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Recd 2/24/2011

February 24, 2011

Hand-Delivered

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

RE: Docket Nos. FDA–2000–P–0102, FDA–2000–P–0133, and FDA–2006–P–0033

Dear Sir/Madam:

Enclosed for filing is Pharmavite LLC's consolidated Petition for Stay of Action and Citizen Petition. Accompanying this letter is an original and four copies for filing as a Citizen Petition. We understand that FDA will assign a docket number to this Citizen Petition, but we have referenced those existing dockets that also pertain to the subject matter of this Citizen Petition. We will forward copies for filing as a Petition for Stay of Action under the referenced docket numbers under separate cover.

Sincerely,

Anthony L. Young

Enclosures

[redacted]

PSA

**BEFORE THE**

**UNITED STATES OF AMERICA**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**FOOD AND DRUG ADMINISTRATION**

# PETITION FOR STAY OF ACTION

# AND

# CITIZEN PETITION

**BY**

**PHARMAVITE LLC**

February 24, 2011

**Docket Nos. FDA–2000–P–0102, FDA–2000–P–0133, and FDA–2006–P–0033**

The undersigned, on behalf of Pharmavite LLC ("Pharmavite") submit this consolidated Petition for Stay of Action and Citizen Petition pursuant to 21 C.F.R. §§ 10.30, 10.35, 101.14, 101.83 and Section 403(r) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 343(r).

Pharmavite is the manufacturer and marketer of Nature Made® products. Pharmavite has been in business for more than 30 years and makes and distributes high quality vitamins, minerals, herbs, and other dietary supplements that promote wellness and help maintain good health. Pharmavite is headquartered in Northridge, CA, with other facilities in San Fernando and Valencia, CA. Nature Made® manufactures and markets CholestOff®, a dietary supplement containing a unique blend of free phytosterols and phytostanols,[1] a product that is adversely affected by the decision for which Pharmavite seeks a stay of action and submits this Citizen Petition.

## I. DECISION INVOLVED

In 2000 FDA published an interim final rule ("IFR") authorizing use of a health claim on the labels of certain convention foods describing the relationship between phytosterol esters and coronary heart disease. Three years later, after reviewing additional data submitted in response to the IFR, FDA issued "enforcement discretion letters" permitting use of the health claim in a broader range of circumstances, including use on dietary supplements containing nonesterified, or "free" phytosterols. In those letters, FDA cautioned that the final rule may impose different or additional requirements than the IFR: "The agency cautions manufacturers that the final rule may differ from the broadened criteria listed above and that manufacturers would then be required to change their labels to conform to the final rule."

The dietary supplement industry has marketed products bearing the health claim in accordance with the limitations expressed in these enforcement discretion letters for almost eight years. Pharmavite makes the phytosterol health claim for its product CholestOff®, a dietary supplement containing a unique blend of free phytosterols.

In December 2010 FDA abruptly announced that, starting on February 21, 2011 it would exercise enforcement discretion not under the terms of the 2003 enforcement discretion letters, but rather under a different set of circumstances outlined in the Agency's newly proposed rule, 21 C.F.R. § 101.83. Later, on February 18, 2011, FDA announced that this change in enforcement discretion would take effect on February 21,

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[1] Like FDA's December 8, 2010 proposed rule, this Petition uses the term "phytosterols" to refer collectively to esterified and nonesterified (or free) plant sterols and stanols, except in cases where specific reference to the form of phytosterols is required for clarity. *See Food Labeling; Health Claim; Phytosterols and Risk of Coronary Heart Disease,* 75 Fed. Reg. 76526 (Dec. 8, 2010).

2012. In connection with that change, FDA determined to discontinue enforcement discretion for dietary supplements containing free phytosterols. This sudden discontinuation of enforcement discretion for free phytosterols in dietary supplement form directly contradicts FDA's 2003 enforcement discretion letters, wherein the Agency unequivocally stated that such a change would not be made until issuance of a final rule.

## II. ACTION REQUESTED

By this Petition for Stay, Pharmavite requests that the Food and Drug Administration stay the February 18, 2011 decision to discontinue enforcement discretion as of February 21, 2012 for those dietary supplements containing free phytosterols that have been shown, through an adequate and well-controlled clinical trial, to reduce low-density lipoprotein cholesterol ("LDL-C") and total cholesterol, pending issuance of a final rule addressing the health claim for phytosterols and the risk of coronary heart disease ("CHD").

