THOMAS O. HENTELEFF
KINSEY S. REAGAN
PETER R. MATHERS
ANTHONY L. YOUNG
ANNE V. MAHER
BONNIE A. BEAVERS
DANIEL R. DWYER
SCOTT M. LASSMAN
STACY L. EHRLICH
JENNIFER A. DAVIDSON
JOSHUA S. KIM
JAMES W. WOODLEE

KLEINFELD, KAPLAN AND BECKER, LLP
1140 NINETEENTH STREET, N.W.
WASHINGTON, D.C. 20036-6601
TELEPHONE (202) 223-5120
FACSIMILE (202) 223-5619
WWW.KKBLAW.COM

OF COUNSEL:
WILLIAM J. HARDY

March 18, 2011

Division of Dockets Management Branch
U.S. Food and Drug Administration (HFA-305)
Department of Health & Human Services
5630 Fishers Lane Room 1061
Rockville, MD 20852

Re: PETITION FOR ADMINISTRATIVE STAY OF ACTION
Docket Nos. FDA–2000–P–0102, FDA–2000–P–0133, and FDA–2006–P–0033, Health Claim; Phytosterols and Risk of Coronary Heart Disease

Dear Sir or Madam,

This petition for an Administrative Stay of Action is submitted on behalf of Botanical Laboratories, Inc., Ferndale, Washington pursuant to 21 C.F.R. §§ 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).

Botanical Laboratories is the manufacturer of the WELLESSE® brand (www.wellesse.com), a line of premium liquid dietary supplements in concentrated (2 tsp – 2 tbsp) dosage forms. Botanical Laboratories has been manufacturing dietary supplements for over 20 years. WELLESSE® supplements have found success with consumers who prefer a liquid supplement over harder to swallow bulky capsules or tablet forms. An estimated 40% of consumers find it difficult to swallow pills and tablets and Wellesse provides consumers a viable option to proactively address deficiencies in their daily diet. Consumers currently purchase Wellesse products in select drugstores, club warehouses, and grocery chains throughout the United States.

PSA

Botanical Laboratories is developing, and intends to introduce this year, a liquid dietary supplement containing free phytosterols with a claim that consumption of the product may reduce the risk of heart disease.

I. DECISION INVOLVED

FDA published an interim final rule ("IFR") in 2000 authorizing a health claim on the labels of certain foods containing plant phytosterols that describes the relationship between these nutrients and coronary heart disease. 21 CFR § 101.83. Subsequently, after reviewing additional data, FDA in 2003 issued "enforcement discretion letters" to certain manufacturers permitting use of the health claim in foods, including dietary supplements, using nonesterified, or "free" phytosterols. FDA advised in those letters 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."

On December 8, 2010 FDA announced in the Federal Register that on February 21, 2011 it would no longer exercise enforcement discretion under the terms of the 2003 enforcement discretion letters. 75 Fed. Reg. 76526. Instead, enforcement discretion would be exercised for products meeting the criteria of the newly proposed rule, 21 C.F.R. § 101.83 set out in that Federal Register notice. 75 Fed. Reg. at 76546. The new proposal, if finalized would not allow the health claim to be made for dietary supplements formulated with free phytosterols. This change in enforcement discretion directly contradicts FDA's 2003 letters which advised the dietary supplement industry that no such change would be made until issuance of a final rule. Later, on February 18, 2011, FDA announced that this change in enforcement discretion would take effect on February 21, 2012. 76 Fed. Reg. 9525.

Prior to the amendment of the health claim proposed in December 2010 by FDA, Botanical Laboratories was poised to introduce a heart health liquid dietary supplement featuring sufficient free phytosterols per 2 tablespoon serving to meet the requirements of the 2003 enforcement discretion letters. Except for the fact that it is formulated with free phytosterols, the proposed product conforms in all respects to the requirements for the coronary heart disease health claim set out in the December 8 proposed regulation.

Under the newly proposed rule, the Botanical Laboratories liquid product would qualify for the health claim if it were marketed as a food. The WELLESSE® brand has historically been limited to dietary supplements, and the product under development at

the time the proposed rule published in December was a liquid supplement. The company plans to market the product as a dietary supplement consistent with the company's manufacturing expertise, marketing strategy and channels of distribution. For these business reasons as well as minimizing confusion to consumers, the company has determined to market this product as an extension to their line of dietary supplements and not as a food product. Moreover, as a dietary supplement, Botanical Laboratories is free to include other heart health dietary ingredients that may not be GRAS for use in food.

II. ACTION REQUESTED

Botanical Laboratories 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 in liquid form until the promulgation of a final phytosterol coronary heart disease health claim regulation.

III. STATEMENT OF GROUNDS

Liquid Dietary Supplements Containing Free Phytosterols are Effective in Lowering Cholesterol

Owing to the insolubility of *unformulated* crystalline phytosterols, it is no surprise they are not in the subject of many scientific studies, and those studies that do feature them do not yield favorable results.[1-2] However, in studies where crystalline phytosterols have been made soluble by emulsification, the evidence points to their efficacy in reducing dietary cholesterol absorption.[3-4] When incorporated in tablets that meet USP disintegration standards, free phytosterols have also been shown to be effective. [5-6]

Three intervention studies using phytosterols in dietary supplements were cited by FDA in the published Dec 8, 2010 proposal. In the first, 12 gelatin capsules representing 3 g sitostanol suspended in safflower oil did not significantly reduce total cholesterol or LDL cholesterol.[7] However, there is speculation that sitostanol remained undissolved due to limited dispersion in capsule form.[4] Goldberg, *et al.* (2006) demonstrated that quick dissolve tablets were effective in furthering cholesterol reduction when taken in conjunction with statin drugs.[6] McPherson *et al.* (2005) highlighted two formulations of a spray-dried stanol lecithin preparation, reporting positive results in tablet form (disintegration time <10 min) and negative results in

capsule form (disintegration time >45 min).[5] These three studies demonstrate that formulated sterols/stanols that are easily dispersed have been shown to be effective.

