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Docket Nos. 00P-1275 and 00P-1276 Comments in Response to Reopening of Comment Period for Interim Final Rule on Health Claim for Plant Sterol/Stanol Esters and Coronary Heart Disease

Comments Submitted by
Arent Fox on Behalf of Raisio Benecol, Ltd.

November 16, 2001
(Volume 1 of 2)

00P-1275

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November 16, 2001

VIA FEDERAL EXPRESS

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

Re: Docket Nos. 00P-1275 and 00P-1276
Comments in Response to Reopening of Comment Period for Interim Final Rule on Health Claim for Plant Sterol/Stanol Esters and Coronary Heart Disease

Dear Madam/Sir:

Arent Fox submits the following comments to the Food and Drug Administration ("FDA") on behalf of Raisio Benecol Ltd., Raisio, Finland ("Raisio" or the "Company") in response to the Agency's reopening of the comment period for the interim final health claim rule for plant sterol/stanol esters and coronary heart disease ("CHD").[1]

In the notice reopening the comment period, FDA requested comments on five issues: (1) "Eligibility of Unesterified Plant Sterols and Plant Stanols for the Health Claim"; (2) "Daily Intake Levels Necessary to Reduce the Risk Of CHD"; (3) "Eligibility of Mixtures of Plant Sterols and Plant Stanols for the Health Claim"; (4) "Significance of Apolipoprotein B Concentration as a Surrogate Marker for CHD Risk"; (5) "Issues Regarding Safe Use of Plant Sterol/Stanol Esters in Foods and Advisory Label Statements."[2]

The instant Raisio comments address each of these issues. Further, these comments expand on Raisio's earlier comments opposing the factor(s) proposed by FDA for the conversion of intake levels of sterols and stanols to their corresponding esters.

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[1] 66 Fed. Reg. 50824 (Oct. 5, 2001); 65 Fed Reg. 54686 (Sept. 8, 2000). For purposes of convenience, we have omitted the word "plant" from the terms "plant sterols," "plant stanols," "plant sterol esters," and "plant stanol esters" throughout these comments.

[2] 66 Fed. Reg. 50824.

I. INTRODUCTION AND OVERVIEW

On January 6, 1993, FDA issued a final rule implementing the health claim provisions of the Nutrition Labeling and Education Act of 1990 ("NLEA"), which amended the Federal Food, Drug, and Cosmetic Act, to provide procedures for FDA's regulation of health claims on food labels and in food labeling.[3] In that final rule, FDA set forth the procedure for petitioning FDA to authorize a health claim for a substance-disease relationship, and identified the types of information that must be included in such a petition. It should be noted that FDA did not recognize any procedure other than a petition for initiating the health claim rulemaking process.

In February 2000, FDA accepted petitions for two separate health claims for the reduction of the risk of CHD -- one for sterol esters and one for stanol esters. Lipton submitted its health claim petition for sterol esters at a proposed daily intake level of 1.6 g/d sterol esters (1 g/d sterols). That level was well below the daily amount stipulated in its GRAS notification and recommended on its commercial product labels. McNeil Consumer Healthcare ("McNeil") submitted its health claim for stanol esters at the labeled daily intake level for BENECOL® of 3.4 g/d stanol esters (2 g/d stanols). On September 8, 2000, in response to the two health claim petitions, FDA published its interim final health claims rule ("Interim Final Rule") for sterol/stanol esters and reduced risk of CHD.

A. FDA Interim Final Rule

FDA may authorize a health claim where there is significant scientific agreement among qualified experts that the totality of the publicly available scientific evidence supports the claimed benefit.[4] FDA made the following significant determinations in this rulemaking:

- The data submitted by Lipton supported a health claim for sterol esters at a daily dietary intake level of 1.3 g/d sterol esters (0.8 g/d sterols).

- The data submitted by McNeil supported a health claim for stanol esters at a daily dietary intake level of 3.4 g/d stanol esters (2 g/d stanols). Additionally, FDA recognized that one published study supplied by McNeil supported a significant reduction in serum total and LDL cholesterol at a dose of 1.4 g/d stanol esters (0.8 g/d).

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[3] 58 Fed. Reg. 2478 (Jan. 6, 1993).

[4] 21 U.S.C. § 343(r)(3)(B)(i); 21 C.F.R. § 101.14(c).

[NOTE: The sterol ester and stanol ester values identified above are those reported in the Interim Final Rule. As discussed in Raisio's earlier comments and below, Raisio believes the FDA inappropriately applied different factors for converting quantities of sterols and stanols to their respective ester form.]

FDA requested comments on the Interim Final Rule.

B. Comments Received

In response to FDA's request, many companies and groups, including the American Heart Association,[5] submitted comments to FDA. Arent Fox submitted comments on behalf of Raisio on November 21, 2000, prior to the November 22, 2000 deadline that was set in the rule. Unilever United States submitted comments on behalf of its subsidiary, Lipton, prior to November 22, 2000, and additional comments on February 27, 2001, well after the comment deadline. On May 11, 2001, on behalf of Raisio, Arent Fox submitted additional comments to respond to the issues raised in Lipton's second set of comments in order to ensure a balanced consideration of all studies that FDA was reviewing for the final published rule.

II. SUMMARY OF PREVIOUS RAISIO COMMENTS

A. November 21, 2000 Submission

Raisio's November 2000 submission had the following goals: (1) to demonstrate that data from the scientific studies cited by FDA support a health claim for stanol esters at daily intake levels of 1.4 g/d, equivalent to 0.8 g/d stanols; (2) to highlight the discrepancies in some of the studies relied upon by FDA on the cholesterol-lowering effects of sterols and sterol esters; and (3) to request recalculation of the proposed conversion factors.

- Data Support a Daily Intake Level of 1.4 g Stanol Esters (0.8 g Stanols)

Raisio stated in its comments that FDA acknowledged that a daily intake of 1.4 g stanol esters (0.8 g stanols) produced a statistically significant reduction in serum total and LDL cholesterol in one study (Miettinen and Vanhanen (1994; FDA Ref. 63[6])). In addition to this study, Raisio cited several other studies in its comments, including Hallikainen et al. (2000; FDA Ref. 88), to support

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[5] In its comments, the American Heart Association urged the FDA to amend the Interim Final Rule to recognize a lower qualifying daily dietary intake level for stanol esters.

[6] Unless stated otherwise, reference numbers cited in these comments refer to the reference numbers appearing in the Interim Final Rule.

a health claim for stanol esters at daily intake levels lower than 3.4 g stanol esters (2 g stanols). Raisio, therefore, requested that FDA reconsider its determination that the qualifying daily intake level for stanol esters is 3.4 g/d.

- Discrepancies in Certain Studies on the Cholesterol-Lowering Effects of Sterols and Sterol Esters

Raisio reviewed the studies relied upon by FDA in the Interim Final Rule and found that some of the studies of sterol esters relied upon by the FDA were flawed. These comments focused primarily on serious problems in the Jones et al. study (2000; FDA Ref. 58).

- Problems with Conversion Factors used for Plant Sterols and Stanols

Raisio pointed out that in its Interim Final Rule, FDA used an ester conversion factor of 1.6 for sterols and 1.7 for stanols. Raisio objected to FDA's use of different ester conversion factors for the conversion of the weights of sterols and stanols. Raisio argued that sterol and stanol esters are virtually identical chemically and have virtually identical molecular weights. Raisio concluded, therefore, that there is no scientific justification for using different conversion factors for the two compounds. Raisio expressed its concerns that the selection of different conversion factors unfairly disadvantaged stanol esters.

In light of the issues raised in these comments, Raisio requested that FDA reconsider its proposed qualifying daily intake level of stanol esters required for a health claim. Specifically, Raisio requested that FDA approve a health claim for stanol esters at a daily intake level of 1.4 g/d stanol esters (0.8 g/d stanols), and that FDA base its ester conversion factors for both stanols and sterols on their molecular weights, resulting in an ester conversion factor of 1.7 for both sterols and stanols.

