

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket Nos. 00P-1275 and 00P-1276]

DMB

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Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule; reopening of comment period.

SUMMARY: The Food and Drug Administration (FDA) is reopening for 45 days the comment period for the interim final rule authorizing a health claim on the association between plant sterol/stanol esters and reduced risk of coronary heart disease (CHD). This interim final rule appeared in the **Federal Register** of September 8, 2000 (65 FR 54686). Interested persons were given until November 22, 2000, to comment on the health claim. After the comment period closed, FDA received two requests to reopen the comment period; therefore, this reopening is in response to these requests.

DATES: Submit written or electronic comments by [*insert date 45 days after date of publication in the Federal Register*].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: James Hoadley, Center for Food Safety and Applied Nutrition (HFS-832), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5429.

SUPPLEMENTARY INFORMATION:

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I. Background

In the **Federal Register** of September 8, 2000 (65 FR 54686), FDA published an interim final rule authorizing the use, on food labels and in food labeling, of a health claim on the relationship between plant sterol/stanol esters and reduced risk of CHD (the interim final rule). In the interim final rule, FDA specified requirements for a health claim about the relationship, including types of food eligible to bear the claim, sources and nature of the plant sterol/stanol esters that are the subjects of the claim, daily intakes of these substances needed to reduce the risk of CHD, and analytical methods for assessing compliance with qualifying criteria for the claim. The 75-day comment period closed on November 22, 2000.

After the comment period closed, FDA received comments from two companies, Unilever United States, Inc., and Raisio Benecol Ltd., which included requests for an extension of the comment period. Both comments requested more time for submission of data comparing the daily intake levels of plant sterol esters and plant stanol esters that are effective in reducing the risk of CHD. Because FDA cannot extend a comment period that has closed, the agency considers these as requests to reopen the comment period.

Among the other comments received in response to the interim final rule were requests to expand the types of substances eligible for the health claim to include unesterified plant sterols/stanols and mixtures of plant sterols and plant stanols. We also received a comment advocating the use of serum apolipoprotein B level as a surrogate measure of CHD risk.

Furthermore, in the past year, both the European Commission (EC) and the Australia New Zealand Food Standards Council (ANZFSC) have taken regulatory actions limiting food use of plant sterol esters and requiring advisory labeling statements on foods to which plant sterol esters have been added. Also, a recent publication from the American Heart Association (AHA) (Ref. 1) raised a concern about daily ingestion of plant sterol/stanol ester-containing foods among certain individuals who have abnormally high absorption of plant sterols.

FDA believes that the issues raised by comments and recent events are significant and that thorough evaluation is needed before a final rule is issued. Accordingly, the agency is reopening the comment period for this rulemaking. Given the very tight timeframes that are established by the health claim provisions of the statute, however (see section 403(r)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 343(r)(4)(A)(i))), as well as the agency's interest in ensuring that scientifically valid claims are authorized as quickly as possible, the agency cautions that only on rare occasions might FDA be in a position to reopen the comment period in a health claim rulemaking. In this case, we believe that reopening the comment period to obtain public input on the new issues is important to help us make more informed decisions in the final rule. Although the statutory deadline for this final rule has passed, FDA intends to move as expeditiously as possible to complete this rulemaking.

II. Issues on Which FDA Is Requesting Comment

A. Eligibility of Unesterified Plant Sterols and Plant Stanols for the Health Claim

In the interim final rule, FDA did not include unesterified plant sterols and plant stanols in the definition of substances eligible for the health claim. Several comments requested that the agency allow foods containing the unesterified form of these substances to bear the health claim. While some of the data in support of the interim final rule were from studies involving unesterified plant sterols or plant stanols, the agency requests submission of any additional data on the effectiveness, particularly at lower intake levels, of the unesterified forms in reducing the risk of CHD. FDA also requests data on the effects of various food matrices on the relationship of unesterified plant sterols/stanols and CHD risk.

B. Daily Intake Levels Necessary to Reduce the Risk of CHD

In the interim final rule, FDA required health claims for plant sterol/stanol esters to specify the daily intake necessary to reduce the risk of CHD. The agency set different daily intake levels for plant sterol esters and plant stanol esters (1.3 grams/day (g/d) and 3.4 g/d, respectively), based

on studies that showed differences in the levels of intake that were effective in reducing low-density lipoprotein (LDL) and blood total cholesterol levels. Many comments argued that one of the daily intake levels should be changed; several comments argued that the daily intake levels for plant sterol esters and plant stanol esters should be the same. FDA requests further comment on these issues, including supporting data on the daily intake levels of plant sterols and plant stanols (in either esterified or unesterified form) that are effective in reducing the risk of CHD.

C. Eligibility of Mixtures of Plant Sterols and Plant Stanols for the Health Claim

In the interim final rule, FDA authorized separate health claims for plant sterol esters and plant stanol esters. One comment requested that FDA include mixtures of plant sterols and stanols in the definition of substances eligible to bear the health claim. FDA requests data on the daily intake levels of mixtures of plant sterol esters and plant stanol esters (or mixtures of the unesterified forms) that are effective in lowering CHD risk. If plant sterols and plant stanols (in either esterified or unesterified form) are not equally beneficial at the same levels of intake in reducing CHD risk (as evidenced by validated surrogate markers), FDA also requests data on the relative amounts of plant sterols and plant stanols (in either esterified or unesterified form) in the mixtures that should qualify a food to bear the health claim.

