McNeil
Nutritionals

2756 '01 NOV 19 P1:58

November 19, 2001

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

Re: Dockets 00P-1275 and 00P-1276
Health Claims: Plant Sterol/Stanol Esters and Coronary Heart Disease

Dear Sir or Madam:

Reference is made to the October 5, 2001, *Federal Register* notice announcing the reopening of the comment period on FDA's Interim Final Rule authorizing a health claim on the association between plant sterol/stanol esters and reduced risk of coronary heart disease.

McNeil Nutritionals (formerly McNeil Consumer Healthcare), one of the health claim petitioners, submits the enclosed comments, in duplicate, in response to FDA's request for additional input on various aspects of the interim health claim regulation.

Sincerely,

Richard R. Reo

Richard R. Reo
Director, Regulatory Affairs

Enclosures

00P-1275

C18

McNeil Nutritionals Division of McNeil - PPC, Inc. 501 George Street PO Box 2400 New Brunswick, NJ 08903-2400
Tel 732-524-1900 Fax 732-247-7482

Plant Sterol and Stanol Esters and Coronary Heart Disease Docket Nos. 00P-1275 and 00P-1276 Reopening of Comment Period

Introduction

McNeil Nutritionals (formerly McNeil Consumer Healthcare) is one of the petitioners cited in the September *8, 2000 Federal Register* Interim Final Rule for health claims concerning plant sterol/stanol esters and coronary heart disease (CHD) (Docket No. 00P-1276).

As FDA has stated in previous health claim regulations (21 CFR §101.75, §101.77, §101.81 and §101.82), CHD remains a major health problem and, with over 500,000 victims a year, the number one cause of death in the United States. FDA also provides the figures that one in five American adults, between the ages of 20 and 74, are at high risk, based on their total blood cholesterol levels. An additional 31 percent of adults have "borderline" total blood cholesterol levels, along with other risk factors. This equates to 51 percent of the adult population in the United States being at risk for developing CHD or related illnesses.

Based on its review of the scientific literature, FDA has concluded that foods and dietary supplements containing plant stanol esters may assist consumers in reducing their risk of CHD by lowering serum cholesterol levels. To fulfill the inherent public health benefit of the rule, McNeil wishes to reiterate the importance of the six points excerpted below from our November 17, 2000, comments on the interim final rule (Appendix A). The first of these points has been slightly revised to reflect our current view on daily intake levels for sterol and stanol esters and to be consistent with our comments in response to the specific questions posed in the October 5, 2001, *Federal Register* notice, which follow:

Points from McNeil's November 17, 2000, Comments on the Interim Rule:

1. The available data demonstrate the equivalent cholesterol-lowering effect of dietary plant stanol esters and plant sterol esters. McNeil urges FDA to adopt common daily intake levels for sterol and stanol esters at a "minimum effective" level equivalent to 1.4 g/day. We also request that the agency permit foods to bear a statement indicating that 3.4 g/day of sterol or stanol esters provide a "more highly effective" level.

2. McNeil urges that the foods eligible to bear the health claim be expanded beyond spreads, salad dressings and snack bars to encourage consumer use through a broader array of options. As with points 3 through 5 below, such a

provision will provide consumers with greater choices and product diversity to more easily realize the cholesterol-lowering capability of plant stanol esters.

3. McNeil is requesting a broader exception from the minimum nutrient contribution for foods allowed to bear the health claim based on their stanol esters content (21 CFR §101.14(e)(6)]. Such an exception will benefit consumers by encouraging development of a greater number of food forms containing stanol esters. This will facilitate consumers' ability to attain a stanol ester intake that will provide a cholesterol lowering health benefit.

4. While the Interim Final Rule excepts spreads and dressings for salad from the disqualifying level for total fat per 50g of food, the exception should be extended to include all foods with a serving size of two tablespoons or less, or 30g or less.

5. McNeil supports FDA's target of two servings of plant stanol ester-containing foods taken at different times during the day.

6. We agree with the inclusion of the plant stanol ester-containing dietary supplement as a product approved to bear the health claim.

