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**PETITION TO AMEND THE HEALTH CLAIM FOR PHYTOSTEROLS
AND REDUCED RISK OF HEART DISEASE, 21 CFR 101.83**

**Petitioner: Unilever United States, Inc.
700 Sylvan Avenue
Englewood Cliffs, NJ 07632**

May 5, 2006

Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Nutritional Products, Labeling and
Dietary Supplements (HFS-800)
5100 Paint Branch Parkway
College Park, MD 20740

Unilever United States, Inc., submits this petition pursuant to §403(r)(4) of the Federal Food, Drug, and Cosmetic Act ("the Act") to amend a previously approved health claim about the relationship between phytosterols and reduced risk of coronary heart disease (CHD).

I. SUMMARY OF PETITION

- A. *FDA regulations should be amended to permit the use of the phytosterol health claim for a food that provides the full daily intake of phytosterols in a single serving***

The phytosterol health claim is the subject of an interim final rule, 21 CFR 101.83 (promulgated at 65 FR 54685; September 8, 2000), and is also the subject of a letter of enforcement discretion dated February 14, 2003 (published on the internet at <http://www.cfsan.fda.gov/~dms/ds-ltr30.html>). The regulation covers plant sterol and stanol esters; however, FDA's letter of enforcement discretion has extended the health

2006 P-0316

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claim to include free (unesterified) sterols and stanols. This petition will use the term “phytosterols” to refer to free and esterified sterols and stanols.¹

The health claim regulation currently requires the claim to specify “that the daily dietary intake of [phytosterols] should be consumed in two servings eaten at different times of the day with other foods.” 21 CFR 101.83(c)(2)(i)(H). The regulation specifies the level of phytosterols for twice-a-day use in 21 CFR 101.83(c)(2)(i)(G), which is modified by FDA’s letter of enforcement discretion to be 0.4 g per reference amount customarily consumed (RACC) and 0.8 g per day.

Because the current regulation requires labeling for twice-a-day use, it does not permit the use of a health claim for a food that provides the full daily intake of phytosterols in a single serving. This petition requests that the health claim regulation be amended to permit the use of the health claim for such a food. Specifically, this petition provides data demonstrating that the consumption of at least 2.0 g phytosterols daily in one serving eaten with meals will reduce total and LDL-cholesterol and therefore reduce the risk of CHD. Accordingly, this petition requests that the regulation be amended to permit the claim to specify that a food containing at least 2.0 phytosterols per RACC or per serving may be consumed in one serving per day eaten with meals.²

To achieve this goal, this petition requests that the regulatory language in 21 CFR 101.83(c)(2)(i)(G) and (H) be revised as follows (underlined text represents new language requested by this petition; bracketed text represents new language needed to incorporate the changes made by FDA’s letter of enforcement discretion):

(G) The claim specifies the daily dietary intake of [phytosterols] that is necessary to reduce the risk of CHD and the contribution one serving of the product makes to the specified daily dietary intake level. Daily dietary intake levels of [phytosterols] that have been associated with reduced risk of CHD are:

- (1) [0.8 g or more per day of phytosterols] when consumed at least twice a day.
- (2) 2.0 g or more per day of phytosterols when consumed once a day.

(H) The claim specifies that the daily dietary intake of [phytosterols] should be consumed in two servings eaten at different times of the day with other foods, except that if the food contains 2.0 g or more phytosterols per reference amount customarily consumed or per labeled serving, the claim specifies that the food should be consumed in one serving per day eaten with other foods.

¹ All information about levels of phytosterols is expressed as the weight of free phytosterols, except where the context indicates otherwise.

² Because the studies conducted in support of this health claim used conventional foods, this petition is limited to conventional foods and does not address dietary supplement use.

Further, this petition requests that the language of the model health claim be amended to provide an example of labeling for phytosterol-containing foods that are intended for use in one or more servings per day. Also, because the data discussed in this petition demonstrate that phytosterols should be consumed each day in order to achieve their intended benefit, this petition requests that the language of the model health claim be amended to emphasize the importance of daily consumption of phytosterols. Accordingly, we request that 21 CFR 101.83(e)(1)(i) be revised as follows (underlined text represents new language requested by this petition; bracketed text represents new language needed to incorporate the changes made by FDA's letter of enforcement discretion):

Daily consumption of foods containing phytosterols may reduce the risk of heart disease, as part of a diet low in saturated fat and cholesterol. Recommended intake of phytosterols is at least [0.8 g] total per day when eaten two or more times a day, or at least 2.0 g total per day when eaten once a day. This food provides __ g per serving and should be eaten with meals.

This petition requests only the regulatory changes discussed above. All other aspects of the phytosterol health claim regulation (including specifications for phytosterols and foods eligible for the claim) remain as stated in the regulation and in FDA's letter of enforcement discretion.

