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November 21, 2000

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

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

Dear Sir or Madam:

This letter and comment are submitted on behalf of Novartis Consumer Health, Inc. ("Novartis") and Forbes Medi-Tech, Inc. ("Forbes") to comment on the Interim Final Rule, "Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease," 65 Fed. Reg. 54686 (September 8, 2000).

FDA, by this rule, has finalized a health claim correlating plant sterol/stanol esters and a reduced risk of coronary heart disease. Attached are comments and scientific data supporting Novartis' and Forbes' position on the issues.

We appreciate your review and consideration of these comments. Please feel free to contact me directly at 908-598-7048 with any questions.

Sincerely,

Judith A. Weinstein
Associate General Counsel

00P-1275

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**NOVARTIS CONSUMER HEALTH, INC. AND FORBES MEDI-TECH, INC.
COMMENT ON THE PLANT STEROL/STANOL ESTERS AND
CORONARY HEART DISEASE HEALTH CLAIM**

I. Introduction

Executive Summary

This comment is being submitted to broaden the Interim Final Rule, "Food Labeling: Health Claims; Plant Sterols/Stanol Esters and Coronary Heart Disease," 65 Fed. Reg. 54686 (2000) ("Interim Final Rule"). The comment requests that FDA:

- Recognize that free sterols/stanols are the active phytosterol substances in cholesterol reduction and should be the basis for the health claim regulation;
- Recognize that tall oils are an appropriate source for sterols, as acknowledged in the Interim Final Rule for stanols; and
- Recognize that combination sterols/stanols are as efficacious as the substances contemplated by the Interim Final Rule, and therefore these combinations should also be eligible for the health claim.

In addition, the comment suggests a separate dosage level for sterols and stanols based on science reviewed by FDA in the health claim preamble. The comment is organized in this way to parallel the dichotomy established by FDA in this Interim Final Rule. However, as a more appropriate option, the comment also suggests that FDA revise the health claim to reflect a single claim with a single dosage level equally applicable to sterols, stanols and combination mixtures.

Background

This comment is submitted on behalf of Novartis Consumer Health, Inc. and Forbes Medi-Tech, Inc. (hereinafter referred to as "Novartis") to make recommendations

regarding the Interim Final Rule. FDA, by this rule, has finalized a health claim correlating plant sterol/stanol esters and a reduced risk of coronary heart disease.

The current regulation is narrowly drafted to reflect the specific requests of two different companies who filed health claim petitions – one for plant sterol esters and the second for plant stanol esters. Novartis and Forbes are concerned that the rule does not adequately address other phytosterol substances that have clearly been shown to be equally efficacious in reducing the risk of coronary heart disease through the same science relied upon by the agency for this Interim Final Rule.¹ As FDA has previously recognized, health claims are not intended to be “brand specific.” 56 Fed. Reg. 60559 (1991). In brief, we are recommending that the rule be amended to also include free sterols and stanols, sterols derived from tall oils, and products containing a combination of sterols and stanols, which provide consumers with serving amounts of 0.4 grams free sterols/stanols (or 0.65 grams sterol/stanol esters).

Our recommendations are all contemplated by the preamble discussion of the Interim Final Rule. We have attached additional documents supporting our position and provided a black-lined health claim that identifies the suggested changes. [Ex. 1] Because the agency has recognized that the free forms of sterols and stanols are the active moieties in the referenced substances (plant sterol/stanol esters), conforming changes are necessary throughout to reflect the free form and the corresponding daily and per serving dosage levels for the free form.

We met with FDA on November 7, 2000 to discuss our specific suggestions for broadening the final rule to encompass additional substances. FDA stated that it was appropriate

¹ With the exception of some conforming changes, Novartis does not recommend changes to the description of the “disease” or “health related condition” or the optional language provisions of the health claim.

for Novartis to include the arguments for expanding the rule in our written comments.

Comments are the appropriate vehicle by which to broaden this interim health claim rule to encompass all pertinent substances. (*See, e.g.*, “Food Labeling: Health Claims; Oats and Coronary Heart Disease.” 62 Fed. Reg. 3586 (1997)).

