Unilever

5515 '01 FEB 28 A9:30

February 27, 2001

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

Re: Docket Nos. 00P-1275 and 00P-1276
Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease (Interim Final Rule)
65 Fed. Reg. 54686 (September 8, 2000)

SUBMISSION OF COMMENT, AND REQUEST FOR EXTENSION OF COMMENT PERIOD

To Whom It May Concern:

On November 21, 2000, comments were submitted to the above-referenced dockets by counsel for Raisio Benecol Ltd. ("Raisio"). Those comments included criticism of two of the studies relied on by FDA in reaching its decision on the health claims covered by the interim final rule. In support of these studies, we would like to respond briefly to this criticism.

Because Raisio's comments were received by FDA on the deadline for comments in this rulemaking, we were unable to submit this response by that deadline (which was November 22, 2000). Pursuant to 21 CFR 10.40, we therefore request an extension of the comment period for a period of time sufficient to consider the following information, which is important to a balanced consideration of the studies in question.

RESPONSE TO COMMENTS BY RAISIO

Raisio's comments dated November 21, 2000, discuss the Jones et al. Study (2000) (Ref. 58) and the Weststrate and Meijer study (1998) (Ref. 67). Raisio alleges that these studies are "flawed" for various reasons. In the paragraphs below, we summarize Raisio's allegations and provide our responses:

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I. Jones et al., 2000.

1. **Raisio's Allegation:** Different amounts of sterols and stanols were tested, and small changes in daily intake could yield substantial differences in total and LDL-cholesterol reduction.

   Lipton's Response: From the study report it can be seen that the subjects consumed 1.76 g stanols per day as compared with 1.93 g sterols per day, and that sterols lowered total and LDL-cholesterol (Table 2) more (-0.90 and -0.63 mM, respectively) than the stanols (-0.66 and -0.40 mM, respectively). If we assume a linear intake-response relationship on the very small interval between 1.76-1.93 g stanols and sterols per day, and express the change in total and LDL-cholesterol as a function of the daily sterol/stanol intake, then sterols lowered total and LDL-cholesterol by about 0.47 mM/g and 0.33 mM/g, respectively, and stanols by about 0.38 mM/g and 0.23 mM/g, respectively. This analysis supports a conclusion that "plant sterol and stanol esters differentially lower circulating total and LDL-cholesterol levels...", as the study report states. Thus, the study is not "skewed," as Raisio alleges; rather, it permits an unbiased evaluation of the relative effectiveness of the two compounds.

2. **Raisio's Allegation:** The subjects may not have been representative of hypercholesterolemic subjects with serum total cholesterol levels at or below 300 mg/dl, and therefore not appropriately representative of the U.S. population.

   Lipton's Response: In fact, the study report contains adequate data to indicate that the subjects constituted an appropriately representative sample. For example, the plasma lipid levels at "day 0" as given in Table 2 of the study can be considered as repeated measurements of the screening values. From these, it can be seen that the mean initial total cholesterol level was generally below 6.5 mM or 250 mg/dl. Moreover, it is reported that during the three phases of the trial urinalysis results were obtained for all subjects, which remained within normal ranges. Thus, contrary to Raisio's suggestion, it is unlikely that any of the subjects had severe lipidemias or occult diabetes.

3. **Raisio's Allegation:** The cholesterol-lowering effects of daily stanol ester ingestion occurred much more slowly than those reported by other investigators.

   Lipton's Response: There will always be variations between clinical trials performed with different subjects and investigators, and under different conditions. This study is generally consistent with other studies in that both stanol esters and sterol esters lowered blood total and LDL cholesterol, although the effect was not statistically significant until after 15 days. Raisio's allegation therefore does not provide a sound scientific basis for disregarding the results of this study.

4. **Raisio's Allegation:** The study used very few subjects.

Lipton's Response: The study report accurately indicates that 18 subjects were recruited, of which 15 were included in the final analysis. A dropout rate of 17% for a controlled-feeding study is certainly not exceptional. The study was executed as a complete crossover design and apparently provided enough statistical power to detect a greater LDL-cholesterol-lowering effect of plant sterol esters as compared with stanol esters. Accordingly, the data are valid and must be considered.

5. **Raisio's Allegation:** Table 2 does not show all the data that are shown in Figures 2 and 3.

Lipton's Response: The authors of this paper have chosen to present the data partly in tables and partly in figures, with a certain degree of overlap. However, we are aware of no measured data having been left out of either the tables or figures. Thus, again, Raisio's allegation does not provide a sound scientific basis for disregarding the results of the study.

