Docket Nos. 00P-1275 and 00P-1276
Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease; Interim Final Rule

SUBMISSION OF COMMENT AND REQUEST FOR EXTENSION OF COMMENT PERIOD

Submitted on behalf of
Raisio Benecol Ltd.

May 11, 2001

00P-1275

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

SUBMISSION OF COMMENT AND REQUEST FOR EXTENSION OF COMMENT PERIOD

Dear Madam/Sir:

On November 21, 2000, Arent Fox submitted comments to the above-referenced dockets on behalf of Raisio Benecol Ltd., Raisio, Finland ("Raisio"). As announced in the Interim Final Rule, the deadline for submitting comments was November 22, 2000. On February 27, 2001, Unilever United States, Inc. filed comments on behalf of its subsidiary Lipton. In that submission, Lipton (1) responded to a number of issues raised in Raisio's comments, and (2) requested an extension of the comment period so that the FDA would consider its new submission.

In order to ensure the full and fair consideration of the issues raised in the Interim Final Rule, Raisio's comments, and the recent Lipton submission, Arent Fox is submitting, on behalf of Raisio, a brief response to some of the points raised by and in Lipton's submission. Raisio shares Lipton's stated goal of ensuring a balanced consideration of the studies relied upon by the Agency in the Interim Final Rule.

Because Lipton's submission was made after the deadline for comments in this rulemaking, Raisio was not able to respond by that deadline. Accordingly, pursuant to 21 C.F.R. §§ 10.35 and 10.40, Raisio requests an extension to the comment period so that the Agency may consider the issues raised herein.

I. INTRODUCTION

Raisio included in its comments on the Interim Final Rule a discussion of the studies by Jones et al. (2000)[1] and Weststrate and Meijer (1998)[2]. Raisio discussed Jones et al. to demonstrate that the non-significant results reported in the study for plant stanol esters (hereinafter "stanol esters") were anomalous and inconsistent with the larger body of scientific literature concerning the cholesterol-lowering effects of stanol/sterol esters. Because the FDA relied upon the Jones et al. study to disregard the cholesterol-lowering effects reported in Hallikainen et al. (2000a)[3] for lower doses of stanol esters -- and therefore reject a lower qualifying level of stanol esters for the health claim -- Raisio believed it was necessary to put the Jones et al. results in proper perspective. **Section II** below includes an analysis and graphs of all relevant, available data on the cholesterol-lowering effects of stanol esters. Those data indicate that (1) low doses of stanol esters significantly reduce total and LDL cholesterol levels, and (2) the non-significant results for stanol esters reported by Jones et al. are inconsistent with the larger body of data.

In its comments, Raisio also identified a number of issues concerning study design and reporting in Jones et al. and Weststrate and Meijer. When considered together, these issues suggest that the FDA should not place undue weight on the studies' results. In its submission, Lipton responded to a number of these issues, yet did not dispute that the non-significant results reported in the Jones et al. study are inconsistent with the results reported in other studies. Raisio continues to believe that the Weststrate and Meijer study, and especially the Jones et al. study, should not be relied upon by the FDA.

Although Raisio and Lipton may disagree as to whether stanols are more effective than sterols in reducing total and LDL cholesterol levels, the companies agree that both compounds are effective. This conclusion was also reached by Peter Jones, the first author in Jones et al., in the January 2001 issue of *Nutrition Reviews*. Dr. Jones notes in a paper in this journal that "most recent findings support the position that all current phytosterol mixtures are more or less equivalent in their cholesterol-lowering ability." Jones, P.J., and M. Raeini-Sarjaz, "Plant Sterols and Their Derivatives: The Current Spread of Results," *Nutr. Rev.*, Vol. 59, No. 1, pp. 21-24, 2001. (See Attachment A)

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[1] Reference 58 in the Interim Final Rule.

[2] Reference 67 in the Interim Final Rule.

[3] Reference 88 in the Interim Final Rule.

II. ANALYSIS OF DATA ON CHOLESTEROL-LOWERING EFFECT OF STANOL ESTERS

Raisio has analyzed all available data bearing on the relationship of stanol ester intake to total and LDL cholesterol levels. This analysis involved the data base considered by the FDA in the Interim Final Rule, as well as (i) two additional published papers meeting the FDA's inclusion criteria (Plat et al., 2000, *Eur. J. Clin. Nutr.*, see Attachment B; Hallikainen et al., 2000b, *Eur. J. Clin. Nutr.*, see Attachment C); (ii) one paper that has been submitted for publication (Mensink et al.; data provided to the FDA in Attachment D to Raisio's November 21, 2000 comments); (iii) one unpublished study submitted in the health claim petition for stanol esters (Grundy and Cater); and (iv) unpublished data from Hallikainen et al. (2000a; data provided to the FDA in Attachment B to Raisio's November 21, 2000 comments).