In response to the October 5, 2001, *Federal Register* notice reopening the comment period for Docket Nos. 00P-1275 and 00P-1276, the following summarizes our attached detailed comments related to the five areas of interest specified by FDA:

A. Eligibility of Unesterified Plant Sterols/Stanols for the Health Claim

The available data on the efficacy of free sterols and stanols is simply not compelling when compared with the much greater volume of conclusive information for the ester forms of these ingredients. Additionally, free sterols and stanols are less well characterized than their esterified counterparts. We believe that FDA should separately consider the eligibility of free sterols and stanols, and mixtures thereof, only after full petitions for these substances have been submitted. Moreover, a final health claim regulation for the esterified forms of these ingredients should not be further delayed while FDA considers free sterols and stanols and mixtures thereof.

B. Daily Intake Levels Necessary to Reduce the Risk of CHD

The data currently available to FDA support the establishment of common intake levels for plant sterol and stanol esters. In this regard, the data show that a common intake regimen of 1.4 g/day of stanol or sterol esters is sufficient to provide a significant decrease in LDL cholesterol as a "minimum effective" intake level. The data also support our view and the recommendations of the National Cholesterol Education Program (NCEP) and others that 2.0 g/day of free sterol

or stanol (3.4 g/day of the ester) provide a "more highly effective" level. Accordingly, we believe that FDA should permit statements on the labeling of stanol and sterol ester foods indicating that 3.4 g/day of stanol or sterol ester provides a "more highly effective" level of intake. Moreover, by establishing common intake levels for sterol and stanol esters, FDA would eliminate the inadvertent and erroneous perception that stanol esters are less potent and efficacious than sterol esters.

C. Eligibility of Mixtures of Plant Sterols/Stanols for the Health Claim

We do not believe that the final regulation should permit mixtures of plant sterols and stanols, whether esterified or unesterified. Overall, there is much less data available on the efficacy of mixtures. Moreover we believe that FDA should undertake consideration of mixtures as a separate effort with an eye toward issuance of a separate health claim regulation if the evidence supports this use.

D. Significance of Apolipoprotein B as a Surrogate Marker for CHD Risk

We believe that the existing data support the use of apolipoprotein B as a surrogate marker for the risk of coronary heart disease.

E. Issues Regarding Safe Use of PSEs and Advisory Label Statements

We do not believe that the safe use of plant stanol esters requires that products containing these ingredients bear advisory statements.

There is no compelling evidence to suggest that products containing plant stanol esters pose a safety concern related to their potential effects upon ß-carotene or vitamin A status in any segment of the population, including in pregnant and nursing mothers, or children. Moreover, McNeil sees no need for advisory statements aimed at individuals using cholesterol-lowering drugs. We also note that the incidence of sitosterolemia is extremely rare and that individuals with this condition are subject to ongoing medical care and dietary guidance.

Comments on the Interim Final Rule

A. Eligibility of Unesterified Plant Sterols/Stanols for the Health Claim

McNeil Nutritionals does not believe that unesterified plant sterols and stanols should be eligible for the health claim.

In reopening the comment period, FDA has requested comments on the eligibility of unesterified sterols and stanols for the health claim. These substances were not the subjects of either of the two petitions that were the basis for the Interim Final Health Claim for Plant Stanol/Sterol esters. In its comments, Raisio Benecol Ltd., provides a detailed discussion of the legal reasons why these compounds should not be included in the present health claim rulemaking for sterol/stanol esters. McNeil agrees with those comments and hereby incorporates them by reference in this discussion.

McNeil and Lipton submitted the petitions that led to the Interim Final Rule for plant stanol and sterol esters, respectively. These petitions were supported by a significant number of clinical studies that met the acceptance criteria established by the agency. The agency judged the results of these studies to be sufficiently compelling in demonstrating a reduction in total and low density lipoprotein (LDL) blood serum cholesterol levels to warrant issuing an Interim Final Rule authorizing the health claim on the relationship between stanol/sterol esters and coronary heart disease (CHD). However, in its consideration of available data leading to the Interim Final Rule, the agency evaluated only a few recent studies dealing with unesterified sterols [FDA References #63/64, #65, #74, and #75] *.

Several comments submitted after publication of the interim final rule requested that foods containing unesterified stanols/sterols be allowed to bear the health claim. Largely, these requests were based only on the presumption that, since the active component of stanol/sterol esters responsible for the inhibition of cholesterol absorption was the free sterol/stanol (generated by the hydrolysis of the fatty acid ester bond), foods containing free sterols/stanols would also be

---

* Bracketed [ ] citations to FDA reference numbers correlate directly with "Section XI. References" of the September 8, 2000, *Federal Register* notice, "Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease; Interim Final Rule." Copies of other literature references are contained in Appendix B.

expected to lower cholesterol levels.