II. Weststrate and Meijer, 1998.

1. **Raisio's Allegation:** The study favored sterols because sterol intake was 19% higher than stanol intake.

Lipton's Response: The published report of the study states that the subjects consumed 2.74 g stanols per day as compared with 3.25 g sterols per day, and that sterols lowered LDL-cholesterol (Table 2) more (-0.44 mM) than the stanols (-0.40 mM). If we assume a linear intake-response relationship on the small interval between 2.74-3.25 g stanols and sterols per day, and express the change in LDL-cholesterol as a function of the daily sterol/stanol intake, then sterols lowered LDL-cholesterol by about 0.14 mM/g and stanols by about 0.15 mM/g. This analysis supports a conclusion that "[a] margarine with sterol-esters ... is as effective as a margarine with sitostanol-ester," as the study report states. Thus, the study is not "skewed," as Raisio alleges; rather, it permits an unbiased evaluation of the relative effectiveness of the two compounds.

2. **Raisio's Allegation:** The sterol-ester margarine had a lower saturated and monounsaturated fatty acid content, and a higher polyunsaturated fatty acid content, than the stanol-ester margarine, and this could have accounted for at least 2% of the percentage reduction in serum cholesterol in the sterol group.

Lipton's Response: The published report of the study, at page 341, explains that the maximum effect on LDL-cholesterol levels of the small difference in fatty acid profiles between the two test margarines was about 0.05 mM. Even if the difference in fatty acid composition did contribute maximally to the LDL-

cholesterol lowering effect of the products (i.e., about 1.5%), the products would still not differ statistically significantly.

3. **Raisio's Allegation:** The sterol-ester product tested is different than the commercially marketed product.

   Lipton's Response: The sterol-ester product as well as the stanol-ester product tested in the study contained higher levels of esters than the products currently available on the market. However, in this study (10% sterols or stanols), as well as in subsequent studies (8% sterols or stanols in Jones et al., 2000, Ref. 58; 1.5 g/day plant sterols or stanols in Normén et al.[1], 2000; and 10% sterols or stanols in Hallikainen et al.[2], 2000) it has been consistently demonstrated that plant sterol esters are at least as effective as stanol esters in reducing intestinal cholesterol absorption and consequently blood cholesterol levels.

4. **Raisio's Allegation:** Vitamin E levels were higher in the sterol-ester test product than in the stanol-ester product, possibly confounding the results.

   Lipton's Response: The sterol-ester products are superior to the stanol-ester products in terms of vitamin E content. However, since the effect, if any, of vitamin E on cholesterol reduction is unknown, there is no basis for believing this difference to be a meaningful confounding factor.

In its comments Raisio refers to "a recent, well-designed study by Hallikainen et al. (2000a)" in which, using test products that contain higher levels of sterols or stanols than the commercial products, "[a]fter four weeks with a daily intake of 2.0 g sterol or stanol esters, reductions in serum total and LDL cholesterol were 9.2% and 12.7%, respectively, with the stanol ester spread, and 7.3% and 10.4%, respectively, with the sterol ester spread, compared with control." Raisio does not mention, however, that the authors of this study found that "The cholesterol-lowering effects of the test margarines did not differ [statistically] significantly." Moreover the conclusion of the paper by Hallikainen et al. was that "Stanol ester and sterol ester-enriched margarines reduced significantly and equally serum total and LDL cholesterol concentrations ...." Consequently, Raisio's conclusion that "These results provide conclusive evidence that when comparable products are used in efficacy trials, stanol ester spreads appear to be, if anything, more effective than the same weight of sterol ester spreads" is not consistent with the available data and should be disregarded.

In conclusion, Raisio has not provided a sound scientific basis for diminishing the importance of the Jones et al. and Weststrate and Meijer studies as support for the health claims covered by the interim final rule. We therefore request that the FDA continue to rely on these studies, together with all of the other available data, as support for these claims.

Thank you for your consideration of these comments.

Respectfully submitted,

Nancy L. Schnell
Deputy General Counsel –
Marketing and Regulatory

References:

1. Normen L., Dutta P., Lia A. and Andersson H. (2000). Soy sterol esters and beta-sitostanol ester as inhibitors of cholesterol absorption in human small bowel. American Journal of Clinical Nutrition, 71, 908-13.
2. Hallikainen M.A., Sarkkinen E.S., Gylling H., Erikkila A.T. and Uusitupa M.I.J. (2000). 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, European Journal of Clinical Nutrition, 54, 715-725.

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