Unilever

November 19, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket Nos. 00P-1275 and 00P-1276
Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease (Interim Final Rule; reopening of comment period)
66 Fed. Reg. 50824 (October 5, 2001)

To Whom It May Concern:

Unilever Bestfoods North America (formerly Lipton) submits the following comments in response to the above-referenced notice, in which FDA extended the comment period on the interim final rule and requested comments on five issues. Our comments appear below in lettered paragraphs that correspond to the paragraphs in part II of the agency's notice.

COMMENTS

A. *Additional data are needed to demonstrate significant scientific agreement that unesterified sterols or stanols should be eligible for the health claim.*

FDA requested comments on whether unesterified sterols or stanols would be effective in reducing the risk of CHD, and should therefore be eligible for the health claim.

Under 21 U.S.C. §343(r)(3)(B)(i), FDA may not promulgate a health claim regulation unless there is "significant scientific agreement" that the claim is supported by the totality of publicly available scientific evidence. According to FDA, "[t]he significant scientific agreement standard is met when the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined over time." (FDA, *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*, Dec. 22, 1999.)

00P-1276 C25

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Thus, in order for unesterified sterols or stanols to be eligible for a health claim regulation, there must be significant scientific agreement that they have the intended effect *when formulated into the food that bears the claim.* Although it appears to be accurate to say that free sterols and stanols are the "active moiety" in sterol ester and stanol ester products, the available data do not demonstrate that, when free sterols and stanols are added to any of various food matrices, they will reduce blood cholesterol levels. Indeed, there is only preliminary information on how various food matrices might affect the relationship between unesterified sterols and stanols and cholesterol levels, and new studies might significantly change the current assumptions about this relationship. Accordingly, at this time there is not significant scientific agreement that unesterified sterols or stanols should be eligible for the health claim. The following provides more detailed information.

(1) Additional data are needed to support the use of the health claim for unesterified sterols

A number of studies have been published on the relationship between unesterified plant sterols and the reduction of blood cholesterol levels (as reported previously in our health claim petition). However, almost all of these studies involved the administration of the unesterified plant sterols in non-food matrices; only a few studied the substance administered in food systems.

Unesterified plant sterols exist in a solid crystalline form at room temperature and their solubility in water and edible oils is only about 0.1% and 2%, respectively. Since it is likely that sterols need to be well dispersed in the fat phase within the gastrointestinal tract in order to reduce cholesterol absorption, the crystallinity and limited solubility of unesterified sterols very likely limit their ability to perform this function – unless they are delivered in a soluble form (for example, by esterification or using an emulsifier and/or dietary fat as the vehicle). (Matson, et al. 1982.)

Accordingly, in order to attain significant scientific agreement that unesterified sterols in specific food matrices reduce blood cholesterol, this effect should be demonstrated using a specific level of unesterified sterols in either (a) a specific food matrix that will be eligible to bear the claim, or (b) a variety of food matrices, so that unesterified sterols formulated into any food matrix would be eligible to bear the claim.

(2) Additional data are needed to support the use of the health claim for unesterified stanols

Only a few human studies have been carried out with unesterified plant stanols, and in these the ingredient was dispersed in vegetable oil and administered in capsules. (Hallikainen. *Role of plant stanol ester and sterol ester-enriched margarines in the treatment of hypercholesterolemia.* Thesis; Kuopio University Publications D Medical Sciences 251, 2001 ISBN 951-781-851-3.) The results of these studies have been conflicting: Heineman et al. (1986) studied 6 individuals consuming 1.5 g stanols/day

and demonstrated lowering of total and LDL-cholesterol levels, whereas Denke (1995) reported no reduction in total or LDL-cholesterol levels in 33 men consuming 3 g stanols/day.

Accordingly, as discussed above with respect to unesterified sterols, in order to attain significant scientific agreement that unesterified stanols in specific food matrices reduce blood cholesterol, studies are needed to show that a specific level of unesterified stanols is effective in either (a) a specific food matrix that will be eligible to bear the claim, or (b) a variety of food matrices, so that unesterified stanols formulated into any food matrix would be eligible to bear the claim.

B. ***Additional data are needed to demonstrate significant scientific agreement that plant stanol esters should be eligible for a health claim below 3.4 grams/day.***

FDA requested comments on whether the qualifying levels of sterol or stanol esters should be changed – and in particular whether the level for stanol esters (3.4 g/day) should be reduced to that for sterol esters (1.3 g/d).