Free sterols/stanols must be properly dispersed in a food in a manner that facilitates their ready incorporation into the intestinal micelles if hey are to have a positive effect in inhibiting cholesterol absorption. However, it can not be assumed that free sterols/stanols, when added to foods, will interact with the micelles in the same way as esterified stanols/sterols added to the same foods, or that the will have the same significant effect in inhibiting cholesterol absorption. In addition, equivalence in efficacy with stanol/sterol esters has not been adequately demonstrated in acceptable clinical trials. For example, there are no published studies with actual sterol enriched foods showing that such sterol preparations are effective and stable in different food matrices.

In particular, we note that free sterols and stanols must be dissolved in a product's fat phase in order to be effective. Thus, unlike the esterified forms of these ingredients, the use of free sterols and stanols is restricted to fatty foods. Because the fat content of foods is highly variable, it follows that the efficacy of free sterols and stanols from foods of varying fat content would be inconsistent and would likely result in a highly variable clinical response. Thus, we believe that it is incumbent upon those seeking to include free sterols and stanols in the final rule to provide FDA with a complete petition that demonstrates the efficacy of free sterols and stanols wen incorporated in various food matrices. We also note the difficulty inherent in producing consumer acceptable sterol- and stanol-containing products. However, the information currently available to FDA does not address the likelihood of product-to-product inconsistency in the quantity of free sterol or stanol delivered on a per serving basis, the consumer acceptability of finished formulations, nor the cholesterol lowering efficacy of these food products.

A significant factor, seemingly overlooked by many of those arguing for the inclusion of free sterols and stanols in the final rule, concerns a full characterization of the identity, composition, and specifications for these ingredients. In its GRAS documentation for plant stanol esters (submitted on February 18, 1999), McNeil fully characterized food grade plant stanol esters. As such, the submission included detailed information on the identity, composition, physical properties, caloric value, manufacturing process, raw materials, stability, and potential contaminants of food grade plant stanol esters, as well as a finished product specification. Those interested in the eligibility of free sterols and stanols for a health claim should also develop and provide FDA with a full characterization of their ingredients.

These issues are best resolved through a proper rulemaking process that satisfies all the procedural requirements for authorizing health claims and that focuses specifically on free sterols/stanols. Those who wish to have unesterified stanols/sterols be the basis of a health claim should develop a convincing petition

for consideration by the agency. In the meantime, the original petitioners should not be further penalized by the delays that will undoubtedly occur as a result of this eleventh-hour review of these "piggyback" substances that have not been the basis of a full health claim petition.

To delay completion of the rule making process for sterol and stanol esters is unfair to consumers and to the original petitioners, who were able to compile substantial support in peer reviewed, published studies as the basis for the Interim Final Rule.

In our view, the database currently held by FDA on the efficacy of free sterols and stanols is too limited and the characterization of the substances to scant to support their inclusion in the final health claim at this time. Should FDA attempt to remedy these shortcomings by accepting new data at this late date, it would constitute a significant expansion of the administrative record without the opportunity for notice and comment. Allowing further notice and comment on these new data would needlessly delay the final rule for the ester forms.

Therefore, the final health claim regulation for sterol and stanol esters should not be further delayed. Rather, FDA should separately consider the eligibility of free sterols and stanols and propose a separate health claim regulation, if warranted, after full evaluation of the evidence for their eligibility.

B. Daily Intake Levels Necessary to Reduce the Risk of CHD

By establishing different daily intake levels for plant stanol versus plant sterol esters, the Interim Final Rule inadvertently creates a discrepancy in the perceived efficacy of stanol esters versus sterol esters among professionals and consumers.

McNeil believes that the data available to FDA adequately support an equivalent daily intake level for both ingredients. Moreover, we believe that the available data support and the final rule should establish both a "minimum effective" and a "more highly effective" level for plant stanol and sterol ester-containing foods.

In the Interim Final Rule the agency proposed a daily intake level of 1.3 gm for sterol esters and 3.4 gm for stanol esters as necessary to achieve the cholesterol reductions that can help reduce the risk of CHD.