B. *The requested amendment is supported by significant scientific agreement*

The original petitions for health claims for plant sterol and stanol esters provided data showing that daily use of phytosterols would help reduce the risk of heart disease. In reviewing these petitions, FDA explained its rationale for requiring that the daily dietary intake of phytosterols should be consumed in two servings eaten at different times of the day with other foods:

In the studies showing a statistically significant effect of plant sterols or plant sterol esters on blood total and LDL cholesterol levels, subjects were provided with and instructed to consume the daily intake of plant sterols or plant sterol esters in two [citing four studies] or three [citing two studies] servings at different times of the day, or subjects were provided with the plant sterol-containing food and asked to replace from 25 to 50 g of their typical dietary fat intake with an equal amount of the test food over the course of the day's dietary intake, usually during meals [citing three studies]. The agency concludes that, to be consistent with the conditions of the studies on which the claim is based, the daily intake of plant sterol esters should be consumed in at least two servings eaten at different

times during the day with other foods. ... FDA is specifying two servings as the target number of servings.

65 FR 54685, 54704-705 (September 8, 2000).

Since 2000, the database supporting the ability of phytosterols to lower cholesterol levels has continued to evolve. There are now adequate data upon which to base a conclusion that phytosterols will significantly reduce cholesterol levels, and therefore may reduce the risk of CHD, when consumed once a day. For this reason, FDA's prior rationale for requiring at least twice-a-day use is no longer applicable.

This petition includes information from eleven new studies that involve once-a-day use. Ten studies reported significant reductions in levels of serum total and LDL-cholesterol at a magnitude comparable to data generated from twice- and thrice-a-day use. These studies found significant cholesterol reduction with levels ranging from 1.0 to 3.0 g per day. Most of the studies, including all of the higher quality studies, used levels of 2.0 g per day or higher, and for this reason our petition requests a once-a-day claim for foods containing 2.0 g or more phytosterols per RACC or per serving. The results of the studies indicate that administration of this level of phytosterols at meals will reduce serum total and LDL-cholesterol, and that consumption with a meal is an important factor modulating the cholesterol-lowering efficacy of plant sterol-enriched products rather than the time of administration during the day. Of three studies in which plant sterols were ingested at breakfast, two studies showed significant LDL-cholesterol reductions (Hyun et al 2005, Doornbos et al 2006), and one study did not show a significant impact (Abumweis et al 2006). Notwithstanding this one negative study at a breakfast-time administration, overall the data do not suggest that there is a preferred time during the day when once-a-day intake of a plant sterol-enriched food should occur.

Of these 11 studies, six were of medium-high scientific quality (treatments, intake occasion and methodology well-described, appropriate study design and analyses) and five were of medium-low quality (insufficient description of treatment and methodology and/or no placebo control and/or inappropriate statistical data analyses). To the best of our knowledge and belief, these studies were conducted in compliance with the requirements for informed consent and institutional review set forth in 21 CFR Parts 50 and 56.

Considering these eleven new studies, together with all of the data previously reviewed by FDA in support of this health claim, the totality of publicly available scientific evidence demonstrates that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the amended claim requested by this petition is supported by such evidence.

A detailed discussion of the scientific evidence is provided at Appendix B.

Enclosed with this petition are letters from three independent experts qualified by scientific training and experience to evaluate health claims. These experts are Penny M. Kris-Etherton, Ph.D., RD (Pennsylvania State University); Ernst J. Schaefer, M.D. (Tufts University); and Peter J. Jones, Ph.D. (University of Manitoba). Each of these experts supports the proposed amendment to the health claim and concludes that it is supported by significant scientific agreement. (Appendix D.)

C. *The proposed amendment should be implemented in accordance with the following procedural requests*

We request that FDA grant this petition in accordance with the following procedures:

1. **Enforcement Discretion**

FDA's letter of enforcement discretion of February 14, 2003 had the effect of significantly expanding the numbers and types of foods that could be labeled with the health claim, thereby increasing the extent to which the claim would assist consumers in maintaining healthy dietary practices. The use of such a letter permitted the revised claim to be promptly used when the publication of formal rulemaking could not be accomplished in a timely manner. FDA's use of such a letter for this purpose was appropriate and, indeed, required in light of the right to use truthful and nonmisleading claims under the First Amendment.³

The claim that is the subject of this petition is similar to the claims addressed by FDA's letter of enforcement discretion in that it is truthful, nonmisleading, and necessary to enable consumers to develop and maintain healthy dietary practices. It is therefore appropriate for FDA to take similar action to promptly implement the claim requested by this petition.

Indeed, FDA has acknowledged the importance of prompt action to ensure that the public is aware of the phytosterol health claim. When FDA promulgated the claim in 2000, it determined that prompt implementation of the claim, in the form of an interim final rule permitted by §403(r)(7) of the Act, was necessary for public health reasons. 65 FR at 54713-714.