By the Citizen Petition incorporated herein, Pharmavite seeks FDA acknowledgement that, in light of the enclosed clinical study information: (a) CholestOff® has been shown to effectively reduce LDL-C and total cholesterol, (b) the Agency will continue to exercise enforcement discretion to permit CholestOff® to bear an appropriately worded claim pursuant to the 2010 proposed regulation in the above-captioned docket describing the relationship between phytosterols and reduced risk of CHD, pending issuance of a final rule addressing the health claim for phytosterols and the risk of CHD, and (c) the final rule will allow those dietary supplements containing free phytosterols that have been shown through an adequate and well-controlled clinical trial to effectively reduce LDL-C and total cholesterol, such as CholestOff®, to bear the health claim.[2]

## III. STATEMENT OF GROUNDS

### A. FDA's Initial Review of Data on the Impact of Phytosterols and Phytostanols on Cholesterol Levels

FDA first reviewed evidence showing that phytosterols reduce cholesterol in response to two health claim petitions submitted by Lipton and McNeil Consumer Healthcare. The Lipton petition, submitted on February 1, 2000, requested that FDA authorize a health claim on the relationship between consumption of certain foods containing sterol esters and the risk of CHD. The February 15, 2000 McNeil petition

[2] Pharmavite intends to submit the information in these Petitions as a comment on the proposed rule urging the Agency to include provisions in the final rule allowing those dietary supplements that have been shown to effectively reduce LDL-C and total cholesterol to bear the health claim.

sought authorization to make a health claim about the relationship between consumption of specified stanol ester-containing foods and the risk of CHD.

In response to these petitions, on September 8, 2000, FDA published an IFR authorizing use of a health claim on certain foods containing phytosterol and phytostanol esters, based on their ability to reduce LDL-C and total cholesterol, and thereby reduce the risk of CHD.[3] In reaching these conclusions, FDA carefully analyzed numerous studies investigating consumption of both esterified phytosterols and free phytosterols on blood cholesterol levels. The Agency set forth the specific requirements for use of the health claim in 21 C.F.R § 101.83. While newly adopted 21 C.F.R. § 101.83 authorized use of the health claim only on foods containing phytosterol esters, FDA acknowledged that the free sterol/stanol is the molecule that is incorporated into the intestinal micelles in a manner that prohibits the absorption of cholesterol. In the words of the FDA, "The agency agrees that the active moiety of the plant sterol ester is the plant sterol and has concluded that studies of the effectiveness of free plant sterols in blood cholesterol reduction are relevant to the evaluation of the evidence in the plant sterol esters petition."[4]

The IFR was effective upon publication on September 8, 2000, with a 75 day comment period. FDA received numerous comments, including several comments requesting that FDA allow foods containing free phytosterols to bear the health claim. Other comments requested that FDA broaden the categories of foods eligible to bear the health claim.[5] In October 2001, FDA formally reopened the comment period and sought comments on the eligibility of free phytosterols to bear the health claim and the daily intake levels of phytosterols necessary to reduce the risk of CHD.[6]

The comments submitted to FDA included "substantial additional scientific evidence regarding the cholesterol-lowering efficacy of phytosterols that has been published in peer-reviewed scientific journals" since issuance of the IFR in September

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3 *Food for human consumption: Food Labeling: Plant Sterol/Stanol Esters and Coronary Heart Disease; Health Claims,* 65 Fed. Reg. 54685 (Sept. 8, 2000).

4 65 Fed. Reg. at 54690, 54693. The agency reached the same conclusion regarding sterol esters and sterols. 65 Fed. Reg. at 54691.

5 *Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease,* Interim Final Rule; notice of extension of period for issuance of final rule, 66 Fed. Reg. 30311, 30312 (June 6, 2001).

6 *Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease,* Interim Final Rule; reopening of comment period, 66 Fed. Reg. 50824, 50825 (Oct. 5, 2001).

2000.[7] Others submitted comments requesting that FDA refuse to expand the scope of the health claim authorized in the IFR. Upon review of all of this information, FDA concluded that "currently available scientific support extends to a broader range of phytosterol substances" than the ester forms addressed in that IFR.[8]

Accordingly, on February 14, 2003 the FDA announced that the Agency "intend[ed] to consider the exercise of enforcement discretion, pending publication of the final rule, with respect to certain requirements of the health claim."[9] This "enforcement discretion letter" permitted use of the health claim on products, including dietary supplements, containing free sterols and stanols as long as they delivered at least 0.8 g/day divided over two daily doses and contained a sterol/stanol blend of a certain composition.[10] FDA cautioned that the final rule may impose different or additional requirements: "The agency cautions manufacturers that the final rule may differ from the broadened criteria listed above and that manufacturers would then be required to change their labels to conform to the final rule."

