the rule will incur estimated one-time direct compliance costs of about \$11,650. A small firm that needs to redesign labels for 4 products (about 10 SKU's) would incur costs of about \$14,950, or roughly 1.2 percent of average company revenue. Thus, the assumption that these products are randomly distributed among small firms indicates that very few small businesses would be likely to incur relabeling costs that are greater than 1 percent of average small company revenue. It is possible, however, that some firms will have a disproportionate number of labels to be revised. In the RTI database of 3,000 randomly selected products, only 3 companies (all large) have more than 24 products. Although the data base sample show a number of small companies with up to 24 products, it is very unlikely that all of these product labels would need to be changed due to this rule. If a small company needed to revise 10 products, however, its direct costs of compliance would be about \$37,000. Moreover, although FDA cannot quantify the likelihood, some small firms could lose product sales due to the necessary removal of a disease claim from a product label. Thus, FDA finds that this rule may have a significant economic impact on a substantial number of small companies.

TABLE 1.—ESTIMATED NUMBER OF DIETARY SUPPLEMENT MANUFACTURERS AND REVENUES, BY SIZE CATEGORY¹

Size Category	Number of Companies	Revenues (\$ in billions)	Percentage of Market
>\$100 million	16	3.32	55%
\$20 to \$100 million	38	1.54	25%
<\$20 million	996	1.19	20%
Total	1,050	6.05	100%

¹ Research Triangle Institute, "Economic Characterization of the Dietary Supplement Industry," March 1999, pp. 5–15.

VII. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. References

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

1. Commission on Dietary Supplement Labels, *Report to the President, Congress,*

and the Secretary of the Department of Health and Human Services, November 1997.

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

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

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

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

6. *The Merck Manual*, 17th ed., Merck Research Laboratories, Whitehouse Station, NJ, p. 416, 1999.

7. *Webster's Encyclopedic Unabridged Dictionary*, p. 1057, 1989.

8. *Economic Characterization of the Dietary Supplement Industry*, prepared for DHHS/FDA/CFSAN by Research Triangle Institute, Center for Economics Research under Contract No. 223-96-2290: Task Order 3, Final Report, p. 5-2, March 1999.

9. Herb and Supplement Usage Nears 70 Percent, Natural Foods Merchandiser, www.nfm-online.com/nfm_backs/Feb_98/herbusage.html.

10. Wyngate, P., Consumers Not Supplement Brand Savvy, Natural Foods Merchandiser, www.nfm-online.com/nfm_backs/Mar_98/brandsavvy.html.

11. *Dietary Supplement Sales Information*, prepared for DHHS/FDA/CFSAN by Research Triangle Institute, Center for Economics Research Under Contract No. 223-96-2290:

Task Order 4, Final Report, pp. 5–8, October 1999.

12. Research Triangle Institute, *Economic Characterization of the Dietary Supplement Industry*, p. 5–15.

13. Research Triangle Institute, "Compliance Costs of Food Labeling Regulations," prepared for CFSAN/FDA by RTI under Contract No. 223–87–2097, final report, pp. 5–3, 5–4, January 1991.

14. U.S. Department of Labor, Bureau of Labor Statistics, BLS.

15. Memorandum from R. J. Moore, FDA, to file, review of notifications made pursuant to 21 U.S.C. 343(r)(6).

16. Memorandum from J. Lienesch, FDA, to file, calculation of relabeling cost estimate for final rule on statements made for dietary supplements concerning the effect of the production on the structure or function of the body, December 22, 1999.

List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

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

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

2. Section 101.93 is amended by revising the section heading and by adding paragraphs (f) and (g) to read as follows:

§ 101.93 Certain types of statements for dietary supplements.

* * * * *

(f) *Permitted structure/function statements.* Dietary supplement labels or labeling may, subject to the requirements in paragraphs (a) through (e) of this section, bear statements that describe the role of a nutrient or dietary ingredient intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such

structure or function, provided that such statements are not disease claims under paragraph (g) of this section. If the label or labeling of a product marketed as a dietary supplement bears a disease claim as defined in paragraph (g) of this section, the product will be subject to regulation as a drug unless the claim is an authorized health claim for which the product qualifies.

(g) *Disease claims.* (1) For purposes of 21 U.S.C. 343(r)(6), a "disease" is damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition.

(2) FDA will find that a statement about a product claims to diagnose, mitigate, treat, cure, or prevent disease (other than a classical nutrient deficiency disease) under 21 U.S.C. 343(r)(6) if it meets one or more of the criteria listed below. These criteria are not intended to classify as disease claims statements that refer to the ability of a product to maintain healthy structure or function, unless the statement implies disease prevention or treatment. In determining whether a statement is a disease claim under these criteria, FDA will consider the context in which the claim is presented. A statement claims to diagnose, mitigate, treat, cure, or prevent disease if it claims, explicitly or implicitly, that the product:

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

(ii) Has an effect on the characteristic signs or symptoms of a specific disease or class of diseases, using scientific or lay terminology;

(iii) 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;

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

(A) The name of the product;

(B) A statement about the formulation of the product, including a claim that the product contains an ingredient (other than an ingredient that is an article included in the definition of "dietary supplement" under 21 U.S.C. 321(ff)(3)) that has been regulated by FDA as a drug and is well known to consumers for its use or claimed use in preventing or treating a disease;

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

(D) Use of the term "disease" or "diseased," except in general statements about disease prevention that do not refer explicitly or implicitly to a specific disease or class of diseases or to a specific product or ingredient; or

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

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

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

(vii) Augments a particular therapy or drug action that is intended to diagnose, mitigate, treat, cure, or prevent a disease or class of diseases;

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

(ix) Treats, prevents, or mitigates adverse events associated with a therapy for a disease, if the adverse events constitute diseases; or

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

Dated: October 26, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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