B. May 11, 2001 Submission

Raisio submitted additional comments in May 2001 that included a report and analysis of relevant existing data from a number of different clinical studies in support of a lower daily intake level for stanol esters. As part of these comments, Raisio submitted graphs which plotted the percentage reduction in cholesterol levels against the daily intake of stanol esters. The May 11th submission reinforced the propositions set forth in the previous comments by plotting those data points and providing a framework of analysis to support the minimum qualifying daily intake level.[7] The

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[7] The analysis submitted on May 11 involved the data base considered by FDA in the Interim Final Rule, as well as the following: two additional published papers meeting FDA's inclusion criteria (Plat et al., 2000, *Eur J. Clin. Nutr.*; Hallikainen et al., 2000, *Eur. J. Clin. Nutr.*); one paper

data presented consistently demonstrated reductions in total and LDL cholesterol levels for daily intakes of 1.4 - 6.8 g stanol esters. Raisio, therefore, argued that there is a statistically significant cholesterol-lowering effect at the dose of 1.4 g/day stanol esters. The comments submitted on May 11 also contained a brief response to the comments that were submitted by Lipton in February 2001.

III. RAISIO'S NEW COMMENTS

Raisio provides the following comments in response to the issues raised in the FDA's Federal Register notice on October 5, 2001.

A. The Final Health Claim Rule Should Recognize 1.4 g/day Stanol Esters as the Qualifying Level Because this Quantity Produces a Significant Reduction in Serum Total Cholesterol, LDL Cholesterol, and Apolipoprotein B in Humans, Resulting in a Reduction in the Risk of CHD.

Section 403(r)(3)(B)(i) of the Act requires the FDA (by designation from the Secretary of the Department of Health and Human Services) to promulgate a health claim regulation characterizing a substance-disease relationship only if the totality of publicly available scientific evidence supports the conclusion that there is significant scientific agreement among qualified experts that the claim is supported by such evidence. The totality of scientific evidence on the cholesterol-lowering effects of stanol esters demonstrates that 1.4 g/day stanol esters should be accepted by the FDA as the qualifying daily intake level for the health claim. To support this daily intake level, Raisio includes in this section: (i) a summary of the Company's analysis of relevant published studies on the effects of stanol esters on serum total cholesterol, LDL cholesterol, and apolipoprotein B ("Apo B"); (ii) a discussion of the significance of Apo B level as a surrogate marker for CHD risk; and (iii) a discussion of the factor used to convert a given weight of stanols to the equivalent weight of stanol esters.

1. Published Studies Demonstrate that 1.4 g/day Stanol Esters Will Produce a Significant Reduction in Serum Total Cholesterol, LDL Cholesterol, and Apo B

In order to determine whether 1.4 g/day stanol esters is an appropriate qualifying daily intake level for the health claim, Raisio conducted a comprehensive analysis of published studies measuring

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that had been submitted for publication (Mensink et al.); one unpublished study submitted in the health claim petition for stanol esters (Grundy and Cater); and unpublished data from Hallikainen et al., 2000 (FDA Ref. 88).

the cholesterol-lowering effects of stanol esters. This analysis expanded and refined the analysis submitted with Raisio's comments on May 11, 2001, by relying in part on an exponential model that fits biological systems better than other models. The analysis included a description of the quantitative relationship between daily dose of stanol esters and the resulting decrease in serum cholesterol. Establishing a quantitative relationship between dose and reduction in serum cholesterol provides a precise description of the existing relationship. More importantly, it makes it possible to determine the reduction in cholesterol that would occur at any dose between zero and the highest tested without actually testing this dose. As noted above, the analysis relied on an exponential model that is commonly used to evaluate dose-response relationships in both humans and animals. This exponential model was used to determine whether consumption of 1.4 g/day stanol esters produces a significant reduction in serum total cholesterol, LDL cholesterol, and Apo B. As discussed in detail in the attached report (see **Attachment A**) and as summarized below, these data, when taken together, confirm that 1.4 g/day will produce a significant reduction in these measures and, therefore, that 1.4 g/day is an appropriate qualifying daily intake level for the health claim.

a. Background

Before discussing the relevant published studies, it is important to understand the derivation of this body of data. As discussed below, three published papers specifically reporting the effects of 1.4 g/day stanol ester demonstrate that this is an appropriate qualifying daily intake level for the health claim (Miettinen et al., 1994 (FDA Ref. 63); Hallikainen et al., 2000 (FDA Ref. 88); Vanhanen et al., 1994 (FDA Ref. 94)). Nonetheless, Raisio recognizes that the majority of stanol ester studies evaluated the effects of higher levels of consumption. The Raisio efficacy testing program did not focus on the lowest dose delivering a significant reduction in serum total and LDL cholesterol. Rather, the program was initially set up to determine the dose that would produce a substantial reduction in serum cholesterol and that could reasonably be expected to be consumed as part of a normal diet. This approach is routine when developing a new pharmaceutical product to be evaluated by the FDA's Center for Drug Evaluation and Research ("CDER"). Determining the lowest dose that provides a "significant effect" will maximize the number of patients who fail to respond to the "lowest dose" and requires very large sample sizes, because the smaller the difference being detected, the more subjects needed. Testing a higher dose is a better approach to determining effective doses of stanol esters. This development approach is particularly relevant to stanol esters because (i) there have been no adverse effects associated with consumption, thus obviating the need to determine a low dose, and (ii) the benefit of reducing cholesterol is profound -- as described in **Attachment B**, a 1% reduction in serum LDL cholesterol levels is expected to yield a 1.3-2.3% reduction in CHD risk. Raisio's testing program has yielded a consistent body of data demonstrating that approximately 3.4 g/day stanol esters is the daily intake level that produces near maximal reductions in serum total cholesterol and LDL cholesterol.

Raisio recognizes that for the stanol ester health claim rulemaking, the FDA is interested in determining the lowest daily intake level that produces a significant reduction in serum total cholesterol and LDL cholesterol. Accordingly, the Company has analyzed the data base upon which the FDA relied in the Interim Final Rule, together with more recently published studies that meet the same criteria. These studies, representing the totality of publicly available scientific evidence, demonstrate that the Agency should recognize 1.4 g/day stanol esters as the qualifying daily intake level for the health claim.

b. Raisio Analysis of Data on the Effectiveness of Stanol Esters

Raisio's analysis was based upon the same published papers analyzed and relied upon by the FDA in the Interim Final Rule. Raisio also included in its analysis two additional papers that were not included among those analyzed by the FDA.[8] These two papers met the same criteria as the other papers analyzed by the FDA, but had not yet been published at the time of the FDA analysis. Five papers considered by the FDA were not included in Raisio's analysis for the following reasons: two studies (FDA Refs. 64 and 81) reported data from the same studies as two other papers (FDA Refs. 63 and 82, respectively); one study used a diet containing a mixture of unesterified stanols and sterols (FDA Ref. 74); one study lacked an appropriate control diet (FDA Ref. 78); and one study administered unesterified stanol in a gelatin capsule and lacked an appropriate control group (FDA Ref. 97).

Raisio's current analysis was based on a validated dataset derived from fourteen papers published in peer-reviewed journals. From each paper, Raisio calculated the mean reduction in serum cholesterol from baseline for both the treatment group and the control group. The value for the mean percentage reduction in the control group was then subtracted from the corresponding mean percentage reduction in the treatment group to determine the net effect of stanol esters.

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[8] Hallikainen MA, Sarkkinen ES, Gylling H, Erkkila AT, Uusitupa MI. Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet. Eur J Clin Nutr 2000; 54(9): 715-25. (Submitted with Raisio's comments of May 11, 2001.)

Plat J, van Onselen EN, van Heugten MM, Mensink RP. Effects on serum lipids, lipoproteins and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. Eur J Clin Nutr 2000; 54(9): 671-7. (Submitted with Raisio's comments of May 11, 2001.)

Some studies measured serum cholesterol serially over time; for these studies, Raisio used the last on-treatment value for its analysis. Two studies employed a crossover design; for these studies, each dose group was treated as an independent group for the purposes of this analysis. Four of the studies also measured serum Apo B levels in addition to total and LDL cholesterol. From the fourteen papers Raisio considered, twenty-three treatment groups were analyzed for total cholesterol, 21 treatment groups for LDL cholesterol, and 9 treatment groups for Apo B.