### B. FDA's December 2010 Proposed Rule Addressing the Relationship Between Phytosterols and the Risk of CHD

On December 8, 2010 FDA published a proposed rule to amend the regulation authorizing a health claim on the relationship between phytosterol esters and reduced risk of CHD, 21 C.F.R. § 101.83. The proposal would, among other things, modify the nature of the substances that may be the subject of the claim to include free phytosterols, expand the types of foods that may bear the health claim to include a broader range of foods, modify the daily dietary intake necessary to bear the claim, and adjust the minimum amount of phytosterols required for the food to bear the claim.[11] FDA's proposal was based on "an extensive re-evaluation of the scientific evidence regarding the relationship between consumption of phytosterols and the risk of CHD."[12] Specifically, FDA

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7 *See* FDA Letter Regarding Enforcement Discretion with Respect to Expanded Use of an Interim Health Claim Rule About Plant Sterol/Stanol Esters and Reduced Risk of Coronary Heart Disease (Feb. 14, 2003), available at: http://www.fda.gov/Food/LabelingNutrition/LabelClaims/HealthClaimsMeetingSignificantScientificAgreementSSA/ucm074779.htm

8 *Id.*

9 *Id.*

10 *Id.* Specifically, the mixtures of phytosterol substances were to contain at least 80 percent beta-sitosterol, campesterol, stigmasterol, sitostanol, and camperstanol (combined weight).

11 *Food Labeling; Health Claim; Phytosterols and Risk of Coronary Heart Disease*, 75 Fed. Reg. 76526 (Dec. 8, 2010).

12 75 Fed. Reg at 76528.

considered those intervention studies published since 2000 that satisfied FDA criteria and were located by FDA and the Agency for Healthcare, Research and Quality.[13]

With respect to free phytosterols, FDA evaluated the five studies on free sterols/stanols it previously considered in issuing the IFR as well as an additional twelve studies conducted since that time.[14] The Agency concluded that the blood cholesterol-lowering efficacy of conventional foods containing free phytosterols is comparable to that of foods containing esterified phytosterols. Accordingly, the proposed rule defines the substances eligible for the health claim to include both esterified phytosterols and free phytosterols.[15]

Despite the Agency's conclusion that free phytosterols effectively lower blood cholesterol levels, the proposal provides that dietary supplements bearing the health claim must contain esterified phytosterols. *See* 21 C.F.R. § 101.83(c)(2)(iii)(B) (proposed). FDA proposed to impose this limitation because the results of the three published studies on the efficacy of supplements containing free phytosterols it considered were inconsistent. Specifically, FDA concluded that one study showed that a particular supplement had no impact on blood cholesterol levels, whereas two studies on a different formulation were positive.[16] According to the Agency the particular formulation of the supplement is critical. In the words of FDA, "The available scientific evidence for the cholesterol-lowering effects of phytosterols in dietary supplements shows that formulation of the supplement product is an important factor in the effectiveness of the product in lowering cholesterol and that esterifying the phytosterol is one way to ensure effectiveness."[17] FDA further explained that it is "difficult to predict the effectiveness of nonesterified phytosterols in lowering cholesterol when consumed as ingredients in dietary supplements."[18]

Because the results of the free sterol/stanol studies were inconsistent, FDA "tentatively conclude[d]" that the evidence for a relationship between dietary supplements containing free phytosterols and CHD does not meet the significant scientific agreement standard. FDA concluded its preamble discussion of dietary

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13 75 Fed. Reg. at 76528-29.

14 75 Fed. Reg. at 76530-31.

15 75 Fed. Reg. at 76531; *see* 21 C.F.R. § 101.83(c)(2)(ii)(A) (proposed).

16 75 Fed. Reg. at 76540.

17 *Id.*

18 *Id.*

supplements by inviting submission of additional data on the cholesterol-lowering efficacy of free phytosterol supplements and stating that it would "reevaluate its tentative conclusion regarding the eligibility of dietary supplements containing both esterified and nonesterified phytosterols in light of any additional data received."[19]

In addition to explaining the basis for the proposed modifications to 21 C.F.R. § 101.83, the preamble to FDA's December 2010 proposal also states that beginning on February 21, 2011[20] FDA will no longer exercise its enforcement discretion based on the February 2003 letters. Instead, FDA announced its intent to exercise its enforcement discretion when a health claim is made in a manner consistent with the requirements of the newly proposed rule.[21] In a Federal Register Notice published on February 18, 2011, FDA stated that this change in enforcement discretion would go into effect on February 21, 2012.[22]

### C. Pharmavite's Phytosterol/Phytostanol Dietary Supplement, CholestOff®

Pharmavite manufactures and distributes CholestOff® under its Nature Made® brand. CholestOff® contains a unique blend of free sterols/stanols supplied by Forbes Medi-Tech. Inc. under the brand name Reducol™. Reducol™ was the subject of a specific GRAS (generally recognized as safe) food use notification to the FDA in 2001.[23] In addition, Reducol™ was the subject of a new dietary ingredient notification submitted to the FDA, along with information establishing that this ingredient is reasonably expected to be safe for use in dietary supplements at 1.8 g/day.[24] Finally, while FDA issued its initial February 2003 enforcement discretion letter in response to a request from Cargill Health & Food Technologies, FDA also issued the same letter to Forbes Medi-

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19 75 Fed. Reg. at 76541.