This determination was based on the agency's review of the available literature for each substance, i.e., stanol esters and sterol esters, as distinct entities. This analysis failed to take into account that the two groups of studies dealt with a somewhat different spectrum of exposure levels. The studies dealing with sterol esters were largely designed to assess lower exposure levels, presumably to establish the "minimal effective" level. The studies dealing with stanol esters, on

the other hand, tended to be designed to establish the "most highly effective" exposure level. As a consequence, studies with stanol esters tended to be skewed to higher intake levels. This difference was discussed in depth in the September 12, 2001, comments on the Interim Final Rule submitted on behalf of Raisio Benecol Ltd.

McNeil also submitted comments to the Interim Final Rule that disagreed with the agency's approach to the analysis and argued that the two substances (i.e., stanol esters and sterol esters) should be considered as one universe. This conclusion was based on the observation that there are no convincing data to suggest that these two substances behave differently in lowering LDL cholesterol. In fact, the available data (Hallikainen, et al, 2000; Law, 2000; and Normén, et al, 2000) would argue that stanol esters and sterol esters behave similarly with regard to their cholesterol lowering potential. In a recent study (Thompson, et al, personal communication) the relative efficacy of stanol ester and sterol ester spreads was tested in patients with familial hypercholesterolemia and a group of normal subjects. These investigators found the two products to be equally efficacious in lowering LDL cholesterol levels after four weeks.

To support this argument, McNeil presented a statistical analysis, which clearly showed that, when considering all of the studies FDA evaluated in its development of the Interim Final Rule, one could not demonstrate that the dose response relationship for stanol esters was different than that for sterol esters, i.e., the slopes of the two lines were not statistically different.

Thus, this analysis supported the argument that the level of stanol esters or of sterol esters in foods, which would allow products to bear the health claim, should be identical. In addition to the submitted regression analysis, McNeil cited the review papers by Law (2000) and by Plat, et al (2000) which support the parity of the two substances. As a result of this assessment, McNeil requested in its initial comments to the Interim Rule that the agency establish an identical minimal level for stanol/sterol esters in foods permitted to bear the health claim, but did not suggest a specific level.

The agency is now requesting comments on what that level ought to be. First, it is important to consider the purpose of the selected level. If the object is to select a "minimal effective" dose level, the available literature would support a level of 1.3 -1.4 gm/day for the ester forms (~ 0.8 gm per day on an unesterified basis) (Law, 2000; Plat, et al 2000). On the other hand, if the desire is to encourage intake levels that will provide a "more highly effective" LDL cholesterol reduction, the intake level should be set at 1.8 – 2.0 gm per day on a stanol/sterol basis (3.2-3.4 gm per day on a stanol/sterol ester basis). This conclusion is supported by the recent reviews of Law (2000) and of Plat, et al (2000) and is consistent with the recent recommendations of the National Cholesterol Education Program, Adult Treatment Panel III (*Special*

Communication, JAMA, 2001) and The American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Dyslipidemia and Prevention of Atherogenesis (*Endocrine Practice, Vol. 6, No. 2: April 2000).*

Furthermore, a statistical analysis of the available stanol ester data supports a maximal response at intakes of 1.8 – 2.0 gm of stanol per day, i.e., 3.0-3.4 gm stanol ester (Comments submitted May 11, 2001, to Docket Nos. 00P-1275 and 00P-1276, on behalf of Raisio Benecol Ltd.).

After consideration of all of the available data McNeil has concluded that FDA should permit foods to bear the health claim, if they contain ½ the "minimal effective" daily intake level, assuming two servings per day, i.e., 0.4 gm of stanol or sterol equivalent as the ester. Thus, products containing 0.7 gm of either stanol or sterol ester (0.8 gm stanol x conversion factor of 1.7 / 2 = 0.68 gm) should be allowed to bear the health claim.

Further, the agency should modify the rule to allow products containing stanol or sterol esters at the "more highly effective" levels, i.e., products providing 1.5 to 1.7 gm sterol ester/stanol ester per serving (equivalent to 3.0 to 3.4 gm sterol/stanol ester per day or to 1.8 to 2.0 gm stanol/sterol per day) to bear a statement indicating this higher level of effectiveness in reducing cholesterol. The proposed "more highly effective" daily intake level is derived from an analysis of the available literature and from the review analyses of Law (2000) and of Plat, et al (2000).