Further, Devaraj *et al.* (2004) showed a significant reduction in total and LDL cholesterol versus placebo when free phytosterols were included in an aqueous suspension of orange juice.[8] Spilburg *et al.* (2003) also studied free phytosterols in beverage form administered as a stanol-lecithin preparation in a reconstituted lemonade powder. Using this medium, cholesterol absorption was reduced by 32.1%.[9] The suspension of free phytosterols in these liquid mediums closely mimic the delivery proposed for the WELLESSE® heart health liquid dietary supplement .

While the composition of the suspension of phytosterols differs between these liquid mediums, Botanical Laboratories is not aware of any evidence showing an aqueous suspension of nonesterified phytosterols is not effective. Therefore, it is not reasonable to conclude that the different emulsion systems in these liquid mediums would significantly differ in dispersion of the phytosterols in the gut.

FDA's conclusion that "the results [of dietary supplement studies] have been inconsistent and highlight how difficult it is to predict the effectiveness of nonesterified phytosterols in lowering cholesterol when consumed as ingredients in dietary supplements"[10] is not well founded, as these studies do show that some formulations of free phytosterols are effective. Therefore, it is unfair to conclude that all forms of dietary supplements containing free phytosterols should be barred from using the health claim.

The simple issue posed by this petition is whether or not free phytosterols in a liquid dietary supplement can reduce cholesterol absorption. Substantial evidence exists that free phytosterols are effective and that the form of the dietary supplement matters[10] in setting a requirement for supplements eligible for the health claim, this petition for stay seeks to allow the claim for nonesterified emulsified phytosterols in aqueous liquid forms, where they would be easily dispersed. The simple and overriding predicate for doing so is that such products in food form are permitted to make the claim because FDA has determined that there is significant scientific agreement that they are effective.

A. 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 set forth below, each of these requirements is met with respect to Botanical Laboratories petition:

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

The economic impact to Botanical Laboratories includes the costs invested in product development and marketing research, and the prevention of the launch and anticipated sales of a viable product that meets the needs of consumers looking for an efficacious and affordable phytosterol supplement in liquid form.

. If FDA refuses to stay discontinuation of enforcement discretion under the terms of the 2003 enforcement discretion letters, Botanical Laboratories product development work would need to be redone to determine whether esterified phytosterols can be formulated into a shelf stable palatable liquid dietary supplement. Moreover, esterified phytosterols are more expensive than the free form. This means that a finished liquid product containing that form may be cost prohibitive and not commercially viable. Thus, failure to grant a stay will likely doom this proposed product.

Botanical Laboratories proposed product and a comparable food product are functionally equivalent. Not allowing Botanical Laboratories to make the health claim for its dietary supplement form is particularly damaging in this context because it is difficult to conceive that the health claim would not be truthful or in any way misleading for the proposed product. Indeed, FDA has agreed in its proposed regulation that the health claim has been shown to be substantiated, and is truthful and not misleading for liquid food products. Therefore, Botanical Laboratories has a First Amendment right to make the claim. *Pearson v. Shalala,* 164 F.3d 650, 655 (D.C. Cir. 1999). Interference with these 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).

FDA has already determined that dietary supplements are an appropriate class for phytosterols and has proposed that dietary supplements using esterified phytosterols can make the health claim. Foods in liquid form containing free phytosterols 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. Botanical Laboratories will be at a competitive disadvantage if it goes to market without the health claim, which can be expected to negatively impact sales, thereby irreparably harming Botanical Laboratories.

(2) Botanical Laboratories position is not frivolous and is being pursued in good faith.

Botanical Laboratories case is strong, simple and compelling, and is not frivolous. Botanical Laboratories has requested that the Agency abandon a blanket approach and instead adopt an approach narrowly tailored to address the concern that certain dietary supplement formulations may not effectively reduce cholesterol. A stay of the discontinuation of enforcement discretion for those products that are in liquid formulations similar to food products is consistent with FDA's public health mandate by allowing free phytosterol - containing dietary supplements in liquid form to be made available to consumers.

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

As discussed above, were FDA to proceed as announced in its December 2010 proposal, Botanical Laboratories would be forced to discontinue use of the health claim for its proposed product, despite the fact that the liquid food products with free phytosterols could continue to make the claim, or to embark on an investigation into reformulation of the product at great cost of time, effort and resources. 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. Sound public policy grounds therefore 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 Botanical Laboratories is narrow and would apply only to those products which are similar to liquid food products containing free phytosterols. No public health or other public interests are put at risk by the stay sought herein.

IV. CONCLUSION

On the basis of the foregoing, Botanical Laboratories requests that FDA stay the February 18, 2011 decision to discontinue enforcement discretion as of February 21, 2012 for dietary supplements containing free phytosterols in liquid form until the promulgation of a final regulation in this matter.

V. ENVIRONMENTAL IMPACT

Botanical Laboratories 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 certifies, 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,

Anthony L. Young
Jennifer A. Davidson
Kleinfeld, Kaplan and Becker, LLP

Joshua Freeman
Regulatory Scientist
Botanical Laboratories

KKB | KLEINFELD KAPLAN & BECKER, LLP

1140 NINETEENTH STREET, N.W.
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301-827-6860