20 Specifically, FDA indicated it would no longer exercise enforcement discretion based on the terms of the February 2003 letters starting 75 days from the date that the proposed rule publishes, *i.e.*, February 21, 2011.

21 75 Fed. Reg. at 76546.

22 *Health Claim; Phytosterols and Risk of Coronary Heart Disease* (Extension of Enforcement Discretion), 76 Fed. Reg. 9525 (Feb. 18, 2011).

23 *See* FDA Letter to J. Weinstein Responding to GRAS Notice No. GRN 000039 (April 24, 2000), available at http://www.cfsan.fda.gov/~rdb/opa-g039.html.

24 *See* FDA Letter to I. Scott Bass Responding to New Dietary Ingredient notification No. 77 (Aug. 30, 2000) available at http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0077.pdf.

Tech.[25] Each serving of CholestOff® provides 900 mg of phytosterols and phytostanols, and when taken twice a day as directed, CholestOff® provides 1.8 g of these compounds per day. CholestOff® thus contains over twice the 0.8 g/d threshold amount specified in the enforcement discretion letters. CholestOff® also contains the qualifying sterol/stanol blend specified in the enforcement discretion letters.[26]

The bottle and carton label for CholestOff® bear the CDH health claim, using language consistent with the IFR, as modified by the enforcement discretion letters. *See* Exhibit A. However, if FDA proceeds as announced in the December 2010 proposed rule and February 18, 2011 notice, Pharmavite will have to consider whether to continue to market CholestOff® with the CDH health claim while this Citizen Petition is pending, to discontinue use of the CDH health claim, or to reformulate CholestOff® to contain esterified phytosterols.

### D. A Well Designed and Conducted Study Shows that CholestOff® Reduces Cholesterol

The cholesterol-lowering effectiveness of CholestOff® has been confirmed in a randomized, placebo-controlled, double blind crossover trial conducted by Kevin C. Maki, Ph.D. and colleagues and funded by Pharmavite.[27] After a 5-week Therapeutic Lifestyle Changes ("TLC") diet and single-blind placebo lead-in, subjects received CholestOff® (total of 1.8 g/d phytosterols) or matching placebo tablets for 6 weeks. Subjects then received the opposite study product for 6 weeks while continuing the TLC diet. Subjects were instructed to take four tablets daily with water or another beverage (two with each of two meals) at consistent times each day. This mirrors the labeled

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[25] *See* Letter to C. Butt from C. Taylor (Feb. 26, 2003), available at: http://www.fda.gov/ohrms/dockets/dailys/03/Apr03/040303/8005c37a.pdf responding to Letter to K. Ellwood from C. Butt (Feb. 21, 2003), available at: http://www.fda.gov/ohrms/dockets/dailys/03/Apr03/040303/8005c379.pdf FDA has also posted the letter on the section of its website devoted to health claims for foods and supplements that meet the significant scientific agreement standard of 21 U.S.C. § 343(r)(3) and 21 C.F.R. § 101.14(c). *See* http://www.fda.gov/Food/LabelingNutrition/LabelClaims/HealthClaimsMeetingSignificantScientificAgreementSSA/ucm074779.htm

[26] Reducol™ principally contains four types of phytosterols/phytostanols derived from coniferous trees: sitosterol, campesterol, sitostanol, and campestanol.

[27] The study is described in the attached abstract, poster, and manuscript. *See* Exhibits B, C, and D, respectively. While this study has not been published in a peer reviewed journal, it is clearly relevant information that FDA is obligated to consider in the context of the health claim regulation. *See* Committee on Energy and Commerce , House Rep. 101-538, 101ST Cong, 2d Session, Nutrition Labeling and Education Act of 1990 (June 13, 1990), p. 21 ("While the studies relied on to support a [health claim] need not necessarily be published in peer review journals, the Secretary may look to publication as a factor in evaluating the weight to be given the study").

directions for use of Cholestoff®, "Take two caplets two times daily with a glass of water or other beverage before meals." *See* Exhibit A.[28] Fasting lipid concentrations were assessed in duplicate at baseline (at the end of the diet lead-in at weeks -1 and 0) and at the end of each treatment period (weeks 5 and 6 and weeks 11 and 12).

