



Memorandum

AUG 30 2000

Date

From

(Acting) Division Director, Division of Standards and Labeling Regulations, Office of  
Nutritional Products, Labeling and Dietary Supplement, HFS-820

Subject

75-Day Premarket Notification for New Dietary Ingredients

To

Dockets Management Branch, HFA-305

New Dietary Ingredient:

tree oil phytosterols

Firm:

Novartis Consumer Health, Inc.

Date Received by FDA:

June 19, 2000

90-Day Date:

September 16, 2000

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and  
Cosmetic Act, the attached 75-day premarket notification for the aforementioned new  
dietary ingredient should be placed on public display in Docket No. 95S-0316 after  
September 16, 2000.

*Felicia B. Satchell*  
Felicia B. Satchell

955-0316

RPT 77



AUG 30 2000

Scott Bass, Esq.  
Sidley & Austin  
1722 Eye Street, NW  
Washington, DC 20006

Dear Mr. Bass:

This is to notify you that the submission you filed on behalf of your client Novartis Consumer Health, Inc. pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act), dated June 16, 2000, concerning the marketing of a substance (i.e., tall oil phytosterols) that Novartis Consumer Health, Inc. asserts is a new dietary ingredient was received by the Food and Drug Administration on June 19, 2000. This submission will be kept confidential for 90 days from the date of receipt and, after September 16, 2000, will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Please contact us if you have any questions concerning this matter.

Sincerely yours,

Felicia B. Satchell  
(Acting) Division Director  
Division of Standards  
and Labeling Regulations  
Office of Nutritional Products, Labeling  
and Dietary Supplements

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June 16, 2000

Office of Special Nutritionals (HFS-450)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C Street, SW  
Washington, DC 20204

*Received*  
*6/19/00*  
*RFP*

Re: New Dietary Ingredient Notification

Dear Sir or Madam:

On behalf of Novartis Consumer Health, Inc. ["Novartis"], we submit the attached information, pursuant to section 413(a) of the Federal Food, Drug and Cosmetic Act, in support of Novartis' marketing of the new dietary ingredient tall oil phytosterols (under the trade name Reducol™). Novartis intends to market this ingredient for dietary supplement use.

Novartis submitted to the Agency on December 13, 1999, a summary of information pertaining to the use of tall oil phytosterols as a food ingredient, in the format outlined in proposed regulation 21 CFR 170.36 [62 FR 18938, Substances Generally Recognized as Safe (GRAS)]. This submission informed the Agency of Novartis' conclusion, and that of its Expert GRAS Panel, that tall oil phytosterols are generally recognized as safe (GRAS) for use in vegetable oil spreads.

On April 24, 2000, the Food and Drug Administration informed Novartis in a letter that, based upon their 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. The Agency's response, the evaluation and conclusion of an Expert GRAS Panel, and the

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6/19/00

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WASHINGTON, D.C.

Office of Special Nutritionals (HFS-450)

June 15, 2000

Page 2

scientific information cited in the submission, serve as the scientific basis for Novartis' conclusion that the tall oil phytosterols as a dietary ingredient can "...reasonably be expected to be safe."

Respectfully submitted,



L. Scott Bass

cc: Judith Weinstein, Esq.  
Associate General Counsel  
Novartis Consumer Health, Inc.

**New Dietary Ingredient Notification**  
**for Tall Oil Phytosterols**  
**(Trade Name Reducol™)**

**Novartis Consumer Health, Inc.**

**June 16, 2000**

**SECTION 1**

**The name and complete address of the manufacturer or distributor of the dietary supplement that contains the dietary ingredient, or the dietary ingredient.**

The distributor of the dietary ingredient will be:

Novartis Consumer Health, Inc.  
560 Morris Avenue  
Summit, New Jersey 07901-1312

Attention: Judith Weinstein, Esq.  
Associate General Counsel

## SECTION 2

### **The name of the dietary ingredient.**

The dietary ingredient is tall oil phytosterols (trade name Reducol™).

Tall oil phytosterols are derived from the unsaponifiable matter of oil derived from trees. Tree oil is commonly referred to as tall oil. The dietary ingredient contains significant levels of sitosterol, campesterol, and the naturally occurring saturated (stanol) compounds, sitostanol and campestanol. Stigmasterol and other sterols are also found in minor quantities. The phytosterols are in a free non-esterified form.

### SECTION 3

**Description of the dietary supplement or dietary supplements that contain the dietary ingredient including (i) the level of the dietary ingredient in the dietary supplement, and (ii) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement.**

The dietary ingredient, tall oil phytosterols, will be marketed for use in products meeting the definition of "dietary supplement" in section 201(ff) of the Federal Food, Drug and Cosmetic Act. The tall oil phytosterols will be clearly labeled and promoted as dietary supplements. Each serving of the dietary supplement will contain 0.6 g of tall oil phytosterols. Consumption of up to 3 servings per day will be suggested or recommended in the label directions, resulting in maximum daily consumption of up to 1.8 g of tall oil phytosterols. This level of intake is within the level of dietary exposure considered safe for use in food.