The Raisio analysis sought to address several questions including the following:

- Is there a relationship between the daily dose of stanol esters and the reduction in serum total cholesterol, LDL cholesterol, and Apo B, and, if so, how can this relationship be described mathematically?

- What is the likelihood that a stanol ester dose of 1.4 g/day will produce a reduction in serum total cholesterol, LDL cholesterol, and Apo B?

While the attached report provides detailed answers to these questions, the answers may be summarized as follows.

Several conclusions can be drawn from a simple visual inspection of the data points derived from the validated dataset. Specifically, there is a dose-response relationship between stanol esters and a reduction in serum total cholesterol, LDL cholesterol, and Apo B. Increasing the dose of stanol esters increases the reduction in serum cholesterol and Apo B. Raisio sought to identify an appropriate mathematical equation (or model) that could best describe the reductions in the three serum levels for a particular dose of stanol esters, while taking into account the known pharmacological properties of stanol esters.

The attached report first applied the simplest mathematical model by fitting the data to a straight line using a least-squares regression technique, and the following equation:

$$Y = A + BX$$

where

Y is the reduction in total or LDL cholesterol
X is the dose of stanol esters
A is the y-axis intercept
B is the slope of the line

The fitting procedure gives the values of A and B that best predict the value of Y for a given value of X. The resulting straight line represents the magnitude of the reduction in total or LDL cholesterol that will occur with a given dose of stanol esters. The slope of the line is significantly

different from zero, indicating that there is a significant dose-response relationship. As described in **Attachment A**, the linear model predicts that total cholesterol would be expected to decrease 0.71% for each gram of stanol esters consumed daily, while LDL cholesterol would be expected to decrease 1.26% for each gram of stanol esters consumed daily.

The linear models are not, however, consistent with the known pharmacological properties of stanol esters. First, one would expect a dose of 0.0 g stanol esters/day to yield no change in total or LDL cholesterol -- that is, the resulting lines should pass through the origins of the graphs. However, the y intercepts for total cholesterol and LDL cholesterol are significantly different from zero (4.62 and 4.28, respectively), and the lower bounds of the 95% confidence interval are greater than zero. Second, the effects of stanol ester are expected to plateau at higher doses because there is only a limited amount of cholesterol in the gut, the absorption of which may be blocked by stanol esters.

To address these limitations with the linear model, the analysis applied the following exponential model to the data:

$$Y = Ymax\ (1\text{-}e^{-kX})$$

where
Ymax is the maximum value of Y (the maximum percentage decrease in total or LDL cholesterol)
k is an exponential constant that relates dose to reduction in cholesterol

This exponential model is commonly used to describe dose-response relationships when it is apparent that increasing doses will eventually produce an effect that cannot be increased further. Like the linear equation, the exponential equation has two parameters that relate Y to X, only here the parameters are Ymax and k. This model yields curves that pass through the origin and that result in a plateau at higher doses. Comparing the sum-of-squares from the linear model to that for the exponential model confirms that the exponential model is a better fit of the data for both total cholesterol and LDL cholesterol.

The exponential model not only provides a good description of the relationship between stanol ester dose and reduction in serum cholesterol, but can also be used to predict the effect on cholesterol levels from a dose of 1.4 g/day stanol esters. The model predicts that 1.4 g/day would be expected to yield a decrease (upper and lower bounds of 95% confidence interval) in total and LDL cholesterol of 4.75% (3.46, 6.03) and 5.04% (2.47, 7.60), respectively, with the lower bounds of the 95% confidence intervals well above zero. The 95% confidence intervals (shown in parentheses) indicate that one can be 95% certain that a dose of 1.4g/day of stanol esters will produce a reduction in total cholesterol and LDL cholesterol within these ranges.

The exponential model also may be used to calculate the ED_{50}, i.e., the stanol ester dose that produces a half-maximal reduction in serum cholesterol levels. The ED_{50} for total cholesterol is 1.24 g/day and produces a 4.75% reduction in total cholesterol levels, while the ED_{50} for LDL cholesterol is 1.90 g/day and produces a 6.36% reduction in LDL cholesterol levels. The 95% confidence intervals for these values both include 1.4 g/day, further indicating that this dose is likely to produce a significant reduction in total and LDL cholesterol.

Finally, three papers reported results for 1.4 g/day stanol esters. (FDA Refs. 63, 94, and 88.) Two of the studies, which may involve the same treatment cohort, reported statistically significant ($p<0.05$) reductions in total and LDL cholesterol. (FDA Refs. 63 and 94.) The third study (FDA Ref. 88) reported reductions in total and LDL cholesterol, but these were not statistically significant. This study did, however, report a significant reduction in Apo B and, therefore, as discussed below, supports the efficacy of this dose level.

Four studies measured Apo B in addition to total and LDL cholesterol. Raisio applied the same exponential model to the Apo B data. With this model, the calculated reduction in Apo B at 1.4 g/day stanol esters is 9.25% (7.3, 11.2). Again, this indicates that one can be 95% certain that 1.4 g/day stanol esters will yield a significant reduction in Apo B. As referenced in the previous paragraph, the one study measuring Apo B at a dose of 1.4 g/day stanol esters reported a significant reduction in Apo B (9.3%, $p<0.001$) (FDA Ref. 88). And as discussed in Section III.A.2 below, Apo B has been validated as a risk factor for CHD risk in a number of large-scale clinical studies over the past decade. Further, Apo B is one of the primary efficacy endpoints required by FDA's Center for Drug Evaluation and Research ("CDER") in any evaluation of lipid-lowering drugs.[9]

In sum, Raisio's analysis of publicly available scientific evidence concerning the dose-response relationship between stanol esters and reductions in serum total cholesterol, LDL cholesterol, and Apo B demonstrates that there will almost certainly be a significant reduction in serum cholesterol and Apo B with a stanol ester dose of 1.4 g/day. As summarized in the Raisio analysis, this conclusion is based on the following observations:

- Visual inspection of the data for the reduction in serum total cholesterol, LDL cholesterol, and Apo B suggests that 1.4 g/day stanol esters will produce a significant reduction in these measures.

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[9] Guidelines for the Clinical Evaluation of Lipid-Altering Agents in Adults and Children (Sept. 1990).

- When the data for total and LDL cholesterol are fit to a linear model, the lower 95% confidence interval at a stanol ester dose of 1.4 g/day is greater than zero for both total and LDL cholesterol. These results indicate that with the best fit line, one can be 95% certain that a stanol ester dose of 1.4 g/day will produce a reduction in both total and LDL cholesterol.

- When the data for total and LDL cholesterol are fit to an exponential model, the lower bound of the 95% confidence interval is greater than zero for the calculated reduction in both total and LDL cholesterol at a stanol ester dose of 1.4 g/day. These results indicate that with the exponential model, one can be 95% certain that a stanol ester dose of 1.4 g/day will produce a reduction in both total and LDL cholesterol.

- Three studies tested a stanol ester dose of 1.4 g/day or less and reported reduction in total and LDL cholesterol.

- When the data for Apo B are fit to an exponential model, the lower bound of the 95% confidence interval is greater than zero for the calculated reduction in Apo B at a stanol ester dose of 1.4 g/day. This result indicates that with the exponential model, one can be 95% certain that a stanol ester dose of 1.4 g/day will produce a reduction in Apo B.

- One study measured Apo B at a stanol ester dose of 1.4 g/day and reported that the reduction was statistically significant.

2. Apo B Level is an Appropriate Predictor of CHD Risk.

Raisio's comments of November 21, 2000, explained that Apo B is a marker for LDL levels. As noted in the earlier comments, Apo B is the major apolipoprotein of low density lipoproteins, with more than 90% of serum Apo B residing in the LDL fraction of lipoproteins. Because there are several different forms of LDL particles, each with varying proportions of cholesterol, measurement of Apo B levels provides a more accurate reflection of the number of LDL particles than does calculation of LDL cholesterol levels. It is the number of LDL particles that is believed to be most relevant to atherosclerosis.