The qualifying level for sterol esters is supported by significant scientific agreement based on the totality of publicly available scientific evidence, as determined by FDA. (We are aware of no question about the accuracy of this determination.) In order to reduce the qualifying level of stanol esters, this same requirement must be met: that is, the level selected must be supported by significant scientific agreement based on the totality of publicly available scientific evidence.

There are a few published studies where the efficacy of sterol esters and stanol esters has been compared directly in the same study or in separate studies at similar intake levels in the same food matrix. It appears from these studies that sterol esters and stanol esters show equivalent efficacy at most dose levels tested (Hallikainen et al. 2000a, Hendriks et al. 1999, Jones et al. 2000, Weststrate and Meijer 1998, Piironen et al. 2000). However, these studies did not evaluate the effect of stanol esters at levels near or below 1.3 g/d, and therefore they do not provide a basis for concluding that stanol esters significantly reduce blood cholesterol at that level. (Hallikainen, et al 2000b; Hendriks et al. 1999.) In the preamble to the health claim regulation, FDA stated that, in its review of stanol esters, it "was unable to find an intake level lower than 3.4 g/d that consistently showed cholesterol-lowering effects for both total and LDL cholesterol." 65 Fed. Reg. at 54704. To our knowledge, at this time there are no new data that would provide a basis for altering this conclusion.

A "compelling and relevant body of evidence" is needed in order to reach a conclusion that a health claim is supported by significant scientific agreement. (FDA, *Guidance on Significant Scientific Agreement.*) Although this level of evidence exists for stanol esters at a level of 3.4 g/d and above, the evidence is neither compelling nor relevant for stanol esters below 3.4 g/d. Accordingly, in order to demonstrate significant scientific

agreement that plant stanol esters should be eligible for a health claim below 3.4 g/d, additional data are needed.

With regard to the qualifying levels for unesterified sterols and stanols in any particular food matrix, additional studies are needed as described in section A above.

C. *Additional data are needed to demonstrate significant scientific agreement that mixtures of sterols and stanols should be eligible for the health claim.*

FDA requested comments on whether mixtures of plant sterols and plant stanols should be eligible for the health claim.

As discussed above, plant sterol esters and plant stanol esters appear to have comparable effects on blood cholesterol levels at the intake levels tested. They may act through a similar mechanism of action. It is possible, then, that mixtures of the two components will have effects on cholesterol equivalent to the sum of the effects of the individual components within the studied dose-response range.

However, as discussed above, a "compelling and relevant body of evidence" is needed in order to reach a conclusion that a health claim is supported by significant scientific agreement. (FDA, *Guidance on Significant Scientific Agreement.*) Although the available data support health claims for sterol esters and stanol esters individually, the evidence is neither compelling nor relevant for mixtures.

Accordingly, in order to demonstrate significant scientific agreement that such mixtures should be eligible for a health claim, additional data are needed.

In addition, we are unaware of any systematic studies on the combination of mixtures of unesterified sterols with esterified sterols and therefore, as discussed in section A above, we believe that further studies would be necessary before drawing conclusions about the effectiveness of such mixtures in any particular food matrix.

D. *Additional data are needed to demonstrate significant scientific agreement that apolipoprotein B concentration is a valid surrogate marker for CHD risk.*

FDA requested comments on whether apolipoprotein B ("ApoB") concentration is appropriate and validated as a surrogate marker for CHD risk.

This issue was raised in a comment to FDA referring to a study by Hallikainen et al. (2000). The population in this study consisted of 22 volunteers. The differences observed in the effects of different doses of plant stanol esters on LDL cholesterol versus ApoB is likely to be attributed to between-subject variation, owing to the small number of subjects in this study.

Currently, the accepted independent marker for CHD risk is LDL cholesterol, and ApoB has not been shown by significant scientific agreement to be superior to or even a substitute for LDL cholesterol. ApoB has been considered in a number of studies as a surrogate marker for CHD (Cubero et al., 1998; Ballantyne et al., 2001; Sharrett et al., 2001), but the data on the predictive value of ApoB for CHD risk are not conclusive at this time, and it is quite possible that new and evolving science could show that ApoB is not an appropriate surrogate marker for CHD risk.

It should be noted that the measurement of ApoB is less accurate and, in addition, less widely available and more expensive than the standard lipid profile assays. It is therefore unlikely that ApoB will be accepted as a surrogate marker for CHD in the near future.