A. Background on Interested Companies

Novartis AG is a world leader in healthcare with core businesses in pharmaceuticals, consumer health, nutrition, generic drugs, eye care and animal health. Novartis was formed in 1996 when Ciba-Geigy merged with Sandoz Ltd. Novartis Consumer Health, Inc. is a division of Novartis with interests in infant and baby nutrition, medical nutrition, over-the-counter pharmaceutical products, and health and functional foods.

Forbes Medi-Tech, Inc. is a Vancouver, BC based biotechnology company dedicated to research, development and commercialization of pharmaceutical, nutraceutical and food products derived from nature. Forbes is the exclusive supplier of Reducol™ to Novartis under the terms of a strategic alliance between the two companies.

In February of this year, Novartis Consumer Health and the Quaker Oats Company formed a joint venture. This new company is named Altus Food Company. Altus represents the first time a global healthcare company and an international food marketing company have come together to create foods with health benefits beyond basic nutrition. Altus Food Company will submit separate comments that are consistent with these comments and also address issues related to additional food forms and matrices.

A. Background on ReduconTM

ReduconTM is a natural phytosterol (plant sterol) product from tall oil derived as a by-product of the kraft paper pulping process.² ReduconTM contains significant amounts of the plant sterols sitosterol and campesterol, as well as the plant stanols sitostanol and campestanol; it contains only minor amounts of the plant sterols stigmasterol and brassicasterol. The phytosterols³ in ReduconTM are in a free, non-esterified form and are comprised of a minimum of approximately 65% by weight plant sterols and 25% by weight plant stanols, with the balance being comprised of minor sterol components. For comparison, the plant sterols and stanols in Take ControlTM and Benecol® are esterified to vegetable oil fatty acids with the result that the sterol/stanol ester substances in these products only contain approximately 60% by weight of plant sterols and stanols (assuming the use of standard vegetable oil fatty acids of nominal C16-18 chain length for esterification). Based on actual analysis of commercial product, the profile of phytosterols in these products is approximately 98% plant sterols and 2% plant stanols in Take ControlTM while Benecol® phytosterols are approximately 87% plant stanols and 13% plant sterols.

Sterol	Take ControlTM (Sterols from ADM and Cargill)	ReduconTM	Benecol®
Sitosterol	42	60	4
Campesterol	25	7	3
Stigmasterol	18	trace	
Brassicasterol	5	trace	
Sitostanol	2	22	64
Campestanol		3	23
Minor Sterols and/or Stanols	8	8	6
Total Plant Sterols	98	75	13
Total Plant Stanols	2	25	87

² Earlier submissions and discussions with the agency have identified the ingredient as PhytrolTM. The trade name that Novartis has chosen to use in connection with the marketing of its product is ReduconTM.

³ The term "phytosterols" is used throughout the scientific literature to mean both sterol and stanol components and will be used throughout this comment in the same manner.

Reducol™ is intended for use as an ingredient in food to reduce the absorption of cholesterol from the gastrointestinal tract. Novartis plans to add Reducol™ to select food products in amounts which will satisfy the per serving amount specified of free sterols when two or three servings per day are consumed.

C. Reducol™ is Safe and Lawful for Food and Dietary Supplement Use

1. *GRAS Submission*

Under the general health claim regulation, 21 C.F.R. §101.14(c)(ii), FDA requires that an ingredient must have “been demonstrated by the proponent of the claim, to FDA’s satisfaction, to be safe and lawful under the applicable food safety provision of the Federal Food, Drug and Cosmetic Act (“FD&C Act”) at the levels necessary to justify a claim. As the subject of a prior Generally Recognized As Safe (“GRAS”) notification, the Reducol™ substance meets that standard.

We recognize that FDA has previously stated that a GRAS notification may not automatically suffice to establish the safe and lawful standard under 21 C.F.R. §101.14(c)(ii). “Food Labeling; General Requirements for Health Claims for Dietary Supplements,” 59 Fed. Reg. 395 (1994). At the same time, the agency has suggested that such GRAS findings may indeed meet the standard, in the health claims context, upon review by FDA.