#### SECTION 4

**The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer has concluded that the dietary supplement will reasonably be expected to be safe.**


A summary of information pertaining to the use of tall oil phytosterols as an ingredient in food was submitted by Novartis Consumer Health, Inc. on December 13, 1999 as part of a GRAS notification to the Agency. The information served as the foundation for Novartis Consumer Health's conclusion that tall oil phytosterols are safe (GRAS) for use in vegetable oil spread. Of primary importance was the evaluation and conclusion of the Expert GRAS Panel.

The April 24, 2000 letter from the Food and Drug Administration stated that, following their evaluation of the materials, FDA had no further questions regarding Novartis Consumer Health's conclusion that, at a level of 0.5 g of tall oil phytosterols per serving (referenced to 70 kg bw) of food for up to 3 servings per day, tall oil phytosterols are GRAS for use in food.

The opinion that the dietary ingredient tall oil phytosterols meets the statutory requirement under section 413(a)(2) that it will be "...reasonably expected to be safe..." is based upon the materials and information submitted in support of the GRAS notification, updated to include information available since the December 13, 1999 notification, the Expert GRAS Panel Report, and the April 24, 2000 letter from FDA.

Information provided to support Novartis Consumer Health's conclusion of safety is as follows:

- Attachment 1 – Statement of the GRAS Expert Panel.
- Attachment 2 – The updated list of scientific articles which form the basis for the opinion of safety. References that have become available since the December 13, 1999 notification, or have been updated with respect to their current publication status, are identified in **bold**.
- Attachment 3 – April 24, 2000 letter from the Food and Drug Administration to Novartis.
- A copy of the listed references is included with the original document.

  
Judith Weinstein, Esq.



## EXPERT PANEL STATEMENT

### DETERMINATION OF THE GRAS STATUS OF TALL OIL DERIVED PHYTOSTEROLS USED AS AN INGREDIENT OF VEGETABLE OIL-BASED SPREADS

The undersigned, an independent panel of recognized experts (hereinafter referred to as Expert Panel), qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Novartis Consumer Health Inc. to determine the Generally Recognized as Safe (GRAS) status of a natural product from tall oil (wood pulp derived). This product, which shall be referred to in this document as Phytrol™, contains phytosterols and stanols for addition to a vegetable oil-based spread at a level up to 12%. Phytrol™ is manufactured by Forbes Medi-Tech, Inc. and supplied to Novartis Consumer Health Inc. for manufacture of the spread product. The intended purpose of Phytrol™ is to help maintain normal cholesterol levels in blood. Because the phytosterol/stanol ingredients in two similar products, Benecol™ and Take Control™, are in many ways the same as Phytrol™ and are currently being marketed for the same intended use with FDA's knowledge and consent, the principal focus of this review and evaluation is on the nature and relevance of any differences between these marketed products and Phytrol™. A comprehensive search of the scientific literature for safety and toxicity information on phytosterols or stanols and their presence in food was conducted through October 1999 and made available to the Expert Panel. A report by CanTox U.S. Inc. based on this comprehensive literature review and analysis of safety and nutritional studies of phytosterols and stanols aided and facilitated the work of the Expert Panel. The Expert Panel independently evaluated materials submitted by Novartis Consumer Health Inc. and its agent, CanTox U.S. Inc., as well as other materials deemed appropriate or necessary. Following independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein.

The composition of Phytrol™ is intermediate between that of the phytosterol/stanols ingredients of Take Control™ and Benecol™. Henceforth, for the purpose of this document, these ingredients will be simply referred to as Take Control™ and Benecol™. Table 1 compares approximate compositions of the three products. While significant natural variation may occur in specific component content of each product, the data in Table 1 indicate that on average, levels of the individual component phytosterols in Phytrol™ do not significantly exceed the highest level present in either Take Control™ or Benecol™. Both of these products are marketed in the US with FDA's knowledge and consent based solely on independent self-GRAS determinations. Thus, in terms of the main phytosterol and stanol components, the Expert Panel concludes that Phytrol™ is substantially the compositional equivalent to a mixture of Take Control™ and Benecol™ and that the main components are considered GRAS for their intended use in vegetable oil-based spreads at a level not to exceed 12% for any given product or portion size.

