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Food and Drug Administration

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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 (insert date 30 days after date of publication in the FEDERAL REGISTER).

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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 use 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 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.

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 ½ Gross Rubber Prophylactics, 65 F. Supp. 534, 535 (D. Minn. 1946), aff'd sub nom. Gellman v. United States, 159 F.2d 881 (8th Cir. 1947); 59 FR 6084, 6088 (February 9, 1994) (terms "antibacterial," "antimicrobial," "antiseptic," or "kills germs" constitute implied drug claims that cause products carrying them to be drugs); 58 FR 47611, 47612 (September 9, 1993) (labeling indicating that "hormones" are present in a product constitutes implied drug claim); 58 FR 28194, 28204 (May 12, 1993) (products carrying term "sunscreen"

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Under proposed § 101.93(g)(2)(ii), a statement would be considered a disease claim if it explicitly or implicitly claimed an effect (using scientific or lay terminology) on one or more signs or symptoms that are recognizable to health care professionals or consumers as being characteristic of a specific

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

FDA specifically requested comment on the distinction between maintaining normal function, which is potentially the basis for an acceptable structure/function claim, and preventing or treating abnormal function, which is potentially a disease claim. FDA noted that the members of the Commission were divided on this issue, but that the final report concluded that "statements that mention a body system, organ, or function affected by the supplement using terms such as 'stimulate,' 'maintain,' 'support,' 'regulate,' or 'promote' can be appropriate when the statements do not suggest disease prevention

or treatment or use for a serious health condition that is beyond the ability of the consumer to evaluate" (the report, p. 38).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(Report at pp. 38 and 39.)

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

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

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