Men and woman 21-79 years of age, each with a fasting LDL-C level of ≥130 mg/dL and <220 mg/dL and in good general health were eligible for the study. Individuals were excluded from participation if they had a body mass index >42.0 kg/m$^2$, fasting blood glucose ≥126 mg/dL or diabetes mellitus, resting blood pressure ≥160 mm Hg systolic and/or ≥100 mm Hg diastolic, or CHD or a CHD risk equivalent.

The study was conducted in 31 men (41%) and women (59%) with a mean age of 57.6 years and a mean body mass index of 27.4 kg/m$^2$. Mean baseline lipid concentrations (mg/dL) were: total cholesterol 228; non-HDL-C 182;[29] LDL-C 156, HDL-C 45, and triglycerides 134. Differences from control in responses (CholestOff® minus placebo control) were significant ($p < 0.05$) for LDL-C (-4.9%), non-HDL-C (-3.6%), and total cholesterol (-2.8%). Triglyceride and HDL-C responses were not significantly different between treatment conditions. The authors conclude that CholestOff® resulted in significant reductions in artherogenic lipoprotein lipids in individuals with hyerpcholesterolemia, and would be expected to reduce the risk for cardiovascular disease if consumed in the longer term.

In the proposed rule FDA described its process for identifying those intervention studies from which scientific conclusions could be drawn about the relationship between phytosterols and CHD. In particular, the Agency first located all intervention studies evaluating the cholesterol-reducing effect of foods and supplements containing phytosterols published since 2000. FDA then excluded various types of studies that did not, in the Agency's view, generate sufficiently reliable information, such as those studies without a control group, those that did not conduct statistical analysis between the control and treatment groups, and those that evaluating phytosterols along with other substances that could have a beneficial effect in reducing cholesterol.[30] Based on the description published in the proposed rule, the above-described Maki study satisfies FDA's criteria, and the study must therefore be considered in determining the Agency's regulatory approach to use of the phytosterol health claim for dietary supplements.

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[28] The statement following this direction, currently on CholestOff® labels – "For optimal effectiveness, take this product between 15 and 30 minutes before eating a meal" – is being discontinued at the next label printing.

[29] Non-HDL-C was measured as the difference between total cholesterol and HDL-C.

[30] *See* 75 Fed. Reg. at 76528-29.

### E. A Stay is Necessary and Appropriate for CholestOff® because it has been Shown to Effectively Reduce Cholesterol

For the past eight years, since February 2003, FDA has permitted dietary supplements containing free phytosterols to bear the CDH health claim through operation of enforcement discretion letters. Those letters indicated that enforcement discretion would continue until issuance of a final rule. Though FDA's December 2010 publication was only a proposed rule that reflects "tentative" conclusions about dietary supplements containing free phytosterols, the Agency nevertheless announced abrupt cessation of its longstanding enforcement discretion. In the same December 2010 publication FDA acknowledged that at least one free phytosterol supplement formulation has been shown to effectively reduce cholesterol and confirmed its decade-old general finding that free phytosterols effectively reduce cholesterol.

The Maki study described in the preceding section establishes that the CholestOff® formulation does effectively reduce cholesterol when taken as directed, specifically LDL-C, non-HDL-C, and total cholesterol. The study is well-designed and was conducted in a manner that is consistent with generally recognized scientific procedures and principles. *See* 21 U.S.C. § 343(r)(3)(B)(i). The study demonstrates cholesterol-lowering effects that are consistent with data accepted to support CHD health claims for other food categories.[31] These data address FDA's only stated concern with the continued use of the CDH health claim on the labels of free phytosterol dietary supplements, namely, that certain formulations may not effectively reduce cholesterol. Accordingly, FDA should continue to exercise enforcement discretion with respect to CholestOff® specifically, pending issuance of a final rule, and should include provisions in the final rule permitting use of the health claim for dietary supplements containing free phytosterols that have been shown to effectively reduce LDL-C and total cholesterol, such as CholestOff®.[32]

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[31] Specifically, the results are comparable to results achieved by subjects consuming whole grain oat cereal in a study that served as the basis for the inclusion of that form of oat food in the CHD health claim regulation for soluble fiber from certain foods. 21 C.F.R. § 101.81. "The results of the study showed that subjects consuming the whole grain oat cereal experienced a significant decrease in total cholesterol (4.4 percent or 10.0 milligrams (mg)/deciliter (dL)) and LDL-cholesterol (4.9 percent or 7.8 mg/dL), and no significant difference in HDL-cholesterol, compared to the placebo group. These results are consistent with the findings for oat bran and rolled oats, i.e., positive effects on blood total- and LDL-cholesterol levels in mildly hypercholesterolemic subjects adhering to a diet low in saturated fat and cholesterol." 62 Fed. Reg. 3584, 3586 (Jan. 23, 1997).

