CARGILL
Health & Food
Technologies

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November 16, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
Parklawn Building
Room 1061
Rockville, MD 20852

RE: Dockets OOP-1275 and OOP-1276; Comments to Interim Final Rule for Health Claims: Plant Sterol/Stanol Esters and Coronary Heart Disease

Dear Sir or Madam:

Cargill, Incorporated ("Cargill") respectfully submits the following comments in response to the reopening of the comment period for the interim final rule authorizing a health claim for the association between plant sterol/stanol esters and reduced risk of heart disease, published October 5, 2001 (65 Fed. Reg. 50824)).

Recommendations

We urge the Agency to conduct an expeditious review of the comments filed during this open comment period in order to issue a final rule that will provide market opportunities for the food industry and desirable products for consumer.

Additionally, Cargill provides comments on the following issues raised by the FDA:

1. Allow Unesterified Plant Sterols to be Eligible for the Health Claim

The FDA concluded that substances eligible to bear the health claim are plant sterol esters and plant stanol esters (101.83(c)((2)(ii)(A) and (B). However, FDA noted sterol esters and stanol esters are hydrolyzed to free sterols and free stanols prior to their biological activity in lowering serum cholesterol (65 FR 54690). Thus, the Agency agrees that the active moiety of the plant sterol esters and plant stanol esters are the plant sterols and stanols themselves.

Cargill requests that the final health claim rule recognize both the esterified forms as well as the free forms of sterols as substances eligible for the health claim based on the following. First is the recognition that the free and esterified forms are both effective in reducing elevated cholesterol levels. Cholesterol absorption decreases when either free or esterified plant sterols are added to food. (Volpe et al, 2001; Christiansen et al, 2001; Pelletier et al, 1995; Sierksma et al, 1999).

Another reason to establish free sterols as eligible substances is to enhance the food application opportunities by eliminating the restriction to fat-based food matrices. While plant sterol esters can be formulated into consumer-valued food matrices, the broadening of the eligible substances provides consumers with more potential product sources and a greater ability to achieve a health benefit. Sterol esters are ideally suited for use in a fat-based food matrix, and not in dry or water-based systems. Therefore, establishing free sterols as eligible substances, which are better suited in dry and water-based systems, provides greater potential opportunity to benefit consumers seeking alternative options.

To further enhance the potential incorporation of sterols into food products, Cargill also requests that the final rule be flexible enough to allow for phytosterols that may be manufactured in conjunction with other food grade substances through physical association to be eligible to bear the health claim. The benefit of this action is to endow these products with properties favorable for incorporation into water-soluble matrices and thus, expand the options from which manufacturers and subsequently, consumers have to choose.

Recent studies provide support that physical modifications do not change the efficacy profile of the substance and thus, should be eligible to bear the health claim. Microcrystalline plant sterols reduced both serum total and LDL-cholesterol concentrations significantly. The cholesterol lowering effect of the two doses evaluated in the study, 1.5 g and 3.0 g plant sterols per day, did not differ from one another. The investigators concluded that plant sterols in a microcrystalline form are as effective as in a fat-soluble ester form. They further suggest the effective surface area of the plant sterol crystals is large and thus, achieves a highly effective trapping of cholesterol molecules in the intestinal lumen. (Christiansen et al, 2001).

Another study demonstrated that sitostanol, when consumed by humans in the form of a lecithin-emulsified micelle, effectively inhibited cholesterol absorption from the gastrointestinal tract (Ostlund et al, 1999). The study compared the cholesterol-lowering properties of sitostanol to lecithin-emulsified sitostanol and found that the micellar form was effective.

Finally, in support of the inclusion of free sterols as eligible substances, it should be noted that the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) "encourages use of plant stanols/sterols as therapeutic dietary options to enhance lowering LDL cholesterol". (NCEP, May 2001)

2. Daily intake levels of free sterols necessary to reduce the risk of CHD should correlate with the levels established for esterified forms.

It is our recommendation that FDA allow free sterols incorporated into food products to be eligible to bear the health claim, assuming they are present at the level consistent with a meaningful cholesterol lowering effect. The agency found the lowest effective amount for sterol esters to be 1.3 grams of sterol esters per day. Therefore, based on the fact that 60% of the esterified form is comprised of sterol, we recommend establishing 0.78 (or 0.8 grams) for free sterols as the level eligible to bear a health claim.

3. Advisory label statements are not warranted to ensure the safe use of sterol esters

FDA is considering whether changes to the health claim regulation, advisory labeling or other actions are needed to ensure the safe use of plant sterols and stanols (esterified or unesterified) in foods based on information made available by European Community ("EC"), the Australia New Zealand Food Authority (ANZFA) and the American Heart Association. The Agency seeks comments on whether the information is "material" and what action, if any, is needed, with particular focus on the intake of phytosterols on serum carotenoid levels and sitosterolemia.