In the Interim Final Rule, FDA reviewed both the Lipton GRAS notification, submitted January 11, 1999, and the McNeil GRAS notification, submitted February 24, 1999, and concluded that each respectively “reveals significant evidence supporting the safety of the use of plant [sterol] [stanol] esters at the levels necessary to justify a health claim.” 65 Fed. Reg. 54689. As such, in both cases the agency concluded that the petitioners had “satisfied the

requirement of Sec. 101.14(b)(3)(ii) to demonstrate that the use of plant [sterol] [stanol] esters in conventional foods at the levels necessary to justify a claim is safe and lawful.” *Id.* The Novartis phytosterols meet that same standard.

On December 13, 1999, Novartis similarly submitted a GRAS notification to FDA that included a summary of information pertaining to the use of tall oil phytosterols as a food ingredient. [Ex. 2] The format of that submission followed that outlined in the proposed GRAS notification regulation, 21 C.F.R. §170.36 [62 Fed. Reg. 18938, Substances Generally Recognized as Safe (GRAS)]. This submission informed the agency of Novartis’ conclusion, and that of its Expert GRAS Panel, that Reducol™ (previously Phytrol™) tall oil phytosterols are GRAS for use as a nutrient in vegetable oil spreads to reduce the absorption of cholesterol from the gastrointestinal tract at a level up to 12% free phytosterols. The GRAS notification provides a summary of the clinical basis of this determination and contains detailed information about the structure and composition of the substance, its intended use, the expected consumer exposure, and details of the absorption, distribution, metabolism and excretion of the substance.

On April 24, 2000, FDA informed Novartis in a letter that, based upon its evaluation of the submission and other available data, the agency had no questions regarding Novartis’ conclusion that tall oil phytosterols are GRAS under the intended conditions of use. [Ex. 3] The agency’s response, the evaluation and conclusion of an Expert GRAS Panel, and the scientific information cited in the submission, serve as the scientific basis for Novartis’ conclusion that the tall oil phytosterols as a food ingredient are “safe and lawful.”

2. *New Dietary Ingredient Submission*

On June 16, 2000, Novartis submitted a New Dietary Ingredient (“NDI”) notification, pursuant to section 413(a) of the FD&C Act, in support of Novartis’ marketing of

Reducool™ (previously Phytrol) as a dietary ingredient for dietary supplement use. [Ex. 4] The notification specified that each serving of Novartis' dietary supplement would contain 0.6g of tall oil phytosterols labeled for consumption up to 3 times per day. The notification noted that this level of intake was within the level of dietary exposure considered safe for use in food.

As recognized by FDA in the Interim Final Rule discussion regarding McNeil's NDI submission for plant stanol esters, when FDA finds that the safety standard in section 413(a)(2) of the FD&C Act has been met, it will not send a letter stating this conclusion. Other than to acknowledge the filing, FDA did not respond to Novartis' NDI submission, establishing that in the agency's view, Reducool™ is also safe and lawful for dietary supplement use. 65 Fed. Reg. 54689-90.

D. Reducool™ Is A Nutrient

Under 21 C.F.R. §101.14(b)(3)(i), a substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 C.F.R. §170.3(o), to the food and must retain that attribute when consumed at the levels that are necessary to justify a claim.

As described earlier in these comments, and in Novartis' GRAS notification, phytosterols are intended for use as an ingredient in food to reduce the absorption of cholesterol from the gastrointestinal tract. The scientific evidence shows that the cholesterol lowering effect of the plant sterols and plant stanols contained in Reducool™ is achieved through an effect on the digestive process. The digestive process is one of the metabolic processes necessary for the normal maintenance of human existence. As such, the plant sterols and stanols in Reducool™ meet the "nutritive value" requirement of 21 C.F.R. §101.14(b)(3)(i).

In the Interim Final Rule, FDA recognizes that plant sterol esters and plant stanol esters, which act in the same way as Reducol's™ phytosterol composition in the body, meet the "nutritive value" requirement. According to FDA, this is accomplished because nutritive value "includes assisting in the efficient functioning of classical nutritional processes and of other metabolic processes necessary for the normal maintenance of human existence" (59 Fed. Reg. 407) and because plant sterol esters and stanol esters act through an effect on the digestive process. 65 Fed. Reg. 54688. FDA's determination that the esters are nutrients applies automatically to the free sterols, because: (i) free plant sterols are the primary source; (ii) esters are formed from free sterols/stanols; and, (iii) sterol/stanol esters are cleaved to free sterols/stanols in the gastrointestinal tract.