[32] Pharmavite recognizes that FDA has proposed changes to 21 C.F.R. § 101.83 that modify the text of the CDH claim. Pharmavite intends to conform its CDH claim text to the requirements of the proposed rule at the next label printing.

Failure to exercise enforcement discretion with respect to CholestOff® would be detrimental to the public health. In enacting the health claim provisions of the FFDCA. Congress found that truthful health claims can aid consumers in maintaining healthy dietary practices.[33] FDA has long recognized the specific public health benefits associated with the phytosterol health claim, which enables consumers to select phytosterol containing foods in lieu of alternatives that do not reduce the risk of CHD. In explaining its decision to issue an immediately-effective IFR in 2000. FDA described the benefits of the phytosterol health claim as follows:

> The agency agrees with the plant sterol ester and plant stanol ester petitioners that authorizing the health claim immediately will help consumers develop and maintain healthy dietary practices. As discussed above. FDA has concluded that there is significant scientific agreement that plant sterol/stanol esters reduce blood total and LDL cholesterol levels. The reported reductions in blood total and LDL cholesterol levels are significant and may have a profound impact on population risk of CHD if consumption of plant stanol esters becomes widespread. The agency has determined that issuance of an interim final rule is necessary to enable consumers to be informed promptly and effectively of this important new knowledge regarding the nutritional and health benefits of plant sterol/stanol esters. The agency has also determined that issuance of an interim final rule is necessary to ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible. [34]

Similarly, the IFR itself describes the public health significance of CHD as follows:

> CHD is a major public health concern in the United States. It accounts for more deaths than any other disease or group of diseases. Early management of risk factors for CHD is a major public health goal that can assist in reducing risk of CHD. High blood total and LDL cholesterol are major modifiable risk factors in the development of CHD.
>
> 21 C.F.R. § 101.83(b)(1).

By granting this Petition, continuing to exercise enforcement discretion and ultimately adopting a final rule that permits use of the health claim on CholestOff®, FDA

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[33] *See* Committee on Energy and Commerce , House Rep. 101-538, 101$^{ST}$ Cong, 2d Session, Nutrition Labeling and Education Act of 1990 (June 13, 1990), pp. 9-10 ("Health claims supported by a significant scientific agreement can reinforce the Surgeon General recommendations and help Americans to maintain a balanced and healthful diet").

[34] 65 Fed. Reg. at 54714; *see also* 75 Fed. Reg. at 76548-49.

will enable continued dissemination of accurate label information concerning the relationship between consumption of phytosterols and CHD. In contrast, if the Agency proceeds as indicated in its December 2010 proposal and February 18, 2011 notice, Pharmavite would be forced to consider other options, including continuing to make the health claim on the basis of the Maki study which establishes that the CholestOff® formulation does effectively reduce cholesterol when taken as directed, specifically LDL-C, non-HDL-C, and total cholesterol.

Pharmavite could consider discontinuing use of the CHD label claim, but the result would be a CholestOff® label that provides only limited information, which would be detrimental to the many consumers seeking a product to help reduce their risk of CHD. Additionally, such a label change would likely cause a great deal of needless confusion among current CholestOff® consumers who rely upon this product to help control cholesterol and who may discontinue use of the product even though it has an established beneficial effect. Obviously, removing the CHD label claim will also do substantial harm to the goodwill accumulated in the Nature Made® CholestOff® brand and the substantial sales that this product brings to the company.

Although Pharmavite could consider reformulation to a phytosterol ester formulation that would fall within the parameters of the proposed rule and newly announced enforcement discretion, the process to do so is resource intensive and costly in light of the clinical trial demonstrating that the present formulation is effective.

Neither of the last two options serves the public health, while continuing to exercise enforcement discretion with respect to CholestOff® has unquestionable public health benefits. For this reason, Pharmavite asks that FDA continue to exercise enforcement discretion to allow use of the health claim on phytosterols and risk of coronary heart disease on the labels for CholestOff® dietary supplement, pending issuance of a final rule addressing the health claim for phytosterols and the risk of CHD. Pharmavite further requests that the final rule include provisions allowing those free phytosterol-containing dietary supplements that have been shown through an adequate and well-controlled clinical trial to effectively reduce LDL-C and total cholesterol to bear the health claim.

### F. The Requirements for a Stay are Satisfied

FDA regulations state that a stay will be granted if four requirements are satisfied. 21 C.F.R. § 10.35(e). As demonstrated below, each of these requirements is met in this case:

(1) Pharmavite will suffer irreparable injury in the absence of a stay.