In summary, we believe that the agency must acknowledge that stanol esters are not inferior to sterol esters in reducing cholesterol, and helping to reduce the risk of CHD. To sustain the disparate intake levels now contained in the Interim Final Rule would continue to foster the unfortunate implication that stanol esters are not as potent or effective as sterol esters.

The available data also support two distinctly different levels of intake for the ester forms. The first, a "minimal effective" level that we propose should be set at 0.7 gm of sterol/stanol ester per serving of foods permitted to bear the health claim (1.4 gm per day). The second, a "more highly effective" level that would permit a foods to bear a statement indicating this higher level of effectiveness in reducing cholesterol when 3.4 grams are consumed daily.

C. Eligibility of Mixtures of Plant sterols/stanols for health claim

As with our comment on the eligibility of free sterols and stanols, McNeil does not believe that mixtures of unesterified sterols or stanols should qualify for the health claim.

This issue is related to the agency's question about the eligibility of individual stanols and sterols. The equivalency of free stanols and sterols to the esterified forms has not been adequately demonstrated in appropriate clinical studies. The consideration of mixtures should be the basis of a separate petition supported by appropriate and relevant published reports. It is McNeil's position that consideration of mixtures of sterols/stanols is beyond the scope of the original petitions, which formed the basis of the present consideration.

To consider including mixtures of unesterified sterols and stanols in the Interim Final Health Claim rule would further delay deliberations of the original stanol and sterol ester petitions and would be unfair. As noted earlier, FDA acceptance of data to support consideration of sterol/stanol mixtures would greatly expand the administrative record and require notice and a new round of comment. Hence, we recommend that FDA proceed with the current petition request and consider other requests if and when full petitions are submitted for consideration.

We also believe that FDA should not continue to delay issuance of the final health claim regulation for plant sterol and stanol esters while evaluating data on the free forms of these ingredients. Instead, we believe the agency should propose a separate rulemaking to expand the current health claim to include mixtures of unesterified sterols/stanols, if the data warrant such action.

D. Significance of Apolipoprotein B as a Surrogate Marker for CHD Risk

The FDA has requested comments on the utility of using serum apolipoprotein B as a surrogate marker for CHD and LDL cholesterol in predicting CHD risk. The interest in apolipoprotein B was stimulated by the Agency's decision to evaluate the significance of an apparent aberrant result in one of the studies on plant stanol esters critical to the determination of appropriate dose. The studies crucial to the dose evaluation and the role apolipoprotein B can play in the overall analysis are described below.

Background:

The FDA evaluated the long list of references on plant stanol esters in preparation of the Interim Final Rule published in September of 2000. Following that review the Agency concluded that a dose of 3.4 g/d or more of plant stanol esters resulted in a statistically significant reduction of both total and LDL cholesterol levels. The FDA agrees that a total daily intake of at least 3.4 g/d of plant stanol esters (equivalent to 2.0 g/d of free plant stanols) represents an amount that has been shown to be effective in reducing the risk of CHD.

The agency also indicated that it had examined the references on plant stanol esters to determine if there was a dose lower than 3.4 g/d, which would also demonstrate a reduction in both total and LDL cholesterol and indeed found such

data. The agency concluded that there was a study with a dose of 1.36 g/d of plant stanol ester [FDA references #63 and #64] that showed such a decrease.

These findings of a decrease in both total and LDL cholesterol in approximately a two-week period of time are consistent with studies by Nguyen, et al, 1999, [FDA Reference #90] and Weststrate and Meijer, 1998, [FDA Reference #67]. However, two references were reviewed that, in the FDA's evaluation, were inconsistent with a reduction in both total and LDL cholesterol at a dose of less than 3.4 g/d of plant stanol esters.

The first of these references was the study by Jones, et al, 2000, [FDA reference #58]. In the study, a dose of 1.36 g/d of plant stanol ester caused a statistically significant reduction in serum total cholesterol, but not LDL cholesterol. Additionally, at a dose of 3.31 g/d plant stanol esters, there was a significant reduction LDL but not in total cholesterol. The comments submitted on behalf of the Raisio Benecol Ltd., in November 2000, specifically addressed the Jones, et al, 2000 study. The analysis clearly demonstrated that the data from the Jones study were inconsistent and, in fact, contradicted the findings of several investigators. Importantly the analysis demonstrated that the quite small Jones et al, study did not utilize the amount of stanol esters described in the study, that the criteria used in subject selection might have prejudiced the results, and that, in total, the number of discrepancies in the study made any conclusions difficult to verify.