Raisio has summarized these data in a set of graphs which plot percentage reduction in cholesterol levels against daily intake of stanol esters. (See Graphs 1 - 7, with accompanying Appendix and Table; see Attachment D) For each study, all reported data points (i.e., measuring or time points) are presented, not just end-of-treatment data points. Further, to ensure consistency in calculations between studies, data were taken directly from figures and tables in the papers wherever possible. The Appendix includes a detailed description of how the graphs were prepared. The Table identifies the studies and data points included in the analysis.

For approximately 60 data points, there were consistent reductions in total and LDL cholesterol levels for daily intakes of 1.3 - 6.8 g stanol esters. Graphs 1 and 2 present the data points for total cholesterol and LDL cholesterol reductions, respectively, with no superimposed dose-response curve. As explained below, Graphs 3 - 7 include the same data points as Graphs 1 and 2, but Raisio has fitted the results with curves to depict the dose-response relationship, which Raisio believes to be curvilinear.

The postulated mechanisms of action of stanol esters on cholesterol absorption are (a) the displacement of cholesterol from intestinal micelles, (b) inhibition of acyl coenzyme A acyltransferase (ACAT), and (c) competition for the putative cholesterol transport protein in the enterocyte. Given these mechanisms, the best description of the relationship between daily stanol ester intake and cholesterol reduction is a curvilinear one. This conclusion is supported by (1) the fact that there can be no effect at an intake of 0 g/day and thus a best-fit curve must pass through the origin of the graph, and, (2) the fact that

because stanol esters block the absorption of cholesterol, the effect would be expected to plateau at some level of intake due to saturation.

A linear least-squares fit of the data (giving equal weight to each investigation, as described in the Appendix) supports this curvilinear dose-response relationship. A linear least-squares fit gives both slopes and y-intercept values significantly different from zero for both measured parameters. (See Graphs 3 and 4.) The slope for total cholesterol is 0.70 ± 0.09 (mean ± SEM) and for LDL cholesterol is 1.24 ± 0.14. Slopes that are greater than zero indicate that there is a dose-response relationship between the decreases in total cholesterol and LDL cholesterol, and stanol ester intake.

The y-intercept value for total cholesterol is 5.40 ± 0.39 and for LDL cholesterol is 6.07 ± 0.61. A linear fit with a y-intercept value of anything other than zero indicates that the relationship between the decrease in total cholesterol or LDL cholesterol and the stanol ester intake cannot be described by a straight line because that straight line would not pass through the origin.

Also, the distribution of the data suggests that the response may be approaching a plateau at higher doses. Together, these observations indicate a curvilinear relationship between dose and response. Without additional information regarding the nature of the dose-response relationship, Raisio has fitted the results with a 2nd order polynomial (the next simplest solution to a straight line), to indicate such a curvilinear relationship between the cholesterol decrease and stanol ester intake. (See Graphs 5 and 6) However, Raisio has found that a 3rd order polynomial (See Graph 7) provides a better representation of the plateau effect for total cholesterol, and more closely parallels the 2nd order curve for LDL-cholesterol.

Raisio believes that these data indicate statistically significant cholesterol-lowering effects at the lowest dose administered, 1.3 g/day stanol esters,[4] and the graphs clearly illustrate those effects. Data from Miettinen and Vanhanen (1994)[5] and unpublished data from

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[4] As discussed in Raisio's November 21, 2000 comments, the quantity of stanol esters depends on the conversion factor applied to the quantity of stanols. If FDA applies a conversion factor of 1.7 to the 0.8 g dose of stanols (the lowest dose tested), the minimum daily intake of stanol esters would be 1.4 g. If FDA applies a conversion factor of 1.6, the minimum daily intake of stanol esters would be 1.3 g.

[5] Reference 63 in the Interim Final Rule.

Hallikainen et al. (2000a)[6] report statistically significant reductions in total and LDL cholesterol at this level of intake. One of the three data points for the 1.3 g/day dose of stanol esters was not statistically significant in reducing total or LDL cholesterol levels (Hallikainen et al., 2000a); levels measured at 4 weeks). As described in Raisio's November 21, 2000 comments, however, the non-significant data points at 4 weeks likely were due to an unanticipated disruption in the subjects' dietary patterns and alcohol intake at 4 weeks in the control period. As noted above, unpublished 2-week data provided by the authors of this study do indeed demonstrate a significant reduction in both parameters at this low dose level, even at this earlier time point.