Raisio has obtained and presented to FDA an expert opinion reviewing existing published literature and concluding that Apo B not only is a marker for the number of LDL particles, but is an independent predictor of CHD risk. Attached is a report prepared by W. Virgil Brown, M.D., The Charles Howard Candler Professor of Medicine at Emory University and Past President of the American Heart Association, discussing the clinical studies demonstrating that Apo B is recognized as a marker for CHD risk. (See **Attachment C**.) As Dr. Brown explains, there is growing evidence that Apo B is a better predictor of CHD events caused by underlying atherosclerosis than is LDL cholesterol. Dr. Brown notes that the strong association of Apo B

with vascular disease may be due to the following: (1) Apo B provides an assessment of the particle number of atherogenic VLDL as well as LDL; and (2) the delivery of lipid into the arterial wall lesions of arteriosclerosis is more closely related to the number of such particles than to the specific amount of cholesterol carried by any group of lipoproteins.

The CDER guidelines also acknowledge Apo B as a predictor of CHD risk. Dr. Brown's report summarizes and emphasize the scientific validity of Apo B as a predictor of CHD risk. Raisio believes that CFSAN must also recognize and accept the validity of Apo B in its assessment of clinical/efficacy data in scientific publications.

As noted in Raisio's comments of November 21, 2000, the Company urges the FDA to reconsider the results reported by Hallikainen et al. (FDA Ref. 88). In the Interim Final Rule, the FDA concluded that the lowest dose tested (1.4 g/day stanol esters) in this study was not effective because the reductions in LDL cholesterol and total cholesterol at 4 weeks were not significant versus the control period. In fact, however, the reduction in Apo B levels at this dose and time point was statistically significant versus the control period. Raisio believes that short-term dietary disruptions (alcohol consumption during a Finnish national festival) immediately before the blood sampling at the 4-week measurement in the control period affected control cholesterol levels, rendering the effect of the treatment apparently non-significant. Because, as explained in Dr. Brown's report, Apo B is a more durable indicator of serum lipid status than LDL cholesterol, Raisio maintains that this study should be relied upon to support a qualifying daily intake level of 1.4 g/day stanol esters. Thus, the three papers reporting the effects at doses of approximately 1.4 g/day stanol esters -- Hallikainen et al., Miettinen and Vanhanen (FDA Ref. 63), Vanhanen et al. (FDA Ref. 94) -- demonstrate that 1.4 g/day stanol ester should be the qualifying daily intake level for the health claim.

3. Conversion Factor

In Raisio's comments of November 21, 2000, the Company explained that the conversion factor used by the FDA in converting free stanols to stanol esters should be the same as the factor used for converting free sterols to sterol esters. It is important to note that the scientific literature almost universally reports daily intakes in terms of free sterols/stanols rather than the quantity of the corresponding ester form. As noted in Raisio's earlier comments, in the Interim Final Rule, FDA reported conversion factors of 1.6 for sterols and 1.7 for stanols. FDA derived these conversion factors from published toxicological reports on the two products.

Raisio submits that the conversion factors should be based on the molecular weights of the sterol/stanol ester products divided by the molecular weights of the free sterols/stanols. For regulatory purposes, the assumption should be made that the fatty acid moiety used in the esters are identical for all products. To assume otherwise becomes impossibly complicated and unworkable. Product analysis shows that the average stanol or sterol ester preparation consists of

approximately 60% stanol or sterol respectively. Thus, the conversion factor should be about 1.0/0.6, i.e., 1.7 (expressed to two significant figures.) Because the molecular weights of sitostanol -- the primary stanol -- and sitosterol -- the primary sterol -- are virtually identical (416.73 g/mol and 414.72 g/mol, respectively), the conversion factors should be the same for both products.

If the FDA continues to use different conversion factors, stanol esters would be unfairly disadvantaged without any valid scientific justification. Sterol ester products purportedly qualifying for the health claim would be permitted to contain reduced amounts of sterols, an outcome distinctly and unwarrantedly unfair to McNeil.

B. There is No Scientific or Legal Basis for Including Free Sterols/Stanols or Mixtures of Free Sterols/Stanols in this Rulemaking.

As explained below, there is no valid scientific basis for permitting free sterols/stanols, or mixtures thereof, to qualify for a health claim. Moreover, even if the scientific support were available, there would be no valid legal basis for including the compounds in the present health claim rulemaking for sterol/stanol esters because: (1) FDA has failed to provide interested parties with adequate notice and an opportunity to comment on the inclusion of free sterols and stanols in the instant rulemaking; and (2) principles of equity and fairness require that the issue of free sterols and stanols be severed from this rulemaking. Each of these points is discussed below.

1. Free Sterols/Stanols and Mixtures Thereof Have Not Been Demonstrated to Reduce Serum Total or LDL Cholesterol Levels.

In preparing the Interim Final Rule, FDA reviewed four plant sterol studies involving the use of free sterols -- FDA Refs. 63/64 (one study), 65, 74 and 75 -- and three plant stanol studies involving the use of free stanols -- FDA Refs. 63/64, 74 and 97.[10] FDA reported that all of these studies met the Agency's specified selection criteria.

Among the three plant stanol studies, two (FDA Refs. 63/64 and 97) showed no efficacy with free stanols. The third study, by Jones et al. (1999; FDA Ref. 74), does not qualify as a free stanol study, since the test material was a sterol/stanol mixture consisting of only 20% stanols. Thus, there are no free stanol studies that were reviewed by FDA, satisfied the Agency's selection criteria, and demonstrated efficacy in reducing serum total or LDL cholesterol.

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[10] 65 Fed. Reg. at 54692-54700.

Among the four free sterol studies, one (FDA Refs. 63/64) showed no efficacy with free sterols. A second study, by Pelletier et al. (1995; FDA Ref. 65), in which free sterols were incorporated into butter (which has a high cholesterol content) rather than a vegetable-based spread (which contains virtually no cholesterol), is described by FDA as being "less relevant in determining a useful daily intake level. (Butter would not be able to bear the claim because it exceeds the disqualifying levels for cholesterol and saturated fat on a 50 gram basis.)"[11] Moreover, this was a crossover study with no washout period, the so-called control butter contained 18% more cholesterol than the butter enriched with plant sterols, and the paper reported no baseline values that would have allowed for the independent calculation of the relative serum cholesterol changes induced by consumption of 50 g/day butter alone and by the butter plus free sterols. FDA noted that the daily intake level used by Pelletier et al. was very close to that used in the study described in FDA Refs. 63/64, in which no cholesterol-reducing efficacy was observed. In the study cited in FDA Refs. 63/64, comparison was made to a run-in period with high daily intake of low erucic acid rapeseed oil that itself effectively reduces serum total and LDL cholesterol. For the purpose of setting a daily intake level for sterol esters, FDA therefore appropriately decided to discard the Pelletier et al. paper and to focus on the third of the four free sterol studies, by Sierksma et al., (1999; FDA Ref. 75).

Sierksma et al. reported efficacy of free sterols versus control spread in reducing both total and LDL-cholesterol. However, the paper reported no baseline values that would have permitted independent calculation of percentage reductions in these parameters. Further, the so-called control spread was a commercial spread ("Flora"). While the specially blended test spread contained only 140 g/kg saturated fat, the commercial control spread contained 160 g/kg (i.e., over 14% more) saturated fat. Thus, it was not a true control.

The only appropriately controlled free sterol study is the fourth study, by Jones et al. (1999; FDA Ref. 74). However, this study reported efficacy only in reducing serum LDL-cholesterol, not total cholesterol. Moreover, the tall oil-derived test material was not a mixture of free plant sterols alone, but included 20% free stanols, as noted above.

In summary, the qualifying scientific literature on the cholesterol-lowering efficacy of free plant sterols reviewed by FDA contains only one study showing reductions in both total and LDL-cholesterol (a study that used an inappropriate control and provided inadequate data), and a second study showing efficacy in lowering LDL but not total cholesterol (a study which used a sterol/stanol mixture rather than free sterols alone). Thus, there is no body of scientific literature showing total and LDL cholesterol-lowering efficacy of either free sterols or free stanols (or, for that matter, efficacy of a mixture of free sterols and stanols).

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[11] 65 Fed. Reg. at 54703.