CholestOff® is one of the best selling products in the Nature Made® brand. If FDA refuses to stay discontinuation of enforcement discretion under the terms of the 2003 enforcement discretion letters, Pharmavite will be forced to abandon use of the phytosterol health claim for the current formulation of Cholestoff® if it wishes to market this product free of FDA enforcement risk. This is an impactful claim, providing those millions of consumers interested in reducing their risk of CHD with important information to aid in selecting foods and supplements to consume. With respect to CholestOff®, the health claim has been shown to be truthful and not misleading. Therefore, Pharmavite has a first amendment right to make the claim. *Pearson v. Shalala,* 164 F.3d 650, 655 (D.C. Cir. 1999). Interference with Pharmavite's first amendment rights constitutes irreparable injury. *Elrod v. Burns*, 427 U.S. 347, 373 (1976) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury"); *see also Whitaker v. Thompson*, 248 F. Supp. 2d 1, 15 (D.D.C. 2002).

Moreover, esterified phytosterol supplements will presumably continue to be marketed with the health claim, as these products are subject to continuing enforcement discretion under the terms of FDA's December 2010 proposed rule and February 18, 2011 notice. CholestOff® will be at a competitive disadvantage if it removes the health claim, which can be expected to negatively impact sales, thereby irreparably harming Pharmavite. As an alternative to attempting to compete in this inequitable environment, Pharmavite could instead reformulate CholestOff® to contain esterified phytosterols. The significant time and costs involved in such a reformulation effort also constitute irreparable harm.

(2) Pharmavite's case is not frivolous and is being pursued in good faith.

Pharmavite's case is strong, simple and compelling, and is not frivolous. Pharmavite has requested that the Agency abandon its over-inclusive, broad brush approach and instead adopt an approach narrowly tailored to address the Agency's one stated concern with free phytosterol supplements, namely, that certain formulations may not effectively reduce cholesterol.[35] A stay of the discontinuation of enforcement discretion for those products shown to reduce cholesterol through an adequate and well-controlled clinical trial is consistent with FDA's public health mission – it would ensure

[35] In this respect, FDA's error in abruptly announce a blanket end to enforcement discretion for free phytosterol supplements is analogous to its repeated errors in refusing to authorize qualified health claims. In both cases, the Agency should not impose requirements more extensive than necessary to serve the interests it attempts to advance, but instead should employ the least restrictive means. *Cf. Pearson v. Shalala,* 164 F.3d 650, 656-59(D.C. Cir. 1999); *Whitaker v. Thompson*, 248 F. Supp. 2d 1, 9 (D.D.C. 2002); *Alliance for Natural Health US v. Sebelius,* 714 F. Supp. 2d. 48, 61-62 (D.D.C. 2010).

that the phytosterol health claim remains truthful and meaningful, but without unnecessarily burdening industry or creating an unjustified unlevel playing field. This is precisely the type of thoughtful regulatory decision making in which all agencies should strive to engage.

The product-specific approach urged in these consolidated Petitions is a reasonable method of addressing the possibility that some free phytosterol supplements do not effectively reduce cholesterol, and can be readily implemented by the Agency. Indeed, the approach is consistent with other health claim regulations which authorize use of a health claim only if the manufacturer has particular data. For example, the health claims for calcium, vitamin D, and osteoporosis and for folate and neural tube defects can only be made for those dietary supplements with specified disintegration and dissolution data. 21 C.F.R. §§ 101.73(c)(2)(ii)(C), 101.79(c)(2)(ii)(B). Similarly, the health claim regulation for soluble fiber is subject to the addition of other forms of fiber upon the submission and review of relevant data and information.[36] In short, the process proposed by Pharmavite is not new or novel and need only to be provided for in the final regulation.

(3) Pharmavite has demonstrated sound public policy grounds supporting the stay.

As discussed above, were FDA to proceed as announced in its December 2010 proposal, Pharmavite would be forced to discontinue use of the health claim for Cholestoff®, despite the fact that the product has been shown to reduce LDL-C and total cholesterol, or reformulate the product at great cost of time, effort and resources. It appears that other free phytosterol supplements may be in the same position, as a Petition for Stay of Action submitted on behalf of Cargill states that Cargill is aware of at least two double-blind, placebo-controlled studies supporting efficacy of dietary supplements containing free phytosterols in tablet form.[37] FDA has already determined, as a matter of public policy, that consumers benefit from dissemination of information about the relationship between phytosterol consumption and the risk of CHD. It is for this very reason that the Agency opted to issue an IFR in 2000, rather than simply a proposed

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[36] "In the 1993 dietary fiber and CVD final rule, in response to a comment regarding the apparent hypocholesterolemic properties of specific food fibers, e.g., oat bran, we agreed that the effectiveness of naturally occurring fibers in foods may be documented for specific food products (e.g., oat bran meeting specified parameters) (58 FR 2552 at 2567). We further stated that if a manufacturer could document, through appropriate studies, that dietary consumption of the soluble fiber in its particular food has the effect of lowering low density lipoprotein (LDL)-cholesterol, and has no adverse effects on other heart disease risk factors (e.g., high density lipoprotein (HDL)-cholesterol), it should petition for a health claim for its particular product (58 FR 2552 at 2567)." 67 Fed. Reg. 71773 (Oct 2, 2002).