McNeil Nutritionals agrees with this analysis and believes that the Jones, et al, study should have been discounted, similar to the FDA decision concerning other studies reviewed in preparing the Interim Final Rule. McNeil Nutritionals agrees with the FDA's previous decision that, when a single study presents data which are inconsistent with the weight of evidence and there is reason to doubt the reliability of the study, much less, if any, credibility should be given to that particular study. McNeil Nutritionals believes that little credibility, particularly in the comparison of stanol and sterol esters, should be afforded the Jones, et al, study until sufficient explanation and repetition of these aberrant results can be developed.

The second study used by the FDA to discount the reduction in total and LDL cholesterol was the work of Hallikainen, et al, 2000, [FDA Reference #88]. In the study, when data from the 4-week time period were examined, no decrease in total or LDL cholesterol was seen at a dose 1.4 g/d plant stanol ester. The same study reported that a dose of 2.7 g/d of plant stanol ester significantly reduced serum total and LDL cholesterol. Raisio Benecol Ltd., evaluated this study very carefully as part of their November 2000 comments in response to this observation by the FDA. Raisio presented quite convincing evidence that, when the study was looked at in more detail, the 1.4 g/d intake level did, indeed, cause a reduction in both total and LDL cholesterol at a very early stage and that the

stanol was acting in a manner beneficial to CHD. The evidence included reliable data from the two-week period of the study, which had not been included in the scientific publication. However, these data are just as accurate and reliable as the four-week data, which show the aforementioned results. Additionally, a plausible explanation was presented for the data at four weeks. McNeil Nutritionals believes that when evaluated in detail, incorporating all the specific evidence for this study as well as the weight of evidence for the

entire database, a conclusion can be reached. This conclusion is that a dose of 1.4 g/d of plant stanol esters significantly reduces both total and LDL cholesterol, as well as other markers and predictors of CHD. McNeil Nutritionals believes that no other analyses are needed to conclude that a dose of 1.4 g/d of plant stanol esters causes a decrease in both total and LDL cholesterol. The question can, and should be asked, if there are other data that are available from the Hallikainen, et al, study that would support or refute this conclusion? Raisio Benecol Ltd., presented such data in their November 2000 comments to the FDA, suggesting that an analysis of the apolipoprotein B data from the study would in fact shed very important light on the analysis.

Apolipoprotein B:

Raisio Benecol Ltd. demonstrated that, indeed, in the Hallikainen, et al, study a dose of 1.4 g/d of plant stanol ester caused a reduction in apolipoprotein B during the time periods in question. Raisio argued in their comments to the Interim Final Rule that these data should influence the analysis of the study, as decreases in apolipoprotein B are a reliable marker for the number of LDL cholesterol particles and, indeed, should be considered an independent predictor of CHD risk. McNeil Nutritionals has examined the possible use of apolipoprotein B data for this purpose.

Lipoproteins are manufactured in the liver and transport cholesterol in blood and lymph. There are two main types, low-density lipoproteins (LDL's) often referred to as the "bad" cholesterol, and high-density lipoproteins (HDL's) "good" cholesterol. Apolipoprotein B is essential for the production of very low-density lipoproteins, which are the precursors to LDL's, and they are the major LDL apolipoprotein. Thus, the level of apolipoprotein B is a marker for the number of LDL cholesterol particles in the blood and lymph. The LDL's are responsible for the transport of the majority of the body's cholesterol to the cells, where the cholesterol is separated from the LDL and utilized. Apolipoprotein B carrying LDL's are largely responsible for the atherosclerotic buildup of fatty deposits on the blood vessels walls, a major factor in CHD and, thus, are an independent predictor of CHD risk. This is why apolipoprotein B was measured in a number of the clinical trials conducted with plant stanol esters, including the Hallikainen, et al, study being discussed. The scientific acceptance of the utility of apolipoprotein B in the assessment of CHD risk is clear, as evidenced by the

increasing use of the parameter in clinical trials and by its acceptance by FDA's Center for Drug Evaluation and Research (CDER).

The apolipoprotein B data from the Hallikainen, et al, 2000 study supply additional support to the conclusion that 1.4 g/d of plant stanol ester is effective in reducing CHD risk, as evidenced by decreases in both total and LDL cholesterol as well as apolipoprotein B.