[NOTE: Raisio notes that Novartis submitted an unpublished study in support of the efficacy of its free sterol product. Because the study is unpublished, FDA may not consider it in this rulemaking. FDA's health claim regulations permit the Agency to authorize a specific health claim "only when it determines, based on the totality of publicly available scientific evidence ... that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence." 21 C.F.R. § 101.14(c). (emphasis added).]

a. The Safety and Efficacy of Free Sterols/Stanols is Dependent on Product Specifications and the Food Matrix.

As explained above, there is no scientific or legal justification for including free sterols/stanols or mixtures thereof in the present rulemaking. If the Agency decides to initiate a separate health claim rulemaking to cover free sterols/stanols, Raisio would urge the Agency to consider two issues that affect the safety and efficacy of these compounds: (1) the need for strict quality specifications; and (2) the nature of the food matrix into which free sterols/stanols must be incorporated to achieve efficacy in reducing serum cholesterol.

i. Need for Strict Quality Specifications for Free Sterols/Stanols

Raisio believes that, whether or not FDA considers free sterols/stanols for a health claim, strict quality specifications must be applied to free sterol preparations intended for use in foods in order to ensure product safety. As commercially available sterol mixtures are obtained from a number of different types of botanical sources, the sterol composition, sterol content and levels of minor natural components vary considerably. There will also be significant variations in levels of impurities and manufacturing residues, such as solvents and oxidized sterols. In order to ensure safety, quality specifications must adequately address the composition of the sterol or stanol blends that are to be incorporated into foods, and must also specify the permissible free sterol content of the finished product in terms of weight percent. Further, the identity and maximum permissible levels of any residual solvent should be specified. Free sterols in products offered for sale for human consumption should, at a minimum, meet the purity level of any corresponding material previously used in safety and toxicity studies designed to demonstrate product safety to FDA. The product specifications for stanol esters set forth in McNeil Consumer Healthcare's GRAS notification comport with this very basic standard.

Quality specifications are more important for free sterols (and, for that matter, sterol esters) than for stanols and stanol esters. The hydrogenation process by which sterols are converted to stanols, and the subsequent stanol crystallization process, represent significant purification steps which have no counterparts in the production of free sterols or sterol esters. Possible byproducts and

impurities stay behind in solution in the mother liquor when it is separated from the crystalline stanols, and any traces of impurities remaining on the surface of the crystals are removed in the subsequent solvent wash. At this point, free stanols will still contain residues of solvent. However, solvent residues are completely removed in the subsequent preparation of stanol esters, especially during the deodorization process, which effectively removes any traces of volatile compounds. All toxicity, safety and clinical studies carried out with stanol esters have employed test materials of the same quality as those used in commercial products.

Furthermore, the safety data relied on in establishing GRAS status for sterol and stanol esters are generally irrelevant when evaluating the safety of free sterols/stanols, and particularly free sterols. It should be noted that free sterols can be derived from different natural sources using a wide variety of extraction processes. The safety determinations of free sterols must consider the source and extraction processes used, and must be established on the basis of safety studies of free sterols/stanols of appropriate grades, not the esterified products. Finally, comprehensive specifications need to be set for free sterols and stanols just as they were established for esterified sterols and stanols, especially if the pivotal safety evaluations that have been performed are based on studies with esterified sterols and stanols.

ii. Nature of the Food Matrix is a Critical Issue for the Efficacy of Free Sterols and Stanols

The cholesterol-lowering action of plant sterols and stanols occurs in the fat phase of human digestion products. The primary sites of action are the so-called mixed micelles in the small intestine, but the enterocytes are believed to be secondary sites. The efficacy of free sterols and stanols is highly dependent on the extent to which they are first solubilized in the fat phase of digestion products. Furthermore, sterols can enter the enterocytes only if they are first solubilized in mixed micelles or other liposome-type entities. As a consequence, the physical form of the free sterols and stanols and the food matrix used to transport them into the digestive system is critical. A key condition is the presence of fat, and the way in which the free sterol or stanol is dispersed within that fat. (Free sterols and stanols for use in the preparation of foods may be in the form of crystals or an amorphous powder, or already emulsified and/or complexed with fat.) Preliminary data from clinical studies show that efficacy of free sterols is reduced when they are dispersed in protein-rich, low-fat food matrices such as low-fat yogurts rather than, for example, fat-based spreads. This problem does not arise with sterol and stanol esters, since such material, by definition, constitutes a fatty acid-containing lipid and will, therefore, be effectively incorporated into the fat phase of the food digest.

2. FDA has Failed to Provide Adequate Notice and Opportunity for Comment.

a. Notice and Comment is Required Under the APA.

One of the fundamental procedural protections guaranteed by the Administrative Procedure Act ("APA") is that before an agency promulgates a legally binding regulation, all interested parties are provided notice and an opportunity to comment. 5 U.S.C. § 553. Courts have made clear that the notice and comment process is not merely *pro forma* but rather a process of reasoned decision making. Particularly important to the reasoning process is the opportunity for meaningful participation by all interested parties. *Connecticut Light and Power Co. v. NRC*, 673 F.2d 525 (D.C. Cir. 1982).

Meaningful participation can occur only when all parties have a full opportunity to present their views and analysis of the proposed regulation. The APA requires, therefore, that an agency publish, for comment, not only the rule it proposes, but also the technical studies and data upon which it relies in proposing a particular regulation. *See, e.g.*, *Building Indus. Assoc. v. EPA*, 247 F.3d 1241 (D.C. Cir. 2001); *Northwest Tissue Center v. FDA*, 1 F.3d 522 (D.C. Cir. 1993); *Solite Corp. v. EPA*, 952 F.2d 473 (D.C. Cir. 1991). In fact, FDA acknowledges this very requirement in its own regulations implementing the APA. Pursuant to 21 C.F.R. § 10.40(b)(vii), a published notice of proposed rulemaking must include a summary of the proposal, and the facts and policy underlying it, including all of the information on which the Agency relies for the proposal.

As the D.C. Court of Appeals has explained, "Integral to the notice requirement is the agency's duty 'to identify and make available technical studies and data that it has employed *in reaching the decision to propose particular rules*. . . . An agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary." *Id.* at 530-31 (emphasis added). Where an agency fails to provide an accurate and complete picture of the reasoning that led it to propose a particular rule, the agency risks decision making based on a one-sided view or a mistaken picture of the issues at stake. *Id.* The necessity of publishing such studies and data is particularly strong when, as in the instant proceeding, the rule(s) at issue are complex. *See Connecticut Light*, 673 F.2d at 530-31. Indeed, FDA recognizes the complexities inherent in making a health claim determination, and therefore explicitly requires a health claim petition to include a summary of scientific data that establishes the basis upon which authorizing a health claim can be justified. 21 C.F.R. § 101.70.

In the instant proceeding, FDA has failed to provide interested parties with the requisite notice and opportunity to comment on the issue of whether free sterols/stanols should be included in the health claim regulation for sterol/stanol esters. Most troublesome, FDA has not published the technical studies and data underlying its decision to consider the inclusion of free sterols/stanols. Yet the APA clearly requires it to do so.

In fact, FDA has not yet even proposed a rule to include these substances in a health claim -- a requirement under the Agency's own health claim regulations (21 C.F.R. § 101.14(d)) -- much less provided any data or studies providing the basis for such a proposal. Instead, FDA has essentially asked interested parties to develop and suggest their own proposals and to provide their own data for such proposals, an approach that deprives the public of adequate notice and of a meaningful opportunity to comment on the Agency's own rationale.

Moreover, the sole notice FDA has provided about the possibility of including on free sterols/stanols – a brief statement contained in its notice reopening the comment period the Interim Final Rule for sterol/stanol esters – does not cure this procedural ill. When the Agency merely states that it has received comments that advocate some position and then requests more information and data on the issue, it has not provided a clear and complete record of its rationale for proposing a rule. It is well established that an agency may not bootstrap notice from a comment. *Fertilizer Institute v. EPA*, 935 F.2d 1303, 1312 (D.C. Cir. 1991) (quoting *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 549 (D.C. Cir. 1973)). In attempting to initiate a new proposed rule via a brief statement in the notice reopening the comment period for the Interim Final Rule, FDA has impermissibly employed a back-door procedure that denies parties a meaningful opportunity to participate. *See Northwest Tissue*, 1 F.3d at 527.

b. Any Health Claim for Free Sterols and Stanols Must be Considered under Separate Rulemaking.