II. The Regulation Does Not Adequately Encompass All Related Efficacious Substances

As currently drafted, the Interim Final Rule does not address phytosterol substances that have been identified in the scientific literature as being structurally comparable and equally efficacious to those included in the health claim regulation. However, with a few minor clarifications, as we discussed with the agency, the rule will cover a broader range of related products, including Novartis' proprietary ingredient Reducol™.

A. Free Sterols and Stanols Form the Basis for the Regulation

The Interim Final Rule covers only sterol esters and stanol esters and does not explicitly include any other form of sterols and/or stanols. *See* 21 C.F.R. §§101.83(c)(ii)(A) and (B). We request that pertinent sections of the health claim rule be modified to include free sterols and free stanols and combinations thereof, as well as the esterified forms of phytosterols.

Such a change would not represent a significant alteration of the Interim Final Rule. In fact, FDA recognized the fact that the free form is the biologically “active moiety” and that the ester forms are actually secondary and created primarily to address manufacturing and marketing issues. 65 Fed. Reg. 54688. Free sterols do not need the presence of fat (or fatty acids) to be included in food products. Therefore, to exclude free sterols would be to prevent, at this time, the inclusion of phytosterols in any non-fat food matrices.

Moreover, in acknowledging that many of the studies presented by the two petitioners assess the efficacy of the free form, FDA has confirmed the equivalent efficacy of free sterols/stanols to esterified sterols/stanols (it is important to note that the two petitioners actually argued to have FDA rely, in part, upon these studies to approve their requested health claims). Indeed, FDA has correlated the dosage amount of the free form, upon which the studies were based, to the ester form in discussing the relevant science. 65 Fed. Reg. 54695.

With respect to sterols, FDA writes:

The plant sterol ester petitioner states that since plant sterol esters are hydrolyzed to free sterols and fatty acids in the gastrointestinal tract (see Refs. 68 through 70), and free sterols are the active moiety of plant sterol esters (see Refs. 69 and 71), the literature on free plant sterols has direct bearing on this petition (Ref. 1, page 14). 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. 65 Fed. Reg. 54690 (emphasis added).

The commentary on stanols is similar:

Stanol esters are hydrolyzed in the gastrointestinal tract to fatty acids and free stanols, and investigators believe there is a physiological equivalence of free stanols and stanol esters in affecting blood cholesterol concentrations. Accordingly, the agency concludes that studies of the effectiveness of free plant

stanols in blood cholesterol reduction are relevant to the evaluation of the relationship between plant stanol esters and reduced risk of CHD when such studies meet the study selection criteria . . . specified in this document. 65 Fed. Reg. 54691 (emphasis added).

In requesting the inclusion of free sterols and stanols as substances eligible for the health claim, Novartis further requests the agency to consider the free sterol/stanol content (as well as esterified forms) in establishing per serving amounts. For example, the proposed per serving amount of plant sterol esters is 0.65 grams. However, due to the dilutive effect of the esterified fatty acids, sterol esters are actually only 60% by weight sterols, assuming the use of standard vegetable oil fatty acids of nominal C16-18 chain length for esterification. (See FDA's discussions at 65 Fed. Reg. 54705 and 54688). Accordingly, 0.65 grams of plant sterol esters is equivalent to 0.39 (approximately 0.4) grams of free plant sterols. Similarly, 1.7 grams of plant stanol esters delivers 1.0 gram of free plant stanols.

Specifying per serving amounts on the basis of sterol/stanol content would provide several advantages including:

- 1) Addressing phytosterol ingredient products with significant market impact, such as Reducol™, which are not used in an esterified form yet are fully active;
- 2) Simplifying claim labeling and more accurately conveying to the consumer the linkage between the health benefit and sterols/stanols respectively;
- 3) Addressing the use of phytosterol products in which the plant sterols/stanols may be only partially esterified or esterified with fatty acids of a chain length and molecular weight which vary significantly from those comprising the majority of common vegetable oils; and,
- 4) Reflecting actual components measured by the analyses required to establish product compliance with claim eligibility standards.