**Table 1 Comparison of Phytosterol Compositions (% by weight)**

<b>Sterol</b>	<b>Take Control™ (phytosterols from Soybean Oil)</b>	<b>PHYTROL™ (Forbes Medi-Tech natural Tall Oil Phytosterols)</b>	<b>Benecol™ (Hydrogenated Tall and Soybean Oil Phytosterols)</b>
Sitosterol	42	47	4
Campesterol	25	14	3
Stigmasterol	18		
Brassicasterol	5		
Sitostanol	2	26	64
Campestanol		5	23
Minor Sterols	8	8	6
Total Phytosterols	98	69	13
Total Phytostanols	2	31	87

*Take Control™ uses vegetable sterols esterified with fatty acids. Data are averages of batches from ADM and Cargill. Benecol™ is a mixture of vegetable and tall oil phytosterols that have been hydrogenated and then esterified with fatty acids. The Phytrol™ values are typical of most batches and fit within current specifications. Percentages refer only to sterol content and are approximations. The estimated sterol proportions will vary depending on the methodology used for measurement. The response factors vary between different sterols when compared within the same detection system, e.g. flame ion detection (FID). Further, the response factors vary between detection systems, i.e. FID versus GC/MS or LC/MS. The Phytrol™ phytosterols were quantitated by the use of GC-FID using in-house standards. The figures for Take Control™ and Benecol™ are area under the curve estimates by GC/MS.*

The difference in constituent phytosterol profiles among the three products arises from two main factors: (1) phytosterol source with respect to Take Control™ and (2) use of hydrogenation processing for Benecol™. A third difference arises from the use of fatty acid esterification of the Take Control™ and Benecol™ products to modify their solubility properties for product application purposes.

Phytrol™, which is derived from tall oil, contains significant levels of sitosterol and campesterol, similar to those occurring in Take Control™ which is derived predominantly from soybean oil. The specifications for Phytrol™ are given in Table 2. Unlike Take Control™, Phytrol™ contains only minor quantities of stigmasterol and brassicasterol but significant levels of the saturated (stanol) compounds, sitostanol and campestanol, as occurs in Benecol™. Benecol™, which is also derived from tall oil, utilizes hydrogenation to saturate double bonds present in the sterol components, thus converting most

phytosterols to stanols, predominantly sitostanol and campestanol. However, a minor portion of the phytosterols remain unhydrogenated following hydrogenation processing of Benecol™ as indicated by the data in Table 1. Many of the minor components in each of the three products are unsaturated congeners of the same saturated structures. Consequently, hydrogenation tends to reduce, somewhat, the level and diversity of minor components. However, Benecol™ still contains a low percentage of minor component phytosterols that remain unsaturated, in the range of 2% to 3% (ref. Benecol™ submission).

**Table 2**

**Proposed food-grade specifications for Phytrol™**

Phytosterol content	> 95%
Sitosterol	38% to 60%
Sitostanol	14% to 34%
Campesterol	9% to 18%
Campestanol	2% to 14%
Total major sterols	> 86%
Loss on drying (water)	< 5%
Solvents	< 0.5%
Residue on ignition	< 0.1%
Heavy metals	< 10 ppm
Lead	< 0.25 ppm
Total aerobic count	< 10,000 CFU/g
Combined molds & yeasts	< 100 CFU/g
Coliformes	negative
E. Coli	negative
Salmonella	negative

The phytosterols in Take Control™ are not hydrogenated and contain up to 8% by weight of minor sterol and non-sterol components (see Table 1). Similarly, Phytrol™ contains a number of minor components primarily representing variations in the position and/or number of double bonds within sitosterol (C29) and campesterol (C28) structures. Also present are trace quantities of C<sub>15</sub>-C<sub>25</sub> saturated aliphatic alcohols. These minor, long chain alcohol components are substances commonly found in the diet and the Expert Panel concluded they were not toxic contaminants and their presence does not adversely affect

general recognition of safety of the intended use of Phytrol™.

The only potential, safety related difference in composition among the three products lies with their minor phytosterol-like components. Comparative analysis of these substances in Take Control™, Benecol™, vegetable sterols (produced by ADM) and Phytrol™ revealed a total of 45 major and minor sterol components. Twenty-two were present in Phytrol™. None were unique to Phytrol™ as all 22 components were found either in Take Control™, Benecol™, or vegetable sterols or reported present in vegetable oils in the scientific literature. Of the 22 phytosterol-like components in Phytrol™, 15 were found in Take Control™, 11 in Benecol™ and 12 in vegetable sterols. Three phytosterol-like components were found in Phytrol™ which were not identified in Take Control™, Benecol™, or vegetable sterols. These were sitosta-4, 6, 22-triene (C<sub>29</sub>H<sub>46</sub>), 24-methylene lophenol (C<sub>29</sub>H<sub>48</sub>O), and alpha-1-sitosterol. All three have been previously reported present in vegetable oils by Mennie et al [1994]; Goad [1966]; Grob et al [1994]; and Bortolomeazzi et al [1996]. The Expert Panel concludes that the presence of Phytrol™'s phytosterol-like minor components in either GRAS products or vegetable oils allays any safety concern about these components under the intended conditions of use of Phytrol™.