Under the APA, the only appropriate forum in which FDA can consider whether to adopt a health claim for free sterols/stanols is a new notice-and-comment rulemaking in response to a petition for a proposed rule. In the instant proceeding, FDA has not received such a petition. Instead, it has received only vague allusions to the potential merits of including free sterols/stanols in the current rulemaking. Notably, those suggestions were submitted as part of comments responding to an interim final health claims rule for different substances, sterol/stanol esters.

Raisio recognizes that agencies may, in limited circumstances, modify their proposals without having to institute new rounds of rulemaking. *Kooritzky v. Dept. of Labor*, 17 F.3d 1509 (D.C. Cir. 1994). Courts, however, have narrowly circumscribed the circumstances under which such modifications are legally permissible, and the instant rulemaking does not qualify for this limited exception. Such circumstances are limited to the rare case where the final rule represents the "logical outgrowth" of the original proposal. *Fertilizer Inst. v. EPA*, 935 F.2d at 1311; *see also AFL-CIO v. Donovan*, 757 F.2d 330, 338 (D.C. Cir. 1985). A health claim for free sterols/stanols is certainly *not* a logical outgrowth of one for sterol/stanol esters. Indeed, as explained above, the qualifying scientific literature does not establish the cholesterol-lowering efficacy of free sterols/stanols.

The key to the "logical outgrowth" test is whether the following three purposes of notice and comment have been adequately served: (1) to expose the proposed rule to diverse public comment; (2) to provide fairness and an opportunity to be heard; and (3) to enhance judicial review. *Building Indus. Ass'n v. Babbitt*, 979 F. Supp. 893, 901 (D.D.C. 1997), *aff'g sub nom, Building Indus. Assoc. v. EPA*, 247 F.3d 1241 (D.C. Cir. 2001). None of these purposes would be served by the inclusion of free sterols/stanols in the health claim that is the subject of the current rulemaking proceeding.

- There has been no opportunity for diverse public comment because there has been no clear and succinct proposed rule on the issue of free sterols/stanols and no justification for it.

- Interested parties have not had adequate notice and an opportunity to be heard on the issue to the extent that they are guaranteed under the APA and to the extent required for an issue of this importance.

- To permit advocates of a health claim for free sterols and stanols to ride on the coattails of the petitioners in this proceeding is inherently unfair to parties that have invested the extensive time and financial resources in rulemaking proceeding for a health claim for sterol/stanol esters. This point is discussed further below.

- There are insufficient data in the administrative record to support a determination of whether a health claim should be permitted for free sterols/stanols. Therefore, should the Agency attempt to make such a determination at this time, it would be entirely unclear as to what information the Agency properly relied upon in making its decision.

The few cases wherein courts have upheld agency rulemaking based on studies not received until during the comment period are readily distinguishable. For example, in this proceeding, the studies submitted during the reopening of the comment period *cannot* merely add supporting data that confirm the hypothesis and findings delineated in the proposal, because, to date, FDA has not delineated any hypothesis, or any findings, or any proposal. *See Building Indust. Assoc. v. EPA*, 247 F.3d 1241 (D.C. Cir. 2001). As one court has so aptly described the present situation, "Something is not a logical outgrowth of nothing." *Kooritzky,* 17 F.3d at 1513.

Nor is this a proceeding wherein the studies FDA would rely on, without public comment, are not critical to FDA's final determination. *See Time Warner v. FCC*, 240 F.3d 1126 (D.C. Cir. 2000). Necessarily, any data relied on to promulgate a health claim for free sterols/stanols is critical to FDA's determination, because virtually no studies have been previously discussed or made available for public comment. And while some studies cited by petitioners and commenters in this proceeding may have involved free sterols/stanols, the discussion of those studies occurred solely within the context of the efficacy of sterol/stanol esters, not free sterols/stanols.

Finally, the inclusion of free sterols/stanols cannot be said to be merely a "part of series of refinements" on FDA's health claim for esters. *Appalachian Power Co. v. EPA*, 135 F.3d 791, 815 (D.C. Cir. 1998). As previously discussed, this is far from a mere refinement; it is an entirely separate scientific issue. As discussed above, the efficacy of free sterols/stanols has not been adequately demonstrated in qualifying scientific studies and, in any case, appears to be highly dependent on the nature of the food matrix into which the free sterols/stanols are incorporated.

Aside from some of the data in support of the Interim Final Rule tangentially involving free sterols/stanols, the only other basis that FDA provides for it now considering the inclusion of free sterols/stanols is that some of the comments received in response to the Interim Final Rule requested a health claim for foods containing the free form of the substances at issue in this proceeding. 66 Fed. Reg. 50824, 50825 (Oct. 5, 2001). It is well established, however, that commenting parties cannot be expected to monitor all other comments submitted to an agency. Instead, the agency must itself provide notice of a regulatory proposal. Ambiguous comments and weak signals sent by an agency do not provide any meaningful notice or opportunity to comment. *Northwest Tissue v. FDA*, 1 F.3d at 528; *see also Shell Oil Co. v. EPA*, 950 F.2d 741, 751 (D.C. Cir. 1991) (explaining that comments by members of the public do not constitute adequate notice because the APA requires that notice come from the agency"); *American Fed'n of Labor v. Donovan*, 757 F.2d at 340 (holding that notice cannot be attributed to interested parties "on the basis of an assumption that they would have monitored the submission of comments"); *Fertilizer Institute v. EPA*, 935 F.2d at 1312 (noting that "[c]ommenting parties cannot be expected to monitor all other comments submitted to an agency").

While the issue of whether scientific data ultimately support a health claim for free sterols/stanols may be an important one, this is neither the time nor the proceeding to make such a determination. Rather, a determination of such importance should be made only after considering all available data. The only way to ensure that FDA has access to such data is by proposing a rule, including a full explanation of its current thinking and the underlying data and policies for its proposal, inviting the analysis and critique of all interested parties, and then evaluating that analysis and critique.

c. Conclusion

In sum, the procedures followed by FDA in this matter come perilously close to foreclosing any useful participation during the rulemaking process. Despite FDA's broad discretion to regulate matters affecting public health, FDA's approach cannot be permitted because it circumvents the careful procedures and requirements embodied in the APA and in FDA's regulations governing the promulgation of health claims. For the reasons discussed above, the promulgation of a health claim on free sterols/stanols as part of the current rulemaking proceeding does not comply with the notice-and-comment requirement under the APA, and FDA should therefore abandon this sort of procedural brinksmanship.

3. Principles of Equity and Fairness Require FDA to Sever the Issue of Free Sterols/Stanols from this Rulemaking.

Finally, Raisio believes that, in the interest of fairness, FDA should conclude this rulemaking after the completion of this comment period without adding free sterols/stanols to the Final Rule for the following reasons: (1) equity principles require that FDA treat the petitioners the same as similarly situated companies seeking health claims; and (2) this rulemaking has been unreasonably long and placed undue hardships on the petitioners.

a. All Companies Seeking Health Claims Must Follow the Same Procedures.

FDA should require all companies seeking the cholesterol-lowering health claim to follow the same procedures and to submit the same quantity and quality of scientific data in support of their products. It is a well-established principle that an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so. *Independent Petroleum Association of America v. Babbitt*, 320 U.S. App. D.C. 107, 92 F. 3d 1248, 1258 (D.C. Cir. 1996)(*citing National Association of Broadcasters v. FCC*, 239 U.S. App. D.C. 87, 740 F.2d 1190, 1201 (D.C. Cir. 1984). Indeed, disparate treatment of similarly classified products constitutes "the essence of arbitrary and capricious." *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997). The U.S. District Court for the District of Columbia applied this same principle to FDA in a case involving ultrasound agents. *Id.*

In *Bracco*, three manufacturers of injectable contrast imaging agents for use with diagnostic ultrasound equipment -- which FDA regulated as new drugs -- filed suit because a virtually identical injectable agent was regulated by FDA as a device. FDA required the manufacturers of the products considered to be new drugs to produce exhaustive scientific data demonstrating the safety and effectiveness of their ultrasound agents. *Id.* at 24. The company that manufactured the same ultrasound agent that had been classified as a device was permitted to conduct much less rigorous testing and submit less robust information and results. *Id.* Based on these facts, the court stated that:

> [w]hat the FDA is not free to do ... is to treat them dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason. Plaintiffs merely maintain that the same tests and studies should be required of each product before it is approved.... The Court agrees.