E. Issues Regarding Safe Use of PSEs and Advisory Label Statements

McNeil concludes that changes to the interim health claim regulation (21 CFR §101.83), advisory labeling, or other actions related to the safe use of plant stanol esters are unwarranted.

We have reviewed the available literature, information from preclinical studies, and other data to assess the need for advisory statements to product labeling, or to otherwise restrict the availability of plant stanol ester-containing foods among certain population subgroups. For the reasons cited below, we have found no compelling information suggesting a need for advisory label statements.

Sitosterolemia

Sitosterolemia is an autosomal recessive disorder characterized by increased absorption of cholesterol and other sterols from the intestine and a reduced ability to excrete sterols. This condition leads to hypercholesterolemia, coronary atherosclerosis and early death (Bhattacharyya and Connor 1974; Berge, et al, 2000). We note that this genetic defect principally affects individuals who are homozygous and this represents a very small number of individuals – maybe less than a hundred individuals worldwide (Salen, 2000; Patel, et al 1998). Moreover, these subjects are under constant supervision by medical doctors who provide ongoing dietary guidance.

Accordingly, an advisory statement about plant stanol esters, aimed at individuals who suffer sitosterolemia, would be inappropriate.

ß-Carotene

McNeil has previously addressed with FDA the safety of stanol esters, including the effect of stanol esters on ß-carotene (February 18, 1999: "Benecol -- Voluntary Submission of Safety Information on Plant Stanol Esters"; April 30, 1999: Presentation by McNeil's Dr. Ed Nelson; May 4, 1999: "Benecol – Voluntary Submission of Safety Information on Plant Stanol Esters"; November 17, 2000: Dockets 00P-1275 and 00P-1276 -- "Health Claims: Plant Sterol/Stanol Esters and Coronary Heart Disease"; and February

10, 2000: "Plant Stanol Ester Health Claim Petition").

Because ß-carotene is a Vitamin A precursor, and because repeated use of plant stanol esters may result in a small decrease in ß-carotene blood levels, some have questioned whether plant stanol ester consumption can lead to a decrease in Vitamin A blood levels. Numerous studies show, however, that consumption of plant stanol ester has no effect on Vitamin A blood levels. This includes data from 8 human clinical trials with a duration of 8 weeks to 12 months and numerous animal studies with very high stanol ester intakes. These studies are specifically discussed in two of the aforementioned documents previously provided to FDA and attached (April 30, 1999, presentation by McNeil's Dr. Ed Nelson, and May 4, 1999, "Benecol -- Voluntary Submission of Safety Information on Plant Stanol Esters").

The absence of an effect on Vitamin A is also supported by the general safety record of stanol esters. Plant stanol esters are generally recognized as safe (GRAS) by experts qualified by scientific training and expertise to conduct GRAS safety assessments. These experts specifically considered the potential for plant stanol esters to decrease Vitamin A availability. Included among them was an independent panel convened to assess the safety of plant stanol esters. (The Expert Panel's report is included in McNeil's documentation of plant stanol esters as GRAS substances and is referred to in McNeil's February 18, 1999, submission to FDA: "Benecol -- Voluntary Submission of Safety Information on Plant Stanol Esters".)

The effects of stanol esters on ß-carotene have not been found to correlate with Vitamin A status. On the other hand, the effects on ß-carotene have been found to correlate with reductions in LDL, which is an expected result. This follows from the fact that stanol esters are effective in reducing LDL cholesterol and that ß-carotene is transported to the bloodstream in association with LDL. A few studies show no residual effect of stanol esters on ß-carotene when one controls for the effect on LDL.

Although some others show a residual decrease in ß -carotene when the LDL effect is controlled for, no clinical significance has been assigned to these changes in light of several factors: One noteworthy factor is that, following stanol ester treatment, ß-carotene levels are always within the normal range, despite any observed decreases. This may be a result of the small degree of change relative to the normal fluctuation of ß-carotene levels observed in the population. Plasma ß-carotene concentrations can normally fluctuate quite widely. For example, changes in dietary intake of fiber and cholesterol, use of statins, changes in body weight, and innate differences in cholesterol metabolism and storage have all been associated with decreases in ß-carotene levels.