It is clear that the agency has already contemplated the comparability of esterified sterols and stanols to that of free sterols and stanols. FDA should therefore take action to modify

the final rule not only to include free sterols and stanols, but also to utilize the free form as the backbone for the rule. This need not change the model health claims for the ester forms; it would merely provide for use of the claims for either the free or ester forms. The claims would differ only in terms of the daily or per serving dose amounts recommended for either the free or ester form.

B. Tall Oil As A Source of Sterols and Stanols

The Interim Final Rule, 21 C.F.R. §101.83(c)(2)(ii)(B)(1), currently states that plant stanols from the byproducts of the kraft paper pulping process (*i.e.*, "tall oils") as well as those derived from edible oils are eligible to bear the health claim. In contrast, 21 C.F.R. §101.83(c)(2)(ii)(A)(1) currently states only that plant sterols from edible oils are eligible to bear the health claim. This oversight suggests that plant sterols derived from tall oils in the kraft paper pulping process may not bear the health claim. However, as discussed by the agency on page 54706 of the Interim Final Rule, "plant stanols," including those from tall oil, are prepared by hydrogenation of the natural sterol/stanol mixtures isolated from their respective vegetable or tree sources. In the absence of hydrogenation, the natural sterol/stanol mixtures are predominantly sterols.

We suggest that FDA correct this oversight so that products containing plant sterols derived through the kraft paper pulping process are also eligible to bear the health claim. FDA already recognizes the comparable efficacy of such sterols by relying in part on studies based on sterols derived from tall oil. *See* 65 Fed. Reg. 54689 (discussing Ref. 46) and 65 Fed. Reg. 54693 (discussing Ref. 74). Reference 74 is the study by Jones *et al.* (1999) which demonstrated the efficacy of a tall oil sterol/stanol mixture. We ask that FDA make such

recognition explicit in the sterol "Nature of the Substance" segment of the rule, 21 C.F.R. §101.83(c)(2)(ii)(A)(1). See Jones study attached for reference. [Ex. 5].

C. Sterol/Stanol Combinations Should Also Be Included

Finally, in order to encompass all phytosterol products that have been proven efficacious for reducing the risk of coronary heart disease, we believe that the rule should be further modified to reflect the value of combination sterol/stanol products (including dietary supplements)⁴. This can be done in the context of the model claims as currently drafted.⁵ Indeed, the agency specifically requested comments on whether its identification of the substance, including its component make-up, was appropriate. 65 Fed. Reg. 54705, 54706. These comments directly address that issue.

- 1) All products considered by the agency are mixtures/composites

All phytosterol substances investigated and considered under this rule-making by FDA represent mixtures, in varying proportions, of plant sterols and plant stanols; no product is believed to be 100% sterols or 100% stanols. While some substances, such as those contained in Take Control™, are predominantly composed of sterols (approximately 98%) and some substances, such as those in Benecol®, are predominantly stanols (approximately 87%), each also contains stanols and sterols respectively.

⁴ Dietary supplements are already included within the *stanol* section of the regulation, and should be included in the sterol section as well.

⁵ This could be achieved in a number of ways. The first option would be to finalize a single claim for phytosterol products. (See Ex. 1, pg. 10A) A second would be to draft new subsections that describe the components of a combination phytosterol product (a new 101.83(c)(ii)(C)) and provide for a new model claim specific to those products (a new 101.83(e)(3)). Novartis would support any of these solutions provided our substantive recommendations are fully incorporated.

Reducol™ is also a mixture of sterols and stanols but in a more balanced or intermediate proportion equal to approximately a minimum of 65% sterols and 25% stanols, with the balance comprised of minor sterol components.

2) Mixtures such as Reducol™ are efficacious

FDA reviewed studies which involved combination products – not individual sterol/stanol products. Nevertheless, in establishing the health claim criteria, FDA did not include substances such as Reducol™, which have an intermediate sterol/stanol composition and possess demonstrated effectiveness. The effectiveness of Reducol™ in lowering total and LDL cholesterol was investigated by Jones, 1999 (FR ref. 74), who reported it to be significantly efficacious in decreasing LDL cholesterol to a degree comparable to that observed with other sterol/stanol substances.