[37] *See* Petition for Stay of Action, FDA-2006-P-0033, p. 8 (Jan. 7, 2011), available at: http://www.regulations.gov/#!documentDetail;D=FDA-2006-P-0033-0017.

rule.[38] Should FDA issue the requested Stay, the Agency will facilitate dissemination of truthful information on this important relationship. Accordingly, sound public policy grounds support the limited stay requested herein.

(4) The delay that would result from the stay is not outweighed by public health or other public interests.

The Stay sought by Pharmavite is narrow and would apply only to those products shown, through an adequate and well-controlled clinical trial, to reduce LDL-C and total cholesterol. Because these products are, by definition, supported by sound scientific data, they should remain eligible to bear the health claim once FDA issues a final rule. Accordingly, there is no "delay" resulting from the requested stay. Moreover, denial of this Petition would be detrimental to the public health, for it could deprive the public of accurate information on the relationship between phytosterol consumption and the risk of CHD, and could even cause manufacturers to discontinue marketing supplements that effectively reduce cholesterol.

## IV. CONCLUSION

The dietary supplement industry has been marketing phytosterol supplements under the terms of enforcement discretion letters for over eight years. Those letters clearly stated that enforcement discretion would continue until issuance of a final rule on the health claim for phytosterols and CHD. FDA has not issued a final rule, but nevertheless abruptly announced discontinuation of its eight year old policy of enforcement discretion. The exact basis for this change is unstated, but appears to be FDA's assessment that data on the efficacy of supplements containing free phytosterols is inconsistent, and that certain formulations of free phytosterol supplements might not effectively reduce cholesterol. While FDA's analysis of the data indicated that some such formulations have been shown to reduce cholesterol, the Agency prohibited use of the health claim on all supplements containing free phytosterols. The new policy is thus flawed on two separate grounds: it is inconsistent with the terms of the enforcement discretion letters, and it paints with too broad a brush, prohibiting use of the health claim on all free phytosterol supplements when data before the Agency show certain formulations effectively reduce cholesterol.

To address these flaws, and permit dissemination of truthful and not misleading information about the relationship between phytosterols and the risk of CHD, Pharmavite requests that FDA (1) stay the February 18, 2011 decision to discontinue enforcement discretion as of February 21, 2012 or those dietary supplements containing free phytosterols that have been shown, through an adequate and well-controlled clinical trial, to reduce LDL-C and total cholesterol, pending issuance of a final rule addressing the

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[38] 65 Fed. Reg. at 54714.

health claim for phytosterols and the risk CHD, and (2) acknowledge that, in light of the clinical study information enclosed herein: (a) CholestOff® has been shown to effectively reduce LDL-C and total cholesterol, (b) the Agency will continue to exercise enforcement discretion to permit CholestOff® to bear an appropriately worded claim describing the relationship between phytosterols and reduced risk of CDH, pending issuance of a final rule addressing the health claim for phytosterols and the risk of CHD, and (c) the final rule will allow those dietary supplements containing free phytosterols that have been shown through an adequate and well-controlled clinical trial to effectively reduce LDL-C and total cholesterol, such as CholestOff®, to bear the health claim.

## V. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

## VI. ECONOMIC IMPACT

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

## VII. CERTIFICATION

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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February 24, 2011

## EXHIBITS

A Container and Carton label for Nature Made® Cholestoff®

B Maki, KC *et al., A Plant Sterol/Stanol Supplement in Tablet Form Lowers Low-Density Lipoprotein and Non-High-Density Lipoprotein Cholesterol in Men and Woman with Primary Hypercholesterolemia*, J. Clin. Lipidology, Vol. 4, No. 3, June 2010, p. 211-12 (abstract)

C Maki, KC *et al., A Plant Sterol/Stanol Supplement in Tablet Form Lowers LDL and Non-HDL Cholesterol in Men and Woman with Primary Hypercholesterolemia* (poster) presented at the Annual Meeting of the National Lipids Association, May 13-15, 2010, Chicago, IL

D Maki, KC *et al., Lipid-altering Effects of a Dietary Supplement Tablet Containing Plant Sterols and Stanols in Men and Woman with Primary Hypercholesterolemia* (manuscript)