The incidence of phytosterolemia is very small. It is characterized by observable consequences such as elevated phytosterols in the blood, presence of xanthomas and premature atherosclerosis. People with phytosterolemia, once diagnosed, are advised to reduce their intake of phytosterols. Given that there are several obvious clinical signals of this condition, it is not likely the disease would go undetected and thus, pose a risk for those that are not aware of their condition. In addition, information on the content of a product as provided in ingredient labeling has been judged adequate for those individuals seeking to avoid certain

substances. We do not believe this condition warrants any deviation from this policy.

While this is a significant health risk to this population, we do not find that an advisory statement in labeling of these products is warranted nor is it beneficial to the general population. We believe that a label advisory statement suggesting at-risk populations to avoid consumption of foods containing phytosterols would cause more negative consequences, and detract from the potential health benefits that could be achieved by the general population. Such labeling would unnecessarily alarm consumers and would not fairly reflect the safety profile of these substances, which have consistently been shown to be safe and lacking adverse effects in numerous clinical trials, some of which included children (Williams et al, 1999). We find that the most appropriate way to provide meaningful information to consumers, in a format that is familiar to them, is the declaration of the substance(s) in the ingredient declaration, which is consistent with other regulations.

4. Other Issues

a. Acceptable food applications should not be specified

In 101.83(c)(2)(iii)(A)(1), the FDA specifies that the food products containing sterol esters eligible to bear the health claim are restricted to spreads and dressings for salads. FDA acknowledges in the preamble to the interim final rule that this was primarily because these were the only matrices for which the petitioners sought to establish. Due to the lipophilic nature of the sterol esters, fat-based products are the most logical food applications for the substances.

However, the scientific data do not support limitations on specific food applications. While many of the published studies have been done in spreads, salad dressings or mayonnaise, other foods have been shown to be efficacious as well. A recent study confirmed that plant sterols (1 gram per day) in a yogurt-based drink lowers LDL-cholesterol and total cholesterol effectively in patients with primary moderate hypercholesterolemia (Volpe R et al, 2001).

Limiting eligible substances to bear the health claim only to sterol esters, coupled with limiting the food matrices these can be incorporated into, restricts food choices for consumers seeking to make dietary changes. In addition to broadening the eligible substances for the health claim to include free sterols, Cargill also recommends that FDA not specify the food application for which the

health claim is applicable. This will not only serve to provide greater variety of food products, it will greatly enhance the probability consumers will be able to comply with a regimen to include the 1.3 grams of sterols esters (or 0.8 grams of free sterol) per day.

b. Validated Analytical Methods

FDA finds in the final interim rule that other food products to be considered eligible to bear the health claim should "provide a validated analytical method that permits accurate determination of the amount" (65 Fed. Reg. 54707). While we support the contention that a manufacturer should ensure that the minimum amount required by the health claim is contained in the finished food product, we do not believe the Agency should require the submission of this information to the FDA nor should it be subject to pre-clearance. Additionally, we do not support the need for a method that is specific to each food application.

There is relevant precedent for this approach in preceding health claim deliberations. FDA proposed that all substances eligible for the soy protein health claim meet a standard Association of Official Analytical Chemists International ("AOAC") analytical method. Upon comments received that the method was not to be a reliable measure across all available foods, it was decided that a suitable general method would be allowed.

There is presently no recognized AOAC official method of analysis for plant sterols, stanols or their esterified forms. Until such standardized methodology is developed, we believe it is the marketer's responsibility to ensure the product meets the criteria in the health claim and thus, must use reliable methods and maintain adequate records to demonstrate its eligibility. We therefore recommend the FDA specify that the marketer of a product bearing a health claim have in their own files a validated method of analysis showing compliance to the provisions of the final health claim rulemaking.

5. Conclusions

In conclusion, Cargill requests that when finalizing the health claim rulemaking, the Agency:

- Authorize in the final health claim that both free sterols and the esterified forms be eligible to bear the health claim
- Authorize plant sterols that are combined with other food grade materials in order to modify the physical properties of the free sterols be eligible for the health claim;
- Establish the amount of free sterols in order to establish an eligible food product should be 0.4 grams per serving or 0.8 grams per two-servings/day;
- Continue to rely on the ingredient declaration as a means to inform consumers to the presence of the ingredient, and not resort to cautionary label statements;
- Increase the potential of new product matrices by allowing flexibility of food applications in the final health claim; and
- Allow for manufacturers to establish validated analytical methods for determining the amount of the substance in their specific product application, with that information to be made available to the agency upon request.

We appreciate the opportunity to comment and look forward to the finalization of the rulemaking process for this health claim.

Sincerely,

Barbara A. Bentson

Barbara A. Bentson
Director
Regulatory Affairs, Safety and Quality Systems

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