Id. at 28.

Raisio believes that FDA will be committing a similar error if it allows free sterols/stanols to be considered as part of this rulemaking. As required by the health claim regulations, Lipton and McNeil submitted to FDA adequate and well-controlled published studies to support the grant of the health claim. In support of stanol esters, McNeil submitted more than 20 such studies. Manufacturers of free sterols/stanols should be required to adhere to this same standard. None of the previously submitted comments suggesting the inclusion of free sterols/stanols cited to any published data on the safety and effectiveness of those substances; rather, those comments have merely relied on information submitted by McNeil and Lipton. As discussed in Section III.B.1 above, those studies are insufficient to support a health claim for free sterols/stanols. Indeed, only one study supports the efficacy of free sterols in reducing serum total and LDL-cholesterol. The data show that the efficacy of free sterols/stanols is clearly different from sterol/stanol esters, and thus, manufacturers of free sterols/stanols must submit independent effectiveness data before being granted a health claim.

Including free stanols/sterols in the instant rulemaking would thus be arbitrary and capricious. For the reasons discussed below, extending the instant rulemaking would be unfair. Thus, the only path open to FDA would be to institute a separate health claim rulemaking for free stanols/sterols.

b. Further Extension of This Rulemaking Would be Unduly Burdensome to Petitioners.

FDA's extension of this rulemaking would be unfair to the petitioners because this rulemaking has already taken a significant amount of time. Section 403(r)(4)(A) of the Federal Food, Drug and Cosmetic Act gives FDA 100 days to review a petition, and if a proposed regulation is issued in response to the petition, the rulemaking is to be completed within 540 days of the receipt of the petition. Lipton and McNeil submitted their petitions nearly two years ago -- on February 1, 2000 and February 15, 2000 respectively. FDA issued the Interim Final Rule more than a year ago -- on September 8, 2000. Because such a significant amount of time has passed since the initial filing of the petitions, this protracted rulemaking procedure for the health claim for sterol/stanol esters and coronary heart disease should conclude at the end of this comment period.

As FDA has done in its comprehensive review of sterol/stanol esters, prior to finalizing any health claim for free sterols/stanols, the Agency would need not only to review any additional information received concerning the safety and effectiveness of free sterols and stanols, but also to provide a discussion of those data in the a manner similar to that in the Interim Final Rule. Such publication would be necessary in order to provide interested parties with adequate notice and a meaningful opportunity to comment. As discussed above, the notice and opportunity for comment provided by a proposed rule is essential to rulemaking.

Raisio, therefore, respectfully requests that FDA finish this rulemaking on sterol and stanol esters, issue a Final Rule, and review the issue of free sterols/stanols in a separate rulemaking proceeding.

Raisio believes that this is the only way to achieve the goal of ensuring that all parties are treated similarly, while also ensuring that all products covered by a health claim regulation are safe and effective in lowering cholesterol.

C. The Safety of Stanol Esters has been Well-Established and does not Necessitate Special Labeling Requirements.

As a preliminary matter, Raisio supports the comments submitted by McNeil Nutritionals Inc. (formerly McNeil Consumer Healthcare) in response to the FDA's request for comments on potential labeling issues. In addition to those comments, Raisio wishes to address specifically several of the issues raised in the FDA notice.

1. Reductions in Serum Beta-Carotene Levels Following Consumption of Stanol Esters are of no Physiological Significance.

The FDA notice summarizes a concern raised by the EC as to whether sterol/stanol-containing products should include label statements to protect populations whose vitamin A status is not optimal, because these products may cause a reduction in plasma beta-carotene. McNeil addressed this issue in full in its GRAS notification for stanol esters. In that notification, McNeil summarized studies evaluating the effect of stanol esters on vitamin A status and on serum beta-carotene levels. As discussed in detail in the GRAS notification, vitamin A is a nutritional term that describes a family of compounds that are structurally related to retinol and that share its biological activity. Pro-vitamin A refers to certain carotenoids, including beta-carotene, which serve as dietary precursors of retinol. A recent FDA-sponsored review of the health significance of carotenoids has identified no clear-cut health benefit for carotenoids in humans other than as a precursor pool for vitamin A (Food Advisory Committee Meeting on Sucrose Polyester, June 1998). This position was corroborated by a recent report on carotenoids issued by the Institute of Medicine. (Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids. 2000; IOM-NAS Food and Nutrition Board; http://books.nap.edu.\books\0309069351\html\ 325.html.)

As McNeil's GRAS notification concludes, well-controlled, randomized, double-blinded clinical trials of up to 1 year in duration have shown that ingestion of stanol esters does not affect vitamin A status. Many trials have also demonstrated that the effects of stanol esters on plasma levels of carotenoids are variable, similar to effects seen with other foods, and not associated with effects on vitamin A. In addition, carotenoid levels observed are likely to be within the range of normal variation attributable to diet.

More recent studies support these observations. For example, a 1 year study by Brink and Hendriks with 1.6 g/day soysterols administered as a sterol ester spread showed no effects on serum vitamin A levels.[12] Further, Plat et al. investigated the effect of sterol or stanol esters on plasma carotenoid levels in a recently published study.[13] The investigators standardized the results by expressing the absolute changes in carotenoids relative to calculated values of LDL cholesterol. These authors found that decreases in plasma carotenoids plateaued when doses of sterol or stanol reached 2.2 g daily. They also pointed out that despite decreasing significantly, LDL-standardized concentrations of carotenoids always remained within the normal range.

A recent 8-week study by Davidson et al. found no significant physiological effect on serum beta-carotene levels from administration of sterol esters.[14] In this study, subjects received reduced-fat spread and salad dressing providing 0.0 g/day (n=21), 3.0 g/day (n=21), 6.0 g/day (n=19), or 9.0 g/day (n=23) sterol esters. The investigators reported that blood concentrations of all fat-soluble vitamins remained within normal reference ranges, and that there were no differences in serum vitamin responses among the four groups. Alpha- and beta-carotene levels were significantly reduced in the 9.0 g/day group compared to control ($p<0.05$), but all carotenoid values remained within normal ranges throughout the study, even at the high dose.

[NOTE: In Davidson et al., the investigators reported that there were no significant differences among any of the groups in serum levels of total cholesterol or LDL cholesterol. These results raise an important point about the relevance of a single study when considering the totality of available evidence. In the preamble to the Interim Final Rule, the FDA relied on a single study (FDA Ref. 58) to justify the Agency's decision not to grant a qualifying intake level of stanol esters below 3.4 g/day. (See 65 Fed. Reg. at 54704.) In that Unilever-sponsored study, the investigators found a significant effect on LDL cholesterol, but not on total cholesterol at a reported intake level of 3.31 g/day stanol esters. If the Agency were to adopt a similar approach

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[12] Brink EJ and Hendriks HFJ. Long-term follow-up study on the use of a spread enriched with plant sterols. TNO Report V 99.869. March 2, 2000. (Copies of reports are not appended.) Summarized in: Hendriks HFJ, Ntanios FY, Brink EJ, Princen HMG, Buytenhek R, Meijer GW. One year follow-up study on the use of a low fat spread enriched with plant sterol-esters. Ann Nutr Metab 2001; 45(suppl 1): 100 (abstract 2.01.015).

[13] Plat J, Kerckhoffs DAJM, Mensink RP. Therapeutic potential of plant sterols and stanols. *Curr Opin Lipidol* 2000; 11: 571-575. See **Attachment D**.