The graphs also demonstrate that the non-significant results for stanol esters reported in Jones et al. are inconsistent with the results reported in other studies at similar intake levels. The following studies reported statistically significant reductions at similar intake levels (2.7 - 3.3 g/day): Hallikainen et al., 2000a and 2000b; Miettinen et al., 1994; Andersson et al., 1999; Nguyen et al., 1999. Because the Jones et al. study included only 15 subjects, the lack of statistical significance for many of the stanol ester data points very likely results from a Type II error; that is, a false negative result. Although the paper does not provide a value for the $SE_{difference}$, if we assume, based on the data in the study, that the value is 2.0, the study has a power of only approximately 60% to detect the observed difference with a p value of less than 0.05. In other words, the likelihood of a false negative result in the Jones et al. study is 40%.

As noted in Raisio's earlier comments, because the results reported by Jones et al. are inconsistent in a number of respects with the larger body of scientific evidence, Raisio maintains that the results from the Jones et al. study should not be given undue weight in the evaluation of the daily qualifying level of stanol esters required for the health claim.

In short, the totality of the data indicates that daily intake of stanol esters at levels of 1.3 or 1.4 g/day[7] should be expected to reduce total and LDL cholesterol levels significantly.

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[6] Hallikainen et al. (2000a) is Reference 88 in the Interim Final Rule. As noted above, the unpublished 2-week data from this study were submitted in Attachment B to Raisio's November 21, 2000 comments.

[7] See footnote 4.

NOTE: As can be seen in the graphs, the majority of studies on stanols have been conducted at levels of 3-5 g/day stanol esters. It is important to understand the dose selection in the context of the study goals and study designs. Raisio did not design studies to find the lowest dose that would produce a statistically significant reduction in cholesterol. Such studies certainly can be published in the clinical literature, and the information would be useful. However, giving a lower daily dose of stanol esters would necessarily result in a reduced cholesterol-lowering effect, a result Raisio deemed much less desirable clinically.

Raisio's intent in developing the body of data on stanol esters was to ascertain the "optimum intake level," that is, the minimum stanol ester dose that would produce near-maximal cholesterol-lowering effect. The first step in Raisio's approach was to determine a low dose that would produce a significant reduction. Raisio believed that 1.3 g/day of fat-soluble stanol ester would deliver such a significant reduction. The 1994 Miettinen and Vanhanen mayonnaise study accomplished that and demonstrated a statistically significant reduction at 1.3 g/day. Next, Raisio determined the stanol ester doses that would yield the greatest reduction in cholesterol levels. In scientific terms, this is equivalent to determining the dose producing maximal inhibition. A number of studies demonstrate that the maximal cholesterol-lowering effect occurs at doses of about 5 g/day stanol esters (3 g/day stanols).

The third and final step was to determine the optimum dose, the lowest dose that produced a near maximal reduction of cholesterol, and that could be administered in two servings daily to facilitate compliance. In scientific terms, this is equivalent to determining the dose on a dose-response curve where near-maximal effect has been achieved, or where the dose-response curve first begins to flatten. As with the maximum dose, a number of studies demonstrate that the optimum cholesterol-lowering effects occur at doses of about 3 g/day stanol esters (2 g/day stanols).

Raisio purposefully chose not to determine the value for the lowest daily dose that would still produce a statistically significant reduction in serum cholesterol, because Raisio believed that such a dose would not be as clinically significant or beneficial to those suffering from elevated levels of serum cholesterol. Further, Raisio believed the cholesterol reductions had to be substantial enough to gain the support of physicians and dieticians. This development process and approach explains why so few studies have been conducted at low levels of intake. Despite this, the few studies that have been conducted at low levels of daily intake confirm the significant cholesterol-lowering effects of stanol esters even at these low doses.

III. CONCLUSION: ACTION REQUESTED

For all of the reasons set forth in this document and its November 21, 2000 comments, Raisio respectfully requests that the Agency reconsider its proposed qualifying level of stanol esters required for a health claim for reduced risk of coronary heart disease. Specifically, Raisio requests that the Agency approve a health claim for stanol esters at a daily level of 1.3 or 1.4 g.[8]

Very truly yours,

Marsha C. Wertzberger
Counsel to Raisio Benecol Ltd.

[8] See footnote 4 for explanation of minimum intake of stanol esters.