E. *The use of advisory labeling statements or other agency action is not necessary to assure safe use of sterol ester-containing foods.*

FDA has asked for comments on whether foods containing plant sterol esters or stanol esters should be labeled with certain advisory information on the following issues: (1) use by people who want to lower their blood cholesterol levels, (2) use by people who are taking cholesterol-lowering medication, (3) use by pregnant and breast-feeding women, and children, (4) use as part of a healthy diet including fruits and vegetables, and (5) use by people with phytosterolemia. In particular, FDA has asked whether these issues "are material facts and what action, if any, the agency should take to address them." 66 Fed. Reg. at 50826.

In summary, it is our position that these issues are not material to the safe consumption of sterol esters in the United States, and no advisory labeling statements or other agency action are needed to assure safe use of sterol ester-containing foods that are consistent with the existing GRAS determinations. Paragraphs (1) through (3) below outline the detailed basis for this position.

(1) **Advisory labeling statements are not needed to assure safe use of sterol ester-containing foods, because safety has been assured by careful determinations that such foods are generally recognized as safe (GRAS).**

For sterol ester-containing foods, the issues discussed by FDA are not material facts because FDA has already taken appropriate action to address them. Specifically, FDA has already reviewed the safety and GRAS status of sterol esters and has not suggested that there is any safety issue that needs to be addressed by advisory labeling statements. Further, relevant safety data have been published without challenge.

In fact, FDA's review of sterol esters has been particularly thorough: it conducted a detailed review of our GRAS determination (submission dated January 11, 1999), it again reviewed the GRAS status of sterol esters in response to our petition for a health claim (submission dated January 28, 2000), and it successfully reviewed four additional GRAS notifications for sterols and/or sterol esters (GRAS Notice Nos. GRN 61, 53, 48, and 39). None of the GRAS determinations for sterol esters (which have been supported by the views of qualified independent experts), and none of the reviews by FDA has suggested that there is any safety issue. Moreover, no advisory labeling has been considered necessary for purposes of providing nutritional information to consumers.

Accordingly, the issues summarized in section E of FDA's notice are not material to the safe consumption of sterol esters, and no agency action is needed to assure the safe use of sterol ester-containing foods that are consistent with the existing GRAS determinations.

(2) <u>There is no need for any of the potential advisory labeling statements that FDA has inquired about.</u>

The specific advisory labeling statements that FDA has inquired about are unnecessary for sterol ester-containing foods for various reasons, as discussed below:

(a) Advisory statement that the product is for people who want to lower their blood cholesterol levels

This statement is unnecessary for purposes of informing consumers that a product may help reduce the risk of heart disease because this information is already conveyed by the approved health claim. 21 C.F.R. §101.83(c)(2)(i)(B). It is also unnecessary to adopt a regulation requiring the use of a statement about cholesterol reduction because such information is already being voluntarily placed on product labels (pursuant to 21 C.F.R. §101.83(d)(2)). For example, both *Take Control*® (which contains plant sterol esters) and *Benecol*® (which contains plant stanol esters) are labeled with information on cholesterol reduction. Therefore, an FDA regulation is not needed in order to convey this information to consumers.

(b) Advisory statement that patients on cholesterol-lowering medication should consume the product under medical supervision

This statement is unnecessary because persons who are taking prescription cholesterol-lowering medications are already under a doctor's care. Standard medical care should (under current guidelines from public health authorities) provide information to the patient on dietary management of cholesterol, including the use of sterol-ester containing products (or other ingredients covered by health claim regulations, such as soy protein or

soluble fiber), as well as on appropriate drug therapy in light of dietary management practices. (*See, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*, NIH Pub. No. 01-3670, May 2001.)

We also note that the consumption of sterol ester-containing foods together with cholesterol-lowering medication has been studied repeatedly and has been consistently reported to be safe and effective. (*See,* Neil,H.A.W et al. (2001) (statin therapy); Nigon,F. et al (2001) (fibrate therapy).)

(c) Advisory statement that the product may not be appropriate nutritionally for pregnant and breast-feeding women, and children

This statement is unnecessary because advisory labeling is not needed to assure that these population groups choose foods that are nutritionally appropriate for them.

As indicated by FDA, the principal issue is whether the vitamin A status of these population groups might be affected by sterol ester consumption. The European Commission concluded that advisory labeling is needed because the vitamin A status of these groups may not be optimal, and sterol and stanol ester-containing foods may cause a reduction in plasma provitamin A carotenoid beta-carotene.

