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VIA HAND DELIVERY

Division of Dockets Management Branch
U.S. Food and Drug Administration
Department of Health & Human Services, rm. 1-23
5630 Fishers Lane, Room 1061
Rockville, MD 20852

PETITION FOR STAY OF ACTION

For more than seven years, the public has relied on a statement of enforcement discretion with regard to health claims and phytosterols. In the preamble to a proposed rule published on December 8, 2010, FDA stated its intention to abandon this policy of enforcement discretion within a mere 75 days, based in part on tentative conclusions about the effect of phytosterols on coronary heart disease. Such a dramatic shift by FDA would be disruptive to industry and to consumers who rely on these important products. The undersigned, on behalf of Cargill, Incorporated, submit this petition requesting that the Commissioner of Food and Drugs stay the effective date of the change in enforcement discretion.

A. Decision involved

In the December 8, 2010 *Federal Register*,[1] FDA published a proposed rule to amend the regulation currently authorizing, for specified conventional foods and dietary supplements, a health claim regarding the relationship between plant sterol esters and plant stanol esters and reduction in the risk of coronary heart disease (CHD).[2] FDA has stated that beginning 75 days after the date of the proposed rule's publication – *i.e.* February 21, 2011 – FDA intends to stop exercising its enforcement discretion based on its 2003 Letter of

[1] 75 Fed. Reg. 76525 (Dec. 8, 2010).

[2] 21 C.F.R. § 101.83 (2010).

Enforcement Discretion ("2003 Letter"),[3] and begin exercising its enforcement discretion based upon the provisions of the proposed rule.[4]

B. Action requested

Pursuant to FDA's regulations at 21 C.F.R. § 10.35, the undersigned request that the Commissioner stay rescission of enforcement discretion under the 2003 Letter pending issuance of the final rule. This action will have the effect of maintaining until that time the allowance of the phytosterol health claim on the following products (presuming all other applicable criteria are met):

- conventional foods formulated with safe phytosterol ingredients that have not been the subject of a GRAS notification to which FDA responded with a "No Questions" letter;
- conventional foods formulated with phytosterols at 0.4 g free sterol equivalent per reference amount customarily consumed (RACC); and
- dietary supplements containing free phytosterols at 0.4 g free sterol equivalent per RACC.

C. Statement of Grounds

Cargill bases this Petition for Stay of Action on the following grounds.

1. Cargill and its Customers Will Be Irreparably Harmed if the Stay is Not Granted

Cargill will suffer irreparable injury should FDA cease to exercise its enforcement discretion based upon the 2003 Letter on February 21. Cargill is a leading provider of both esterified and free form phytosterol ingredients, which it supplies to its customers for use in conventional foods and dietary supplements. Cargill's interest in helping deliver beneficial phytosterols to a considerably wider range of consumers than would have occurred under the interim final rule motivated the company to ask FDA to expand the categories of foods eligible to bear the health claim in 2003. Since that time, Cargill has developed and marketed a broad range of phytosterol ingredients for use in conventional foods and dietary supplements.

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[3] Center for Food Safety and Applied Nutrition, Food and Drug Administration. Letter of Enforcement Discretion from FDA to Cargill Health & Food Technologies. Docket no. FDA-2000-P-0102 and Docket No. FDA-2000-P-0133. February 14, 2003.

[4] 75 Fed. Reg. at 76546.

Some of Cargill's phytosterol ingredients for use in conventional foods have been the subject of a GRAS notification to FDA to which the agency responded with a "No Questions" letter (GRN 00048). However, additional phytosterol ingredients marketed by Cargill and intended uses in food categories beyond those documented in that notification have been the subject of self-GRAS determinations. Additionally, many phytosterol ingredients have GRAS-notified status for use in foods at less than 0.5 g free sterol equivalent per reference amount customarily consumed (RACC), the new proposed threshold for eligibility of a food to bear the health claim, although Cargill has made self-GRAS determinations for the use of many such ingredients at 0.5 g free sterol equivalent/RACC or higher. As FDA has acknowledged, many uses of phytosterols in GRAS notifications to which the agency did not object are at levels below this newly-proposed threshold.[5] This is due to the alignment of the GRAS notifications with the use levels in the 2000 Interim Final Rule, 0.4 g free sterol equivalent/RACC, to help constrain the cost of phytosterols in food formulations and to expand the food categories eligible for the CHD health claim while maintaining an acceptable margin of safety for total cumulative daily intake. Should FDA begin exercising enforcement discretion based upon the proposed rule, rather than the 2003 Letter, many phytosterol-containing products would no longer be eligible to bear the CHD health claims that were permissible under the 2003 Letter.