Jones' results demonstrate effectiveness at least as great as was reported by Westrate, 1998 (FR ref. 67) for sterol and stanol esters present in Take Control™ and Benecol® respectively. Jones reported 9.1% and 15.5% declines in total and LDL cholesterol respectively, compared to control in subjects receiving 1.8 gram⁶ Reducol™ (previously Phytrol™) per day (1.5g/70kg body weight). This degree of activity compares favorably with the reductions reported by Westrate, 1998 where 3.2 grams of sterols (with a degree of esterification at 65%) representative of those in Take Control™ and 2.7 grams of stanols (all of which were esterified) representative of those in Benecol® produced 7.3-8.3% and 13% reductions in total and LDL cholesterol respectively. Importantly, the Westrate data also support the efficacy of non-esterified sterols in that 35% of those were in the free form. [Ex. 6]

⁶ Although the abstract mentions 1.7g, as noted by FDA, calculations from the body of the study establish that the amount is actually 1.8g.

Comparative Effectiveness of Sterol Products in a Margarine Matrix

Product:	Take Control™	Benecol®	Reducole™ in a Margarine Matrix
Dosage	3 g per day ^a	2.7 g per day ^a	1.5 g/70kg/day ^b
Δ Total Cholesterol ^c	-8.3%	-7.3%	-9.1%
Δ LDL Cholesterol ^c	-13.0%	-13.0%	-15.5%

^a These data are from the Westrate [1998] study, which indicates that the average body weight of the men was 82.5 kg and for women was 66.8 kg. Converting the dose to an equivalent body weight (bw) basis, the dose of Take Control™ would have been 2.5 g /70 kg bw in men and 3.0 g / 70 kg bw in women. The same conversion to an equivalent body weight yields a Benecol® dose of 2.3 g / 70 kg bw in men and 2.9 g / 70 kg bw in women.

^b These data are from the Jones et al. [1999] study conducted in males only.

^c Values are corrected for the change that occurred in the control group.

These comparative data clearly establish that the efficacy of Reducole™ is at least equal to that reported for equivalent or higher intakes of sterol ester substances composed of 80% or greater plant sterols. The effectiveness of Reducole™ has recently been further established in an as yet unpublished dose response study in which the effectiveness of tall oil sterols in a dairy drink on blood lipid levels was studied in 120 hypercholesterolemic men and women. The study was conducted at the Chicago Center for Clinical Research and conducted according to Good Clinical Practices guidelines. In this double-blind parallel-armed placebo-controlled study, the subjects were randomized to one of four groups who consumed three milk drinks per day (90ml per serving) containing 0, 0.3, 0.6 or 1.2g Reducole™ per serving. After 28 days, measurement of blood lipids showed a significant, dose dependent reduction of both total and LDL cholesterol. The level of triglyceride and HDL-cholesterol was unaffected. Analysis of the data indicated that the relative lowering (compared to controls) of LDL cholesterol was 7.4%, 8.6% or 13.2% in subjects consuming 0.9g, 1.8g or 3.6g per day, respectively. These changes were statistically significant ($p < 0.05$; $P < 0.01$; and $p < 0.001$ respectively). This study helps to once again demonstrate that consumption of free sterols and stanols from tall oil significantly lowers cholesterol in a dose dependent manner. [Ex. 7]

- 3) The regulation must explicitly recognize sitostanol and campestanol as potentially useful components in primarily sterol-based substances.

In establishing the nature of plant sterol or plant stanol substances, the agency has identified the primary active sterols as beta-sitosterol, campesterol and stigmasterol. The agency requires that the combined percentage of these three be 80 percent or higher by weight as a condition of eligibility to bear the sterol health claim. 65 Fed. Reg. 54705. Similarly, the agency has identified sitostanol and campestanol as the primary active plant stanols and requires their combined percentage at 80 percent or higher by weight as a condition of eligibility to bear the stanol health claim. 65 Fed. Reg. 54706.

Novartis requests that FDA modify the definition of a substance which may be regarded as a plant *sterol* to accommodate substances which are predominantly sterols but which also contain significant amounts of stanols. The nature of sterol substances should be revised to include a definition of a sterol substance which is comprised of at least 80% by weight from among sitosterol, campesterol, stigmasterol, sitostanol and campestanol. In addition, the majority of the total phytosterol substance must be comprised of sterol components. As cited earlier in these comments, Jones, 1999 has demonstrated the efficacy of such a mixture.