The issue of carotenoid reduction was addressed in the GRAS determination for our sterol ester-containing spreads, which was conducted in 1999. This determination reflected the views of a panel of qualified, independent experts and concluded that, although sterol esters appear to reduce the absorption of dietary carotenoids, these effects will be relatively minor. In particular, the determination noted that a number of factors other than sterol ester consumption influence carotenoid availability and utilization. These factors include the natural variations in carotenoid levels in foods together with variability in stability, bioavailability and absorption of food carotenoids. More recently, a study by Hendriks et al. (2001) indicates that there are large variations within the normal range for plasma beta-carotene, that there are also seasonal variations, and that the reduction of plasma beta-carotene levels by sterol esters is within the normal range.

We also note that there is no safety issue associated with consumption of sterol ester-containing foods by pregnant or breast-feeding women, or children. Our GRAS determination evaluated safety for all population groups. FDA reviewed our GRAS determination and had no questions about it.

Accordingly, the available scientific information indicates that the effect of sterol esters on the absorption of beta-carotene and other carotenoids is reasonably certain to be

insignificant from a public health perspective.[1] Therefore, there is no need for a labeling advisory statement based on this issue. Moreover, we note that our sterol ester-containing vegetable oil spread product, *Take Control*®, is enriched with 10% of the RDI for vitamin A (30% as beta-carotene).

In addition, as a practical matter, a labeling advisory statement is not needed to encourage pregnant and breast-feeding women and children to choose other nutritionally appropriate foods. These population groups are not normally concerned with cholesterol reduction, and therefore they would be unlikely to regularly consume a sterol ester-containing food that is prominently labeled with the approved health claim. Indeed, our consumer survey data indicate that consumers of our sterol ester-containing spreads are predominantly older (over approximately age 55) and live in households with no children.

(d) Advisory statement that the product should be used as part of a healthy diet, including regular consumption of fruit and vegetables

This statement is unnecessary because the health claim on sterol ester-containing products already promotes the use of a heart-healthy diet, and there is no need to specifically refer to fruit and vegetables on the labels of such foods.

The European Commission concluded that advisory labeling on consumption of fruit and vegetables is needed to protect population groups whose vitamin A status may not be optimal because sterol and stanol ester-containing foods may cause a reduction in plasma beta-carotene. As discussed in section E(2)(c) above, the available scientific information indicates that the effect of sterol esters on the absorption of beta-carotene and other carotenoids is reasonably certain to be insignificant from a public health perspective, and therefore there is no need for a labeling advisory statement based on this issue.

Importantly, FDA's sterol ester health claim regulation already requires the claim to refer to the type of diet that is most important for reduction of CHD risk, that is, a diet low in saturated fat and cholesterol. 21 C.F.R. §101.83(c)(2)(i)(A). This is the critical information for purposes of reduction of CHD risk, and therefore this information is appropriately included as part of the health claim regulation. Although the regular consumption of fruits and vegetables is good advice, this advice is already available to consumers from many sources – for example, it can be found on our *Take Control*® website and from publications of various public health authorities. Therefore, an FDA regulatory requirement is not needed (either for sterol/stanol esters or for other dietary ingredients covered by health claim regulations, such as soy protein or soluble fiber) in order to effectively convey this information to consumers.

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[1] For further discussion of this issue and the relevant scientific studies, see our GRAS Notification for Vegetable Oil Sterol Esters used in Vegetable Oil Spreads (Jan. 11, 1999).

(e) Advisory statement that individuals with sitosterolemia not use foods containing plant sterols/stanols

This statement is unnecessary because the very small number of people with sitosterolemia can avoid sterols by referring to ingredient labeling.

The possibility of an advisory statement for individuals with sitosterolemia was raised by FDA in response to comments by the American Heart Association, which recommended that individuals with sitosterolemia not use foods containing plant sterols or stanols. FDA's notice states that persons who are homozygous for sitosterolemia absorb plant sterols excessively and experience adverse reactions, but it is not known whether persons who are heterozygous for this condition experience the same effects.

This issue was addressed in our GRAS determination for sterol ester-containing spreads. That determination, based on the advice of qualified, independent experts, stated that sitosterolemia is very rare, occurring on the order of only a few cases in the total population. It concluded that avoidance of sterols by this very small number of people could reasonably be accomplished by labeling the product with an ingredient name which conveys that the product contains plant sterols. FDA reviewed our GRAS determination and had no questions about this issue.