Even if Cargill submitted GRAS notifications today for all of its phytosterol ingredients for use in conventional foods at the newly proposed level, FDA could not reasonably review those notifications (along with the GRAS notifications it is bound to receive from other industry players) and provide "No Questions" responses by February 21. In addition, insurmountable challenges – including technological difficulties of finished food manufacturers to meet consumer preferences and standards (especially regarding taste and mouthfeel), production schedules, and costs – prevent the reformulation of phytosterol-containing conventional foods and dietary supplements to meet the newly-proposed eligibility criteria. Such reformulations could not be accomplished by February 21, nor can Cargill's customers reasonably relabel products to remove health claims currently used in reliance on the 2003 Letter by that date. Accordingly, the majority of phytosterol-containing conventional foods and dietary supplements may need to be pulled from store shelves on February 21 unless FDA grants the relief requested in this petition.

We understand the statements regarding enforcement discretion in the proposed rule to mean that food products in the following categories would no longer be permitted to bear the health claim as of February 21, 2011, because they lack GRAS notifications for uses at a minimum of 0.5 g free sterol equivalent/RACC:

- beverages (other than fruit & vegetable juices)
- dairy analogs

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[5] 75 Fed. Reg. at 76530.

- baked goods
- standardized and non-standardized bread products (other than white bread products)
- cheese and cream
- breakfast cereal
- pasta and noodles
- sauces
- salty snacks
- processed soups
- puddings
- confections, and
- vegetarian meat analogs.

In order for these foods to again become eligible to bear the health claim under the newly proposed rule, the following actions would be required:

- reassessment of food categories with intake assessments for the higher level of inclusion to assure an acceptable margin of safety for cumulative daily total intake,
- preparation and submission of a GRAS notification,
- FDA assessment of the notification and provision of a "No Questions" response,
- reformulation and package re-design for food products, and
- launch of the reformulated products.

It is estimated that these actions from new intake assessments to reformulation and launch would take a minimum of 16 months and more likely 34 months.

Regarding phytosterol dietary supplement products, virtually all such products are formulated with free form phytosterols. Therefore, based upon FDA's statements regarding enforcement discretion in the proposed rule, these products would no longer be able to bear the phytosterol health claim in accordance with the 2003 Letter as of February 21. This could result in virtually all phytosterol-containing dietary supplements being removed from the market and, thus, being unavailable for consumer use. In addition, FDA's tentative conclusions in the

proposed rule indicate that significant scientific agreement was not reached when reviewing data specifically for tablets and capsules. It should be noted that many phytosterol-containing dietary supplements are in other matrices, such as liquids, gummies, chews, and mix-in powders, which would not have the same dispersibility issues identified in the proposed rule. These alternative matrix dietary supplements are also formulated with free-form phytosterols and therefore would not be allowed to use the health claim as of February 21.

Cargill expects that its customers will very soon cease purchasing its phytosterol ingredients for use in food and dietary supplements, causing Cargill irreparable injury, because most current phytosterol-containing products will not be able to bear the health claim as of February 21 and because of the considerable challenges to reformulation noted above. It is likely that many of Cargill's customers will no longer market such phytosterol-containing products, causing them irreparable injury. Most concerning, however, is the fact that consumers will generally no longer be able to purchase phytosterol-containing foods or dietary supplements. For example, Cargill has already been notified by a large strategic customer that they will be discontinuing their phytosterol-containing food product line. Others customers have indicated that they are re-evaluating their commitment to continue selling their phytosterol-containing products in light of the changes that would be required by the proposed rule. In addition, if manufacturers of current phytosterol-containing foods and dietary supplements are forced to remove the health claims from existing products, consumers may cease purchasing these products based on confusion and a belief that the product no longer offers the benefit of helping to reduce the risk of CHD.

2. Sound Public Policy Grounds Support the Issuance of the Stay

a) FDA Should Continue to Extend its Enforcement Discretion for Conventional Foods

FDA's proposal to disallow the health claim for phytosterol-containing foods that have not been the subject of a successful GRAS notification will deprive consumers of products that may reduce the risk of CHD, without any offsetting consumer benefit. With little explanation, FDA stated in its proposed rule that phytosterols that have been the subject of a successful GRAS notification satisfy the criteria at 21 C.F.R. § 101.14(b) that the substance that is the subject of a health claim be safe and lawful.[6] The agency then proposed that only such substances be eligible to bear the health claim (when used in conventional foods).[7] Submission of a GRAS notification has never been necessary to demonstrate that a food is safe and lawful. Rather, the Federal Food, Drug, and Cosmetic Act allows manufacturers to conclude that their

[6] 75 Fed. Reg. at 76530.