The per serving amount of Redurol™ is currently anticipated at 0.6 grams. Of this amount, approximately 65% or 0.4 grams is composed of the sterols sitosterol and campesterol, while approximately 25% or 0.15 grams is composed of the stanols sitostanol and campestanol. These four sterols and stanols make up approximately 90% by weight of Redurol™ (total mixture) which satisfies the 80% minimum criteria. The 65% sterol content also satisfies the criteria that the majority of the total phytosterol substance be comprised of the

sterol components. Substances of such composition should be eligible to bear the health claim according to the qualifying per-serving amount established for plant sterols.

- 4) In fact, Novartis is aware of no biological basis for differentiating the effective dosage of sterols and stanols.

In §101.83(c)(2)(i)(G), FDA specifies that the intake levels associated with reduced CHD risk are 1.3 g or more per day of plant sterol esters and 3.4 g or more per day of plant stanol esters. As discussed in the preamble, these levels are based on the lowest levels that consistently caused significant blood LDL-cholesterol reductions in clinical studies. Novartis believes that if the studies are considered as a whole, plant sterols and plant stanols have approximately equal ability to reduce blood cholesterol levels. Further, we believe that differentiating the dosage of sterols and stanols will lead to unnecessary consumer confusion, making it less likely that consumers will actually use such products, and they will therefore fail to derive any benefit from a substance FDA identified as being important to public health.

FDA should consider a single dose level for all sterols and stanols (which includes esters of both forms) or blends of these. A single dose is scientifically justifiable, and would avoid consumer confusion engendered by different doses. The agency has already reviewed the relevant studies. Westrate JA, 1998 (FR ref. 67); Miettinen, TA, 1994 (FR ref. 63); Vanhanen, HT, 1992 (FR ref. 64); Jones, PJH, 1999 (FR ref. 74); Jones, PJ, 2000 (FR ref. 57); Hallikainen, MA, 2000 (FR ref. 88); and, Law (FR ref. 100) (65 Fed. Reg. 54694 and 54699). The apparent difference in efficacy between low and high doses is more likely to be an artifact of small sample size than actual differences between sterols and stanols.

In conclusion, Novartis asks that FDA consider reexamining the per serving amount proposed for stanols in establishing a single value for plant sterols and stanols equal to

the value of 0.39 (0.4) grams (or 0.65 grams esters) proposed for plant sterols. (See optional language for a single health claim at Ex. 1, pg. 10A). Novartis believes that FDA has used the correct standard, *i.e.*, the lowest dose that consistently, significantly lowers LDL-cholesterol, and the correct amount (0.8 grams of free sterols per day). The standard is consistent with the belief that even small changes in blood cholesterol will have beneficial public health effects and with the approach taken by FDA in previous health claims regulations. If FDA determines that separate values are required, the values as provided in Novartis' draft regulation correlating free and esterified sterols and stanols are appropriate.

II. Analytical Methodology Should Not Be Product Specific

In the Interim Final Rule, FDA requests comments on other food products eligible to bear the health claim and specifies that such suggestions should "provide a validated analytical method that permits accurate determination of the amount." 65 Fed. Reg. 54707, 54708. We question this requirement for specific analytical methodologies for each food product form, and suggest instead that FDA's requirement for analytical methodology be less product-specific.

A review of prior health claims shows that FDA has not previously requested an analytical method for each category of food eligible to bear a health claim. *See e.g.*, 21 CFR §101.70(f) (general health claim); 21 CFR §101.81(c)(2)(ii) (soluble fiber from certain foods and coronary heart disease).

At the present time, there is no Association of Official Analytical Chemists International ("AOAC") official method of analysis for either plant sterols or plant stanols. It may be that AOAC or the Codex Alimentarius "Committee on Methods of Analysis and Sampling" publishes such a method at some time. At present, we suggest that instead of requiring a specific analytical method for every product form, FDA should allow industry to

work together to standardize an appropriate general analytical method for products containing sterols and/or stanols.⁷ Further, while standardized methodology is being developed, we suggest that companies should use reliable methods and maintain adequate records that would be available to FDA for inspection.