Two other factors that argue against assignment of clinical significance to the

observed ß-carotene differences are these: ß-Carotene levels do not continue to decline, after the chronic use of stanol esters, beyond the initial effects correlated with concomitant LDL decreases. Thus, there is no evidence for a cumulative effect with time. Additionally, increasing the stanol ester dose above the recommended intake does not appear to have any additional impact on ß-carotene. Instead, the effect plateaus in a manner similar to the plateau effect of stanol esters on LDL blood levels.

There are also other important reasons that no clinical significance has been, nor should be, assigned to the ß-carotene changes seen in some stanol ester studies. These include:

- The small magnitude of the observed ß-carotene changes,
- An inconsistency in the observed response when LDL-mediated changes are accounted for,
- An absence of effect on relevant fat soluble vitamins,
- The absence of health effects that might be associated with decreased fat soluble vitamin bioavailability in populations with prolonged use of stanol esters,
- The small proportion of ß-carotene that is normally converted to retinol,
- The large proportion of Vitamin A which is available and obtained independently of ß-carotene intake; and,
- The undetermined health value of ß-carotene, generally.

Each of these reasons has been discussed in the previously referenced materials that McNeil provided to FDA. Taken together, the data do not support any detrimental effect of stanol esters on Vitamin A, nor do they support any clinically meaningful effect of stanol esters on ß-carotene. This is true for the population at large and also extends to the population subgroup of pregnant and nursing mothers, suggested by some as possibly being at risk of Vitamin A deficiency.

First and foremost, double-blind, placebo-controlled clinical trials show no effect of stanol esters on Vitamin A status, despite the observed LDL-decrease-related changes in ß-carotene levels. Secondly, Vitamin A deficiency is not a common event in pregnant or nursing mothers. In fact, in the U.S., Vitamin A deficiency is quite rare (refer to: www.who.int/vaccines-diseases/en/vitamina/advocacy/adv07.shtml).

In total, there is no scientific evidence to support a concern for the effect of stanol esters on Vitamin A status, either in the population at large or in pregnant or nursing mothers.

Finally, the recent hypothesis that ß-carotene may play a role in cancer prevention does not provide a basis for a concern about the use of stanol esters. Results of intervention studies have so far provided no support for this hypothesis, but rather have suggested that the reverse applies (Scientific Committee on Food, "Opinion on the Tolerable Upper Intake Level of Beta Carotene" – SCF/CS/NUT/UPPLEV/37 [November 2000]; Omenn, et al 1996; Rapola, et al 1997). In a review of the role of ß-carotene in cancer prevention, the SCF also stated that "no clinical trial of ß-carotene as a single agent has shown a reduction in the risk of cancer at any specific site."

In light of the current data, no reasonable concerns can be levied against the possibility of stanol esters increasing the risk of cancer by decreasing ß-carotene levels. Moreover, ß-carotene levels, even without controlling for decreased LDL levels, remain within the normal range in response to stanol ester treatment.

Pregnant and Nursing Mothers/Children

McNeil is unaware of any evidence to suggest that pregnant and nursing women and children would be adversely affected by the consumption of plant stanol esters at a daily intake level of 3.4 g/day, the level that would produce a maximal effect in lowering LDL-cholesterol.

In particular, the reproductive and teratogenic potential of plant stanol esters has been evaluated in a teratogenicity study and a two-generation reproductive toxicity study in rats (McNeil Voluntary GRAS Submission dated February 18, 1999). At dietary levels up to 8.5%, plant stanol esters produced no indication of embryotoxic or teratogenic effects, and had no adverse effects on reproductive performance.

Concomitant Use of Cholesterol Lowering Drugs

The agency has also asked about the appropriateness of advisory label statements for individuals using cholesterol-lowering drugs. McNeil sees no reason for such advisory statements. Stanol ester containing foods have been studied in individuals who were chronic users of cholesterol lowering prescription drugs. In a multi-center, randomized, double blind, placebo-controlled investigation, the stanol ester containing foods were beneficial in inducing an incremental LDL reduction of about 10% (Blair et al, 2000). There were no observed adverse events related to the stanol ester ingestion. In fact, based on the available data the NCEP (*Special Communication,* JAMA, 2001) has recommended use of these products to help lower LDL cholesterol levels.

Consequently, this and other similar studies provide no indication for concern in the use of these products and hence no reason for any advisory statements.

In view of the lack of evidence of adverse safety effects due to consumption of plant stanol esters, we strongly urge the agency not to require advisory labeling for stanol ester products or to impose restrictions on the consumption of stanol ester-containing foods by any population sub-group.