[7] Proposed 21 C.F.R. § 101.83(c)(2)(iii)(C).

foods are GRAS (and therefore lawful) without agency review if they satisfy governing criteria for safety.[8]

It is worth noting here that although FDA has not reached a conclusion that phytosterols are GRAS, "FDA is not aware of *any* scientific evidence that phytosterols, whether free or esterified, would be harmful."[9] In addition, FDA has already issued numerous "No Questions" letters to GRAS notifications for phytosterols in many food categories. Moreover, the safety is clearly a non-issue because FDA is doubling the recommended daily intake level for phytosterols. Accordingly, sound legal and public policy grounds support the continued allowance of GRAS substances otherwise meeting the criteria under the 2003 Letter to continue to bear the health claim, regardless of whether such substances have been the subject of successful GRAS notifications to FDA. Such substances have been shown to help reduce the risk of CHD by lowering blood cholesterol, as recognized by the health claim, and are safe and lawful.

Similarly, FDA's proposal to increase the level of phytosterols in foods eligible to bear the health claim as of February 21 will also deprive consumers of beneficial products unnecessarily. Under the current regulation and 2003 Letter, in order to bear the claim, a product must contain at least 0.4 g of free sterol equivalent per RACC.[10] The proposed rule would require the minimum eligible phytosterol content of a food to be 0.5 g per RACC, disqualifying many of the current phytosterol products marketed today. In addition, the proposed rule increases recommended consumption events to 4 per day in calculating the new proposed minimum amount of phytosterols per RACC based on the availability of a wide variety of food categories containing phytosterols. If the proposed 4 servings per day is combined with the current 0.4 g per RACC, the total daily intake would be 1.6 g phytosterols per day. Thus, with no immediate change in amount of phytosterol per serving, consumers would already double the current recommended intake and be within 0.4 g per day of the proposed 2 g total daily intake. As noted in the proposed rule, efficacy of phytosterols are well-established in the 1-3 g per day total daily intake range, and FDA further indicated in the proposed rule that 2.0 g per day was selected because it "is the midpoint of the daily intake range of 1 to 3 g used in the majority of intervention studies." Thus, consumers will continue to receive the benefit of phytosterols with products containing 0.4 g per RACC by increasing their consumption events as acknowledged in the proposed rule. Therefore, requiring the increased amount of phytosterols per serving as of February 21 will unnecessarily deprive consumers of the full range of products offering CHD health benefits.

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[8] 21 U.S.C. § 321(s) (excluding GRAS substances from the premarket review required for food additives); 21 C.F.R. § 170.3(i) (defining "safe" to mean a "reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use").

[9] 75 Fed. Reg. at 76530 (emphasis added).

[10] 21 C.F.R. § 101.83(c)(2)(iii).

Such disqualification would not serve the health interests of consumers. FDA made clear that its proposed findings that 2 g of phytosterols are needed to achieve the cholesterol-lowering effect were only "tentative," and the agency invited submission of additional data regarding such efficacy during the comment period. FDA acknowledged that a number of studies showed statistically significant reductions in total and/or LDL cholesterol levels for plant sterol and stanol intake levels below 2 g per day.[11] Thus, there is enough evidence of a benefit at the lower level of daily intake that FDA should continue allowing those claims eligible under the interim final rule until all comments are evaluated and a final rule is issued.

Should FDA cease the exercise of its enforcement discretion under the 2003 Letter beginning on February 21, many food products currently bearing the health claim would need to be pulled from the shelves on that date, as they could not be reformulated in time nor would such reformulated products likely fit within existing GRAS notifications, and no new GRAS notifications could be prepared and evaluated by FDA before that date. Moreover, finished food manufacturers are unlikely to even begin to reformulate their products unless and until FDA issues a "No Questions" letter for their product. Relabeling of existing products would take time and money would likely not be spent during a period of uncertainty of GRAS status. Even if products could be re-labeled to remove the health claim, consumers may no longer select those products without being informed that these products may help reduce the risk of heart disease. In either scenario, consumers would be deprived by the loss of these heart-healthy products from the market.