This approach has relevant precedent in the health claims arena. In its proposed rule, "Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease," 58 Fed. Reg. 2478 (1993), FDA proposed that all substances eligible for the soy protein health claim meet a standard AOAC analytical method. When numerous parties commented that the method was unlikely to produce a reliable measure of the soy protein content of foods in all available formats, FDA decided to allow for the development of a suitable general analytical method for all eligible products. 64 Fed. Reg. 45934 (1999); 64 Fed. Reg. 57715 (1999). FDA stated that during the intervening time, it would use a standard method of measuring protein when the products contained only soy as the source of protein, but would rely on manufacturers to utilize appropriate methodology and maintain records where the products were comprised of more than one protein source. 64 Fed. Reg. 57715 (1999); 21 C.F.R. §101.82(c)(2)(ii)(B).

While we believe that this is the most prudent course for these products, as Novartis continues to develop new products, it will submit appropriate methods of analyses for additional food formats, if required.

⁷ Note that the development of such a method will be considerably easier for free sterol and stanol products. All current analytical methods with which we are familiar employ steps to permit quantification of the free sterols/stanols present in the product. Further complexity is then required to determine the ester, or fatty acid, fraction so that the total sterol/stanol ester content may be calculated.

III. Exemptions From Disqualifying Levels And Mandatory Nutrient Requirements

Similarly, as products are developed, Novartis may need to seek appropriate exemptions from the regulations governing disqualifying levels and mandatory nutrients. We propose that FDA discuss with industry the most efficient way of requesting these exemptions.

Altus Food Company will be seeking exemptions from the mandatory nutrient level requirements for specific food products. This exemption request will be detailed in the Altus comments to the agency.

IV. REVISED MODEL CLAIMS

- a. We propose the following substantive changes to the regulation:
- Identify sterols/stanols in their free form as the primary constituent(s) in phytosterol products while continuing to reference the ester forms. [(C)(2)(i)(D); (C)(2)(i)(G); (C)(2)(ii)(A); (C)(2)(ii)(B); (C)(2)(iii)(A)(1)&(2); (e)(1)&(2)]
 - Identify tall oil as a source of plant sterols. [(C)(2)(ii)(A)]
 - Identify campesterol and sitostanol as important and appropriate elements of a sterol-based product, provided that the sterol components make up the majority of the total phytosterol substance. [(C)(2)(ii)(A)]
 - Identify dietary supplements as an appropriate category of food eligible to bear a sterol-based health claim. [(C)(2)(i); (C)(2)(iii)(A)(1)&(2)]
 - Provide for a standardized method of analysis to be developed by industry; in the meantime, require manufacturers to use appropriate methods and to maintain records and make them available for inspection. [(C)(ii)(A)(2) & (B)(2)]
- b. Conforming changes will be necessary throughout the regulation.
- Change the reference from “sterol/stanol esters” to “sterols/stanols”, thus reflecting free plant sterols as the primary

constituent. The slash (/) indicates "and/or" and thus can be one or both constituents. [throughout]

V. CONCLUSION

We request that the Interim Final Rule be broadened in the manner described herein to recognize that: (1) free sterols/stanols should be the basis for the health claim regulation; (2) tall oils are an appropriate source of sterols; and (3) combination sterols/stanols substances should also be eligible for the health claim. In addition, we ask that the dosage level for free sterols be established per our comments, or alternatively that a single health claim with dosage levels be established to be equally applicable to sterols, stanols and combination mixtures.

We appreciate the opportunity to comment on the Interim Final Rule. Please contact Judith A. Weinstein, Associate General Counsel, Novartis Consumer Health, Inc. at (908) 598-7048 with further questions.

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**EXHIBITS TO COMMENTS
ON THE PLANT STEROL/STANOL ESTERS AND
CORONARY HEART DISEASE HEALTH CLAIM
(Docket Nos. OOP-1275 and OOP-1276)**

SUBMITTED BY

**NOVARTIS CONSUMER HEALTH, INC.
AND FORBES MEDI-TECH, INC.**

NOVEMBER 22, 2000