Since our GRAS determination was conducted, we have researched this issue further. Our research indicates that the issue of increased consumption of plant sterols is only relevant to the approximately 50 individuals worldwide who are homozygous for sitosterolemia. Accordingly, we continue to believe that avoidance of sterols by this small group can reasonably be accomplished by ingredient labeling which conveys that the product contains plant sterols. The following summarizes our recent research:

(i) *Background Information on Sitosterolemia*

Sitosterolemia is a rare genetic disorder resulting from an inborn error of sterol absorption and excretion. The main biochemical feature of the disorder is elevated plasma phytosterol levels. The disorder was first reported by Bhattacharyya and Connor (1974) and following genetic analysis of a large Amish population was established to be an autosomal recessive trait (Beaty et al., 1986). More recently, genes involved in this disorder have been identified (Berge et al., 2000; Lee et al., 2001). The homozygous state is extremely rare with approximately 50 cases reported worldwide (Patel et al., 1998). The incidence of individuals who are heterozygotes for the gene(s) is not known as these subjects appear to be clinically and biochemically normal.

Typical human dietary intake of plant sterols is in the range of 200 – 400 mg/day with higher levels being observed in vegetarians. Normally, less than 5% of total plant sterols obtained from the diet are absorbed. Although dietary cholesterol intake is similar to

plant sterol intake, the absorption of cholesterol is approximately 10-fold higher than that of plant sterols, with 30 – 60% of total dietary cholesterol being absorbed (Bosner et al., 1999). The small amount of absorbed plant sterols is excreted rapidly, in an unchanged form, by the liver into the bile. The liver preferentially secretes plant sterols into the bile, therefore the net absorption of these sterols is negligible (Salen et al., 1970). Individuals affected with sitosterolemia show an increase in the absorption of total dietary sterols with no discrimination between cholesterol and non-cholesterol sterols. In some sitosterolemics the percentage of plant sterols absorbed can be similar to that of cholesterol but the plant sterols do not interfere with cholesterol absorption. Also, in these individuals the liver has lost the capacity to recognize non-cholesterol sterols, so excretion into the bile is severely reduced resulting in an expanded body pool of plant sterols (Patel et al., 1998). In addition to the defects in absorption and excretion of plant sterols, endogenous cholesterol synthesis is severely reduced (Salen et al., 1997; Patel et al., 1998).

In a study of 20 normal individuals, cholesterol represented around 99.6% of total plasma sterols with the remaining 0.4% being plant sterols (Salen et al. 1997). In contrast, sitosterolemic homozygotes have been reported to have plasma plant sterol levels ranging between 11 and 25% of the total plasma sterol content (Kwiterovich et al., 1981; Salen et al., 1983, 1985; Lutjohann et al., 1995). Sitosterol and sitostanol levels in heterozygotes are similar to controls (Nye et al., 1988; Nguyen et al., 1991; Salen et al.,1992a) but in some heterozygote cases plasma levels have been reported to be slightly raised compared to control values. However, the levels were still considerably lower (10 – 20 fold) than their homozygous offspring (Salen et al., 1997). These slightly elevated levels of plasma plant sterols were well within the normal distribution within a population and similar to those seen in vegetarians (Vuoristo and Miettienen, 1994).

Sitosterol turnover in response to different intakes of plant sterols has also been studied in heterozygotes. Sitosterol absorption was increased 2 to 3 times compared to controls; however, the body pool of sitosterol did not increase because sitosterol removal was rapid, indicating that heterozygotes retain the ability to excrete sitosterol normally (Salen et al., 1992b; Cobb et al., 1997).

In conclusion, sitosterolemic heterozygotes are clinically and biochemically normal while sitosterolemic homozygotes demonstrate elevated levels of plasma plant sterols and cholesterol levels. Therefore, the issue of increased consumption of plant sterols is only relevant to the approximately 50 individuals worldwide who suffer from sitosterolemia, and these people can avoid sterol-containing foods by referring to ingredient labels.

(ii) *Individuals Heterozygous for Sitosterolemia React like Normal Individuals in Studies of Increased Plant Sterol Consumption*

As heterozygotes are clinically and biochemically normal they can only be identified from their relationship to homozygous sitosterolemics. Due to the rarity of the disease, only small numbers can be studied. However, two studies have recently been reported.

Stalenhoef et al. (2001) has reported a study in the heterozygous parents of a sitosterolemic individual from the Netherlands to assess the impact of the increased intake in plant sterols on these individuals who are carriers of the gene(s) but do not have sitosterolemia. In addition, Kwiterovich et al. (2001) has reported on the safety and efficacy of a plant sterol-enriched margarine in 12 obligate heterozygotes for sitosterolemia in the US.

