



October 8, 2003

Hand Delivered

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Re: FDA letter of February 14, 2003 re: health claims for phytosterols;
request for reconsideration and comments on guidance that FDA is
developing.
Docket Nos. 00P-1275 and 00P-1276: Comments, and request to reopen
the comment period.

To Whom It May Concern:

On February 14, 2003, FDA sent to Cargill Health & Food Technologies a letter stating that FDA intends to exercise enforcement discretion with respect to expanded use of health claims about plant sterol and stanol esters and reduced risk of coronary heart disease (CHD). We are writing to comment on, and request that FDA reconsider, this enforcement policy.

In its letter, FDA said that it would issue guidance on the issues discussed in the letter and would later issue a final rule. Our comments are therefore provided as (1) a request for reconsideration under 21 CFR 10.33,¹ (2) input on the guidance document that FDA is developing, under 21 CFR 10.115(f), and (3) comments on the interim final rule, 21 CFR 101.83; 65 Fed. Reg. 54685 (Sept. 8, 2000). For the latter purpose, we request that the comment period be reopened as necessary to receive these comments, which provide important new information that was not available at the time the most recent comment period ended. 21 CFR 10.30 and 10.40.

A. DECISION INVOLVED

In its February 14th letter, FDA said that it would exercise enforcement discretion for health claims about phytosterols in "foods other than those specified in

¹ This request is submitted later than 30 days after FDA's February 14th letter because additional time was needed to obtain and review the scientific studies supporting this request, and to obtain the opinions of experts in the field.

00P-1276

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§101.83(c)(2)(iii)(A),” so long as the food meets the conditions set forth in the letter. Thus, FDA would permit health claims to be made for unesterified sterols and stanols (“free phytosterols”) in a variety of foods beyond those currently listed in the interim final rule – including conventional foods that are low-fat or fat-free.²

B. ACTION REQUESTED

At this time there does not exist significant scientific agreement that a health claim about the relationship between free phytosterols in low-fat or fat-free conventional foods and CHD is supported by the totality of publicly available scientific evidence, as required by section 403(r)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act.

Accordingly, we respectfully request that FDA modify its February 14th letter (and any subsequent guidance document and final rule) to state that:

- Conventional foods that contain free phytosterols are eligible to be labeled with the health claim only if the foods are not “low-fat” or “fat-free,” and they otherwise meet the conditions of the February 14th letter; and
- Persons may submit information to establish that a health claim about free phytosterols in “low-fat” or “fat-free” conventional foods is supported by significant scientific agreement by submitting a petition to amend the final rule.

C. STATEMENT OF GROUNDS

We have reviewed the publicly available studies of the cholesterol-lowering effectiveness of free phytosterols at dose levels corresponding to 400 mg or more per reference amount customarily consumed (RACC). The studies that show a consistent cholesterol-lowering effect have been conducted only on conventional foods that contain relatively high levels of fat (e.g., spreads and mayonnaise). In contrast, studies of free phytosterols in low-fat and fat-free foods are inconclusive with respect to whether free phytosterols consistently result in meaningful levels of cholesterol reduction. It is unclear why this inconclusive result has occurred, but it may have to do with the crystalline behavior of free sterols and stanols. The data suggest that the availability of free phytosterols to interact with cholesterol may be significantly different when they are formulated in low-fat or fat-free foods as compared to when they are formulated in higher fat matrices, and for this reason additional data are needed to establish the effectiveness of the low-fat and fat-free formulations.

² This submission does not address the use of the health claim on the labels of dietary supplements.

For example, the following studies showed a lack of efficacy of free phytosterols in low-fat or fat-free matrices:

- In a study of the effect of added free phytosterols to low-fat and fat-free beverages, the reduction of total and LDL-cholesterol with phytosterol-containing drinks was no different than that caused by a placebo drink. Jones PJH, Vanstone CA, Raeini-Sarjaz M, St-Onge M-P. Phytosterols in low- and nonfat beverages as part of a controlled diet fail to lower plasma lipid levels. *J Lipid Research* 2003;44:1713-9.
- In another study, dietary supplementation with 3 g of the hydrogenated plant sterol sitostanol, suspended in 1 g safflower oil per 250 mg sitostanol, did not significantly lower LDL cholesterol compared with diet alone. Denke MA. Lack of efficacy of low-dose sitostanol therapy as an adjunct to a cholesterol-lowering diet in men with moderate hypercholesterolemia. *Am J Clin Nutr* 1995;61:392-6.

The following study suggested that free phytosterols in low-fat foods are less effective than phytosterol esters:

- Incorporated in low-fat wheat-based breakfast cereal, low-fat wholemeal bread and a soft margarine, 2.4 g plant sterol ester daily lowered LDL-cholesterol (13.6%) more than 2.4 g plant stanol daily (8.4%) incorporated in the same foods. Although the difference was not statistically significant, these data suggest that sterol esters are 60% more effective than free stanols. Nestel P, Cehun M, Pomery S, Abbey M, Weldon G. Cholesterol lowering effects of plant sterol esters and non-esterified stanols in margarine, butter and low-fat foods. *Eur J Clin Nutr* 2001;74:563-4.

Copies of these studies are enclosed.

In addition, we are aware that, at a meeting of the Nutrition Foundation of Italy in March 2001, the participants reached a conclusion that, although free phytosterols can have the same effect on plasma lipoproteins as phytosterol esters, the matrix and emulsification are important, and negative results are not uncommon. Therefore, this group recommended that new food forms be evaluated for efficacy if they differ greatly from previously tested forms. Similarly, a 2002 report of the European Commission's Scientific Committee on Food comments that, "to trigger the cholesterol lowering effect, the food matrix or the background diet is of more importance for free plant stanols than

for esterified plant stanols.”³ Further, we are not aware of any studies that consistently and reliably report successful results using free phytosterols in low-fat or fat-free conventional foods.

We have asked two independent experts in the field to review the publicly available studies and advise us on whether the data support the cholesterol-lowering effectiveness of free phytosterols in low-fat and fat-free foods. These experts are Ernst J. Schaefer, M.D., professor of medicine and director of the Lipid and Heart Disease Prevention Program at Tufts University; and Peter J.H. Jones, Ph.D., professor in the School of Dietetics and Human Nutrition at McGill University. Both of these experts have advised us that, at this time, the available data do not permit a conclusion to be drawn as to whether free phytosterols consistently and meaningfully reduce cholesterol levels when formulated in low-fat or fat-free foods. Copies of these opinions are attached.

Based on this information, at this time there does not exist significant scientific agreement that a health claim about free phytosterols in low-fat or fat-free conventional foods is supported by the totality of publicly available scientific evidence, as required by section 403(r)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act.

Accordingly, we respectfully request that FDA modify its February 14th letter (and any subsequent guidance document and final rule) to state that:

- Conventional foods that contain free phytosterols are eligible to be labeled with the health claim only if the foods are not “low-fat” or “fat-free,” and they otherwise meet the conditions of the February 14th letter; and

³ General view of the Scientific Committee on Food on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on β -carotene (Oct. 3, 2002), p. 12 (http://europa.eu.int/comm/food/fs/sc/scf/out143_en.pdf).

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- Persons may submit information to establish that a health claim about free phytosterols in “low-fat” or “fat-free” conventional foods is supported by significant scientific agreement by submitting a petition to amend the final rule.

Respectfully submitted,



Nancy L. Schnell
Deputy General Counsel –
Marketing and Regulatory

Enclosures

cc: Christine L. Taylor, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
CFSAN