While Take Control™ and Benecol™ have been esterified and Phytrol™ has not, the Expert Panel, based on the following data and discussion, concludes that their esterification does not affect either the safety or effectiveness of these products.

**Table 3: Comparative Effectiveness of Sterol Products in a Margarine Matrix**

Product:	Take Control™	Benecol™	Phytrol™ in a Margarine Matrix
Dosage	3 g per day <sup>1</sup>	2.7 g per day <sup>1</sup>	1.5 g/70kg/day <sup>2</sup>
Δ Total Cholesterol <sup>3</sup>	-8.3%	-7.3%	-9.1%
Δ LDL Cholesterol <sup>3</sup>	-13.0%	-13.0%	-15.5%
Δ HDL Cholesterol <sup>3</sup>	+0.6%	+0.1%	-4.4%

<sup>1</sup> 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.

<sup>2</sup> These data are from the Jones et al [1999] study conducted in males, only.

<sup>3</sup> Values are corrected for the change that occurred in the control group.

Take Control™ and Benecol™ products have been esterified with common vegetable oil fatty acids to enhance their solubility in a vegetable oil product matrix. Lack of esterification does not detract from the observed equivalence of Phytrol™ phytosterols compared to Take Control™ and Benecol™. In fact, the ester forms are rapidly de-esterified *in vivo* through the action of lipase enzymes in order to yield the active free phytosterols. Only the free phytosterol or stanol affect blood cholesterol levels. Thus, equivalence between gut concentrations of the active free phytosterol plus stanols in esterified products (Take Control™ and Benecol™) compared to non-esterified (Phytrol™) is established by clinical studies showing closely similar effects on cholesterol lowering for the time and amount consumed (Table 3). The somewhat lower effectiveness of Take Control™ and Benecol™ on a gram/day basis is probably a reflection of a less than complete de-esterification of the phytosterol and stanols esters in Take Control™ and Benecol™ following their ingestion. These data demonstrate that the tall oil phytosterols in Phytrol™ are substantially equivalent to the other two products in decreasing total and LDL serum cholesterol values. Furthermore, there is no evidence of any significant effect on plasma HDL levels for any of the three products. In the Phytrol™ study reported in Table 3, decreases in mean HDL values of 6.3 and 10.7 % were reported in the control and treated groups, respectively. The 4.4 % difference between the groups attributable to Phytrol *per se* was well within the 6.5% coefficient of variation for this assay procedure in the reported study and is not clinically significant.

As with the previous clinical studies involving Take Control™ and Benecol™, no adverse effects were observed in any of the subjects in the study by Jones *et al* [1999] including those consuming Phytrol™.

As Phytrol™ is intended for use as an ingredient in vegetable oil-based spreads at levels of free phytosterols and stanols similar to that of Take Control™ and Benecol™, Phytrol™'s use and purpose in food are identical to that of the two currently marketed products, Take Control™ and Benecol™. The Expert Panel, based on a critical review of the information assembled and discussed by CanTox U.S. Inc., concludes that plant phytosterols and stanols as described and used by Lipton (Take Control™) and McNeil (Benecol™) in their submissions to FDA of January 11, 1999 and February 18, 1999, respectively, are GRAS by scientific procedures for their intended use in vegetable oil-spreads. The published studies relied upon for this conclusion are listed in Attachment I. In view of these facts and given the compositional equivalency of Phytrol™ to Take Control™ and Benecol™, the Expert Panel concludes that the intended use of Phytrol™ does not raise questions concerning safety, including those related to potential, adverse nutritional effects. Such nutritional matters have been addressed and adequately resolved in the course of establishing the self-determined GRAS status of Take Control™ and Benecol™ based on studies included in Attachment I.

Based on the critical evaluation discussed above, the Expert Panel has determined that Phytrol™, meeting the specifications cited above, is generally recognized as safe (GRAS) by scientific procedures when used in vegetable oil-based spreads for the purpose of helping to maintain a healthy blood cholesterol level, providing it is used in accordance with current good manufacturing practice (21 CFR § 182.1(b)) in an amount not to exceed 12% phytosterol plus stanol in the finished spread.



W. Gary Flamm, Ph.D, F.A.C.T.  
President, Flamm Associates

Walter H. Glinsmann, M.D.  
Adjunct Professor, Georgetown University  
President, Glinsmann Inc.


K. C. Hayes, D.V.M., Ph.D.  
Professor Biology (Nutrition)  
Director, Foster Biomedical Research Laboratory  
Brandeis University



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W. Gary Flamm, Ph.D, F.A.C.T.  
President, Flamm Associates



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Walter H. Glinsmann, M.D.  
Adjunct Professor, Georgetown University  
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K. C. Hayes, D.V.M., Ph.D.  
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