In both studies the daily intake of a plant sterol-enriched spread lowered plasma total and LDL cholesterol levels in heterozygotes consistently with the reductions reported in other studies of normal hypercholesterolemic subjects (Weststrate and Meijer, 1998; Hendriks et al., 1999; Jones et al., 2000). Plasma plant sterol levels in heterozygotes were increased to levels similar to those observed by Weststrate and Meijer (1998) in normal individuals fed plant sterol esters. There was no sign of accumulation of plasma plant sterols over time and, after a wash-out period, levels had returned toward the pretest levels.

In summary, the daily consumption of spread enriched with plant sterols by sitosterolemic heterozygotes did not increase plasma plant sterol levels above those seen in individuals from the general population consuming similar amounts of plant sterols. Therefore, these individuals do not need special labeling information on sterol ester-containing foods. Avoidance of sterols by the small group of homozygous patients can reasonably be accomplished by ingredient labeling which conveys that the product contains plant sterols.

(3) Conclusion

For the reasons discussed above, we urge FDA to conclude that advisory labeling statements or other agency action are not needed to assure the safe use of sterol ester-containing foods that are consistent with the existing GRAS determinations.

In addition, we note that the question of whether advisory labeling is needed in the US should not be unduly influenced by the fact that some other regions have adopted it. The United States has a unique regulatory environment for conventional foods: consumers are familiar with a well-established system for making health claims on food labels, and they have access to information on serving sizes and nutrition labeling that guide their consumption levels. Most other regions do not share this same regulatory environment.

Thus, it is inappropriate to conclude that, if advisory labeling has been adopted in other regions, it should necessarily be adopted in the United States.

FDA has also asked for comment on the Australia New Zealand Food Authority (ANZFA) position that vegetable oil sterols should be allowed for use only in edible oil spreads. It is our understanding that ANZFA concluded that dietary exposure to sterol esters should be restricted to the level at which safety has been demonstrated, and that spread products are the only ones that were submitted for review. This approach is generally consistent with that in the US, where sterol ester-containing foods may only be marketed if they are GRAS for such use, or approved as food additives. 21 U.S.C. §201(s).

(4) Alternative Comments in the Event that FDA Decides to Propose Rules on the Use of Advisory Labeling Statements

It is our position, as discussed above, that the advisory labeling statements referred to by FDA are unnecessary for sterol ester-containing foods. If, nevertheless, FDA decides to propose the use of advisory labeling statements, we provide the following alternative comments to assist the agency. These alternative comments should not be interpreted as altering our position that it would be inappropriate to promulgate regulations on advisory labeling statements for sterol ester-containing foods.

(a) *Any proposed advisory labeling statements should be limited to labeling conveying that a physician should be consulted by pregnant or nursing women, or children, before beginning a cholesterol-lowering diet.* As discussed above, sterol ester-containing foods that are consistent with existing GRAS determinations are safe and do not raise any meaningful public health issues (as evidenced by the fact that they have been marketed in the US for more than two years with no significant adverse effects). Thus, it would be inappropriate to promulgate any regulation that requires labeling information beyond that which provides useful nutritional information to relevant population groups.

(b) *FDA should not require any specific advisory labeling language, but should provide general direction to the manufacturer on the message to be conveyed.* This approach is consistent with FDA's general approach to health claim regulations, which leave the exact wording of the claim up to the manufacturer, with guidance provided by the regulation.

(c) *Any advisory labeling statements should be optional rather than mandatory, and included under "Optional Information" in all health claim regulations to which they are applicable.* Because these statements are not needed to assure safety, they are appropriately treated as useful but non-mandatory information, similar to the advisory information on elevated cholesterol levels provided for under 21 C.F.R. §101.83(d)(6).

In addition, the statements may need to be added to other health claim regulations, such as those for soy protein or soluble fiber.

(d) *Any advisory labeling statements must be the subject of a new proposed rule to amend the sterol ester health claim regulation, as required by the Administrative Procedure Act, 5 U.S.C. §553.* Because sterol ester-containing foods that are consistent with existing GRAS determinations are safe and do not raise any meaningful public health issues, there is no need for FDA to act with undue urgency to implement any advisory labeling statements. Therefore, any proposed rule must be issued under the normal notice-and-comment rulemaking process, and would not become effective upon publication under 21 U.S.C. §343(r)(7). If FDA decides to issue a proposed regulation on advisory labeling claims, we will provide additional comments on the proposal at that time.

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Thank you for your consideration of our comments. If you would like further information, please contact the undersigned at 212-906-4573.

Respectfully submitted,

Nancy L. Schnell /d

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