[14] Davidson et al. Safety and tolerability of esterified phytosterols administered in reduced-fat spread and salad dressing to healthy adult men and women. J Amer Coll Nutr 2001; 20(4): 307-19. See **Attachment E**.

when considering the qualifying intake level for sterol esters, the Agency would be compelled to conclude that the Davidson et al. study precludes recognition of any qualifying intake level for sterol esters. While Raisio does not now advocate that sterol esters be excluded from the health claim rule, the Company urges the FDA to reevaluate the weight it attributes to any single study when determining the qualifying intake level of stanol esters. As set forth in Section III.A, the totality of scientific evidence demonstrates that 1.4 g/day stanol esters is expected to result in significant reductions in total cholesterol, LDL cholesterol, and Apo B, and therefore, should be the qualifying intake level in the Final Rule.]

It is also important to note that many diet-related factors can affect the bioavailability of β-carotene. For example, certain types of dietary fiber, such as pectin, guar, and alginate, have been shown to reduce the bioavailability of carotenoids.[15] Further, cholesterol-lowering medications such as bile sequestrants[16] and statins[17] have been shown to reduce both serum absolute and lipid standardized serum levels of beta-carotene. Most important, the clinical relevance of any variance in beta-carotene levels is unknown, since it cannot be demonstrated that this precursor pool has any significant beneficial health effect other than as a retinol precursor.

Thus, based on currently available scientific data, there is no valid scientific basis for requiring the labels for stanol ester-containing products to bear a statement concerning the effect of the product on beta-carotene levels or vitamin A status.

2. Consumption of Stanol Esters by Individuals Using Cholesterol-Lowering Drugs has never been Associated with Adverse Events.

The FDA notice indicates that ANZFSC recently adopted a standard requiring sterol ester-containing products to bear an advisory statement recommending that people using cholesterol-reducing medication seek medical advice before using such products. While Raisio believes that

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[15] IARC (1998) International Agency for Research on Cancer Handbooks of Cancer Prevention. Vol 2, Carotenoids. IARC; Lyon, France. Copy of report is not appended.

[16] Probstfield JL, Tsai-Lien Lin, Peters J, Hunninghake DB. Carotenoids and Vitamin A: The effect of hypocholesterolaemic agents on serum levels. *Metabolism*: 1985; 34: 88- 91. See **Attachment F**.

[17] Yoshida H, Ishikawa T, Ayaori M, Shige H, Hosoai H et al. Effect of low-dose simvastatin on cholesterol levels, oxidative susceptibility and antioxidant levels of low-density lipoproteins in patients with hypercholesterolaemia: a pilot study. *Clinical Therapeutics* 1995; 17: 379- 389. See **Attachment G**.

seeking such advice may be prudent, there is no valid scientific basis for requiring such a label statement on stanol ester-containing products.

As explained in McNeil's GRAS notification for stanol esters (and consistent with information available to date), there have been no reported drug interactions with stanol ester-containing products. Published and unpublished studies have evaluated the potential for interactions of stanol esters with concomitant medications. In these studies, there have been no reported adverse events related to a drug-stanol ester interaction. The known pharmacology of stanol esters supports this observation. Stanol ester consumption is not expected to affect the absorption of drugs because the mechanisms by which drugs and cholesterol are absorbed differ, and because stanols demonstrate a specific interference with cholesterol absorption rather than a nonspecific interference with intestinal absorption. A number of studies have evaluated subjects receiving cholesterol-lowering drugs, including neomycin, pravastatin, and simvastatin. Although the primary purpose of these studies was to determine whether the cholesterol-lowering effects of stanol esters and statins are additive (they appear to be at least complementary, if not additive), there were no reported adverse events related to a drug-stanol ester interaction.

Thus, again, Raisio does not believe that there is a valid scientific basis for a special label statement recommending that individuals taking cholesterol-lowering medication consult their physicians prior to consuming stanol ester-containing products. Notably, the health claims for dietary fiber and CHD (21 C.F.R. § 101.81) and for soy protein and CHD (21 C.F.R. § 101.81) do not contain such a labeling requirement despite the effects of fiber and soy protein on serum cholesterol levels.

3. Because Stanol Esters are not Absorbed, Patients Suffering from Sitosterolemia may Safely Consume Stanol Esters.

The FDA notice also notes that the AHA has raised a concern about the consumption of sterol/stanol ester-containing products by individuals with sitosterolemia, a disease characterized by unusually high intestinal absorption of sterols. As described in detail in the McNeil GRAS notification, stanol esters are virtually unabsorbed. Thus, sitosterolemic individuals should not be adversely affected by consumption of stanol esters. Sterols, and particularly campesterol, are absorbed to a greater extent than stanols; therefore, Raisio would agree that sitosterolemics would be well-advised not to consume sterol-containing products.

Raisio firmly believes that there is no valid scientific basis for requiring additional label statements on stanol ester-containing products. However, if the Agency determines that additional labeling statements may be required, Raisio agrees with the FDA's proposal that such requirements be initiated via a separate rulemaking in order to enable the full and fair vetting of the issue. In order to remain consistent with legal, scientific, and public policy principles, any

such rulemaking would evaluate all food ingredients -- not just sterol/stanol esters -- that may have the subject effect upon which the rulemaking is based.

IV. SUMMARY AND CONCLUSIONS

For the reasons discussed above, Raisio believes that no scientific or legal justification exists for considering a health claim for free sterols/stanols (or for mixtures of free or esterified sterols and stanols ("mixtures")) in the instant rulemaking for sterol/stanol esters. Including free sterols/ stanols or mixtures in this proceeding would be arbitrary and capricious in that it would deprive interested parties of adequate notice of and an opportunity to comment on the data in support of such a health claim. Further, the data submitted in support of such a health claim for free sterols/stanols are inadequate because only one study meeting FDA's criteria indicates efficacy of free sterols in lowering both serum total and LDL cholesterol, and no studies support the efficacy of free stanols. The data base for mixtures is virtually nonexistent; thus no valid conclusions can be drawn about their efficacy.

A daily intake level of 1.4 g/day stanol esters (0.8 g/day stanols) is justified by the totality of publicly available scientific data, as discussed above and in Attachment A. The mathematical model applied by Raisio demonstrates that one can be 95% certain that such a dose will produce a significant reduction in total and LDL cholesterol. That prediction, taken from the model, is supported by the results of two studies (FDA Refs. 63 and 94) with respect to total and LDL cholesterol reduction. The model's prediction is also supported by the findings in FDA Ref. 88 with respect to the reduction in Apo B. And, as discussed above and in Attachment C, Apo B is an appropriate and validated predictor of CHD risk. Indeed, Apo B is one of the two primary endpoints required by FDA's CDER in any evaluation of lipid-lowering drugs. Raisio believes that CFSAN should also accept Apo B as an appropriate predictor of CHD risk in its evaluation of the scientific literature on low-dose efficacy of stanol esters. Raisio further urges FDA to make its conversion factor for sterol/stanol esters consistent at 1.4 g/day ester = 0.8 g/day free sterol/stanol.

FDA also asked for comments on the need for changes to the health claim regulation, advisory labeling, or other modifications because of potential implications of plasma beta-carotene reductions and sitosterolemia. Raisio urges FDA to reject any additional labeling for stanol esters because there is no scientific justification for any statements. Numerous studies have shown no reduction in Vitamin A levels, even in the face of reductions in beta-carotene. Further, even with reductions in beta-carotene, plasma levels of beta-carotene remained within normal ranges. The condition called sitosterolemia, which is characterized by the unusually high absorption of plant sterols, is not an issue with stanol esters. Unlike sterols, stanols are not absorbed, so there is no danger of stanol accumulation in the body.

V. ACTION REQUESTED

Raisio requests FDA to reconsider its proposed qualifying daily intake level of stanol esters of 3.4 g/day ((2.0 g/day stanol) set forth in the Interim Final Rule. Raisio believes that FDA should accept the same level for stanol esters as that proposed for sterol esters, that is, 1.4 g/day stanol ester (0.8 g/day stanol). In addition, for the reasons discussed above, Raisio requests the agency not to include free sterols/ stanols or mixtures in the instant rulemaking. Finally, Raisio sees no scientific justification for imposing any new labeling requirements on stanol ester products.

Very truly yours,

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