By taking prompt action in response to this petition, FDA will enable consumers to be informed of important new knowledge regarding nutritional and health benefits of food, and ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible. For these reasons, we request that FDA implement the claim requested by this petition in a manner consistent with its prior practice, by issuing a

³ See *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999), rehearing denied 172 F.3d 72 (1999), and FDA's notices implementing the *Pearson* decision of October 6, 2000 (65 FR 59855) and December 20, 2002 (67 FR 73002).

letter of enforcement discretion indicating that FDA will not object to the use of the claim pending the promulgation of a final rule.

2. Interim Final Rule

For the reasons discussed in section I.C.1 above, we request that, when FDA engages in rulemaking on the amendment requested by this petition, it exercise its authority to make proposed regulations effective upon publication, as an interim final rule, pursuant to §403(r)(7) of the Act.

3. Qualified Health Claim

In the event that FDA determines that this petition does not meet the conditions for review as a petition supported by significant scientific agreement, we request that FDA consider this petition under its interim procedures for qualified health claims, as outlined in FDA's *Guidance on Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements* (July 10, 2003).

II. ELEMENTS OF THE PETITION AS SPECIFIED IN 21 CFR 101.70.

The following paragraphs summarize how this petition provides all of the information required by 21 CFR 101.70.

A. *Preliminary requirements*

The phytosterols covered by this petition, and the foods in which they are intended for use, are the same as those defined in 21 CFR 101.83(c)(2)(ii) and (iii), and in FDA's letter of enforcement discretion of February 14, 2003. For the reasons discussed in the interim final rule (65 FR 54685; September 8, 2000), phytosterols meet the eligibility requirements in 21 CFR 101.14(b)(1) (because they are associated with reduced risk of CHD) and 21 CFR 101.14(b)(3)(i) (because they contribute nutritive value to food).

As required by 21 CFR 101.14(b)(3)(ii), the phytosterols covered by this petition have been determined to be GRAS as documented in information previously submitted to FDA in support of the phytosterol health claim and in GRAS notifications. In addition, a discussion of the GRAS status of the use of phytosterols in a food that provides at least 2.0 g per day in a single serving is provided at Appendix A.

This petition hereby incorporates by reference all information previously reviewed by FDA that relate to the definition, effect, safety, and GRAS status of phytosterols, in the interim final rule (65 FR 54685; September 8, 2000), in dockets for the health claim

(Docket Nos. 00P-1275 and 00P-1276), and in GRAS notifications (letters of January 11, 1999 from Lipton and February 18, 1999 from McNeil Consumer Healthcare; GRN Nos. 39, 48, 53, 61, 112, 176, 177, and 181).

B. *Summary of scientific data*

As determined by FDA under the existing health claim, phytosterols are a “substance” within the meaning of 21 CFR 101.14(a)(2). The public health benefit to be derived from the amended claim proposed by this petition, and the intended population, are as defined by 21 CFR 101.83. The intended use of phytosterols that is the subject of this petition meets the validity requirements of 21 CFR 101.14(c) for the reasons provided in section I.B. and in the summary of scientific data at Appendix B.

This petition hereby incorporates by reference all scientific data previously reviewed by FDA relating to the relationship between phytosterols and CHD.

C. *Analytical Method*

The analytical methods for phytosterols are specified in 21 CFR 101.83(c)(2)(ii).

D. *Model health claim*

A proposed model health claim is provided at Appendix C.

E. *Supporting information*

The following information is attached in support of this petition:

- Letters from independent experts qualified by scientific training and experience to evaluate health claims: Appendix D.
- Copy of computer literature search: Appendix E.
- Copies of studies relied on in support of the proposed amended health claim: Appendix F.

The petitioner is aware of no adverse events relating to the consumption of phytosterols.

F. *Environmental Assessment*

The petitioner claims a categorical exclusion from the requirement for an Environmental Assessment or Environmental Impact Statement pursuant to 21 CFR 25.32(p).

III. CONCLUSION

Based on the information presented in this petition, a food that provides at least 2 g phytosterols in a single serving may help reduce the risk of heart disease. A health claim about this effect would assist consumers in maintaining healthy dietary practices. Such a claim is supported by the totality of publicly available scientific evidence, and there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such a claim, that the claim is supported by such evidence. Accordingly, we request that FDA amend 21 CFR 101.83 to permit such a claim, in the manner described in this petition, as soon as possible.⁴

To the best knowledge of the undersigned, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to be pertinent to the evaluation of the proposed amended health claim.

Respectfully submitted,

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⁴ This petition replaces "Comment 3" in comments on the health claim regulation relating to labeling for use in two servings per day that were submitted to FDA's Docket Nos. 00P-1275 and 00P-1276 by Lipton on November 22, 2000.