For the foregoing reasons, FDA should delay implementation of the proposed requirements that all phytosterols used in conventional foods be the subject of GRAS notifications to which FDA has not objected and be present at 0.5 g per RACC until after the agency has received and considered comments on the proposal and promulgated a final rule.

b) FDA Should Continue to Extend its Enforcement Discretion for Dietary Supplements

Rescission of FDA's 2003 Letter prior to issuance of a final rule would exclude nonesterified phytosterol-containing dietary supplements from eligibility for the CHD health claim.[12] In its proposed rule, however, FDA made clear that its findings regarding the cholesterol-lowering efficacy of nonesterified phytosterols consumed as ingredients in dietary supplements were only "tentative," and that the agency invites submission of additional data demonstrating such efficacy during the comment period. Thus, FDA indicated that it will consider more information before making a final determination on this issue. Should the information submitted during the comment period reveal that nonesterified phytosterols in

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[11] 75 Fed. Reg. at 76536-7.

[12] Proposed 21 C.F.R. §101.83(c)(2)(iii)(B).

dietary supplements do produce CHD health benefits, FDA may revisit this aspect of the proposed rule, and include those dietary supplements as eligible for the health claim under the final rule. In addition, FDA's tentative conclusions in the proposed rule indicating that significant scientific agreement was not reached related to data specific to tablets and capsules. In fact, the evaluation of the studies referenced indicated that nonesterified phytosterol supplementation with tablets consistently and significantly lowered cholesterol levels whereas nonesterified phytosterol-containing capsules did not. Indeed, Cargill is aware of at least two additional double-blind, placebo-controlled studies supporting efficacy of dietary supplements in tablet form containing nonesterified phytosterols in lowering total cholesterol. However, these studies have been conducted so recently that they have not been published in a peer-reviewed format. It should also be noted that many sterol containing dietary supplements are in other matrices, such as liquids, gummies, chews, and mix-in powders, which would not have the same dispersibility issues identified in the proposed rule.

Accordingly, a change in FDA's exercise of its enforcement discretion prior to issuance of a final rule is premature. Should the final rule, based upon the information submitted during the comment period, ultimately allow the health claim for dietary supplements using nonesterified phytosterols, dietary supplement firms would have to come into compliance with the proposed rule by February 21, and then have to again come into compliance with different standards under the final rule once it was issued. This would lead to unnecessary disruption and economic loss in the industry, particularly because FDA is not obliged to promulgate its final rule by a date certain. Again, due to the challenges of reformulation and the impaired marketability of phytosterol-containing dietary supplements that do not bear the health claim, Cargill expects that many of its dietary supplement customers will cease marketing such products, and once products are removed from the market they are very unlikely to re-enter the market. If FDA ultimately concludes, upon consideration of the data and information submitted to the docket, that nonesterified phytosterols in dietary supplements do help reduce the risk of CHD, as was anticipated by the 2003 Letter, consumers will have been deprived by the loss of these beneficial products from the market.

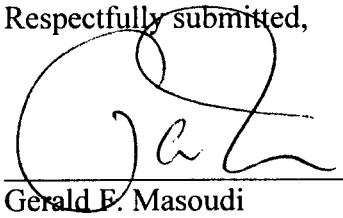
Finally, any delay resulting from a grant of the stay would not injure public health or other public interests. Cargill and other manufacturers have been operating under FDA's exercise of its enforcement discretion under the 2003 Letter for seven years, and it is unlikely that any harm to the public will result by extending that time-frame until the final rule is issued. The benefits of this extension are clear: it would avoid any uncertainty, economic harm, or disruption to the food and dietary supplement industry between the lapse of the 2003 Letter and the issuance of a final rule, and would preserve the viability of the phytosterol industry so that consumers can reap the benefits of those phytosterols FDA has already acknowledged provide demonstrable benefits for heart health, as well as those whose effectiveness may be confirmed by data and information to FDA . Such phytosterols are safe and lawful, and should continue to be available to consumers pending the issuance of a final rule.

For the foregoing reasons, we request that FDA stay the rescission of enforcement discretion under the 2003 Letter pending the agency's issuance of a final rule, and therefore

continue to allow until that time the health claim on: conventional foods formulated with phytosterols at 0.4 g free sterol equivalent per RACC, whether or not the phytosterol ingredient has been the subject of a GRAS notification to which FDA responded with a "No Questions" letter; and dietary supplements containing free phytosterols at 0.4 g free sterol equivalent per RACC.

We would be happy to discuss any comments or questions you may have regarding this petition, either by telephone or in person.

Respectfully submitted,



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