D. Significance of Apolipoprotein B Concentration as a Surrogate Marker for CHD Risk

One comment seeking a lower daily effective intake level for plant stanol esters, argued that plasma apolipoprotein B level is a reliable marker of LDL cholesterol that can be measured precisely and directly, in contrast to serum LDL cholesterol level, which usually is determined indirectly by calculation. The comment further argued that plasma apolipoprotein B level is a reliable marker in evaluating the risk of cardiovascular disease. These comments were discussed in relation to the study by Hallikainen et al. (Ref. 2). In the Hallikainen et al. study, the lowest intake of plant stanol esters that reduced serum LDL cholesterol was greater than the intake that

reduced serum apolipoprotein B. Thus, the comment asserted these results support a lower daily effective intake level for plant stanol esters than that established in the interim final rule.

FDA requests comment on use of serum apolipoprotein B as a validated surrogate marker for CHD and on the relative utilities of apolipoprotein B and LDL cholesterol in predicting CHD risk.

E. Issues Regarding Safe Use of Plant Sterol/Stanol Esters in Foods and Advisory Label Statements

Since the issuance of the plant sterol/stanol esters interim final rule, FDA has become aware of pertinent regulations from other countries. The EC issued a regulation that requires the label of foods to which plant sterol esters have been added to include certain statements (Ref. 3). Such statements include: (1) The product is for people who want to lower their blood cholesterol levels; (2) patients on cholesterol lowering medication should consume the product only under medical supervision; (3) the product may not be appropriate nutritionally for certain segments of the population (pregnant and breast-feeding women, and children under the age of 5 years); and (4) the product should be used as part of a healthy diet, including regular consumption of fruit and vegetables. The EC explained that statements (3) and (4) were necessary to protect populations at risk (people whose vitamin A status was not optimal) since these products may cause a reduction in plasma beta-carotene (Ref. 3).

The ANZFSQ adopted the standard, recommended by the Australia New Zealand Food Authority (Ref. 4), that plant sterol esters should be allowed for use only in edible oil spreads, and that the product must carry an advisory label statement. The advisory label statement informs consumers that plant sterol ester-enriched edible oil spreads are not appropriate for infants, children and pregnant and lactating women, and that people using cholesterol-reducing medication should seek medical advice before using the spreads.

The AHA (Ref. 1) recently published a statement for healthcare professionals on foods containing plant sterol/stanol esters. One of the issues that the AHA raised concerned individuals who have unusually high intestinal absorption of plant sterols. Plant sterols are poorly absorbed

by the human intestine, but individuals who are homozygous for a rare genetic disease, sitosterolemia (also known as phytosterolemia), are high absorbers of plant sterols, resulting in tendon and subcutaneous xanthomas (skin lipid deposits). It is not known if individuals heterozygous for this condition absorb higher amounts of plant sterols than the normal population or if this would lead to adverse effects. In the absence of more data on the genetic mutation involved in sitosterolemia, the AHA recommends that individuals with this condition not use foods containing plant sterols/stanols.

Section 201(n) of the the act (21 U.S.C. 321(n)) states that, in determining whether labeling is misleading, the agency shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations or material with respect to consequences that may result from use of the product. The omission of material facts from the labeling of a food causes the product to be misbranded within the meaning of sections 201(n) and 403(a)(1) of the act. FDA may require disclosure of material facts in labeling by rulemaking or by direct enforcement action (see 21 CFR 1.21).

In light of the issues raised by recent regulatory actions of other countries and by the AHA statement (i.e., whether foods containing plant sterol esters should be used under medical supervision, the appropriateness of consumption of such foods by some subpopulation groups, negative effect of such foods on plasma beta-carotene, and concerns about potential hyper-absorption of plant sterols by some individuals), FDA is considering whether changes to the health claim regulation (§ 101.83 (21 CFR 101.83)), advisory labeling, or other actions are needed to ensure the safe use of plant sterols and stanols (esterified or unesterified) in foods. The agency requests comment on whether the concerns summarized above are material facts and what action, if any, the agency should take to address them. Depending on the comments received and FDA's own evaluation of relevant data, the agency may consider issuing a proposal to amend § 101.83 or initiating a separate rulemaking, as appropriate.

III. Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments by [*insert date 45 days after date of publication in the Federal Register*]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The interim final rule and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

IV. References

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

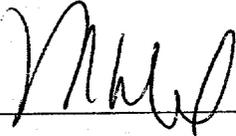
1. Lichtenstein, A. H. and R. J. Deckelbaum for the American Heart Association Nutrition Committee, "Stanol/Sterol Ester-Containing Foods and Blood Cholesterol Levels. A Statement for Healthcare Professionals From the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association," *Circulation*, vol. 103, pp. 1177-1179, 2001.

2. Hallikainen, M. A., E. S. Sarkkinen, and M. I. J. Uusitupa, "Plant Stanol Esters Affect Serum Cholesterol Concentrations of Hypercholesterolemic Men and Women in a Dose-Dependent Manner," *Journal of Nutrition*, vol. 130, pp. 767-776, 2000.

3. Commission Decision of July 24, 2000, on "Authorizing the Placing on the Market of 'Yellow Fat Spreads with Added Phytosterol Esters' as a Novel Food Ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council," *Official Journal L 200*, August 8, 2000, pp. 0059-0060.

4. Australia New Zealand Food Authority (ANZFA), Food Standard Ministers Approve Plant Sterol Esters as a Novel Food Ingredient in Edible Oil Spreads, ANZFA Media Release, June 1, 2001, available at www.anzfa.gov.au.

Dated: 9/28/01
September 28, 2001.



Margaret M. Dotzel,
Associate Commissioner for Policy.

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