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February 12, 2001

Via Federal Express

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. OOP-1275 and OOP-1276
65 Fed. Reg. 54686 (September 8, 2000)

Dear Sir or Madam:

This supplemental comment is submitted on behalf of Novartis Consumer Health, Inc. ("Novartis") and Altus Food Company ("Altus")[1] to provide further support for their November 21, 2000, comments to FDA regarding the Plant Sterol/Stanol Esters and Coronary Health Disease health claim Interim Final Rule. In their original submissions, both Novartis and Altus argued that FDA need not specify food formats to which plant sterols/stanols (hereinafter called "phytosterols") could be added, and need not articulate specific analytical methodologies associated with each and every food format. However, both companies indicated that they would be working towards validating methodologies to assess the phytosterol content in their food formats and would submit them to FDA, should FDA continue to require them by regulation. With this comment, Novartis and Altus are now jointly submitting that validated methodology.

1. Submission of Analytical Methodology

In providing an analytical method at this time, neither company is modifying its original assertion that FDA should not specify by regulation an analytical method for each listed food format. Novartis and Altus recognize that there is presently no official method of analysis for phytosterol content. It is both companies' position that FDA should, as it has done

[1] In February of 2000, Novartis Consumer Health and the Quaker Oats Company formed a joint venture to create foods with health benefits beyond basic nutrition. This new company is named the Altus Food Company.

previously with respect to the Soy Protein and Coronary Heart Disease health claim, defer to industry to develop an appropriate general methodology for products containing plant sterols/stanols. Until that time, the industry would be required to utilize reliable methods for their products and maintain adequate records that would be available to the Agency upon request.

However, should FDA determine that it must include each and every method on a product-by-product or company-by-company basis in the final regulation, the following is a brief description of the validated method being submitted by the companies with this comment.

Validated Method Summary

Total free plant sterols and stanols in Altus' final products are determined by gas-liquid chromatography (GC). The method was developed and validated by the Quaker Oats Company analytical laboratories based on methods used by Novartis. Aliquots of cereals, bars or beverages are extracted with toluene and water. Cereals and bars are ground before sampling. The toluene phases are separated, combined, evaporated, dissolved in pyridine and silylated. The samples are then analyzed by GC with flame ionization detection. Validation studies show that the method is specific, accurate, linear, precise, rugged and stable for the analysis of total sterols and stanols in bars, cereals, and fruit based beverages (validation summary and method attached).

2. The Final Regulation Should Not Specify Food Formats.

Novartis and Altus strongly advise against adoption of a final regulation that lists food formats eligible to bear the plant sterols/stanols health claim. As numerous companies commented in November, it is not necessary for FDA to take on the added burden of defining which food formats can bear the claim, with the result being an amended rule every time a company seeks to add phytosterols to a new food format.

Throughout the Preamble to the Interim Final Rule, FDA reiterated that there may be other food products where the use of either plant sterol esters or stanol esters would be safe and lawful, provided there was a valid analytical method that would permit accurate determination of the amount of plant sterols/stanols in the food. Because the petitioners who originally sought approval of this health claim specified only particular food formats and provided relevant analytical methodology for those food formats, FDA felt constrained to draft the regulation accordingly.

However, it is Novartis' and Altus' and many other commenters' position that the regulation does not need to be so restrictive. The prevailing comment is that the Interim Final Rule should be expanded to cover a wider variety of foods that could allow for more consumer options and greater consumer benefit from phytosterol products. Indeed, studies reviewed by the agency clearly show that phytosterols can be delivered in a variety of different food formats, and

that there is adequate analytical methodology to test for the presence of those phytosterols in the various food formats.

FDA has stated in the preamble to the Interim Final Rule that:

> the plant sterols (esterified or free) were tested in either a spread, margarine, or butter carrier and produced fairly consistent results regardless of the food carrier and apparent differences in processing techniques.

With respect to plant stanol esters, FDA said the following:

> plant stanol esters were tested in either a spread, margarine, butter, mayonnaise or shortening carrier and produced fairly consistent results regardless of the food carrier and apparent differences in processing technologies. Given the variability of amounts and food carriers in which plant stanol esters were provided in the diet studied, the response of blood cholesterol lowering appears to be consistent and substantial.
>
> 65 Fed. Reg. 54701.

FDA's determination, in opening up the stanol segment of the regulation to dietary supplements and snack bars, confirms the position that phytosterols can be delivered in a number of food matrices which are equally effective. Any unnecessary and unjustified restrictions to food categories would create the appearance of health claims for individual companies and would be a disincentive for companies interested in developing a variety of healthy foods delivering phytosterols.

In conclusion, Novartis and Altus respectively submit that FDA, in finalizing the Interim Final Rule on Plant Sterol/Stanol Esters and Coronary Heart Disease, do the following:

1. Recognize that free sterols/stanols are the active phytosterol substances in cholesterol reduction and should be the basis for the health claim regulation;

2. Recognize that tall oils are an appropriate source for sterols as acknowledged in the Interim Final Rule for stanols; and,

3. 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.

4. Permit industry to develop a standardized appropriate general analytical methodology for all products containing phytosterols, and recognize that the regulation must not limit the claim to only specific food formats.

Thank you for considering these additional comments.

Respectfully submitted,

NOVARTIS CONSUMER HEALTH, INC.
Judith Weinstein, Esq.

ALTUS FOOD COMPANY
Fred Shinnick, Ph.D.

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By _____
J. Scott Bass

DETERMINATION OF STEROLS AND STANOLS IN FOOD PRODUCTS

METHOD VALIDATION REPORT

QUAKER OATS STANDARD ANALYTICAL METHOD 210

January 18, 2001

Identity of compounds of Phytosterol:

There are two major sterols and two major stanols in Reducol, the phytosterol mixture used in Altus Food Company products. They are:

Campesterol
Campestanol
β-Sitosterol
Sitostanol

The identity of these compounds was confirmed by several procedures.

1) Campesterol and β-sitosterol are available commercially. These standards were used for identification.
2) A reference mixture of four sterols from Novartis was also used to confirm the identity of the peaks. Chromatograms of the reference mixture and beverage analyzed by Novartis were received and compared with the current work.

Method Summary

Principle: Quaker Method # 210 determines free sterols and stanols in food products by gas-liquid chromatography (GC). Free stanols and sterols are extracted from samples with toluene. Toluene is evaporated and the free stanols and sterols are silylated with BSTFA [N,O-Bis(trimethylsilyl)trifluoroacetamide] in pyridine. Silylated sterols and stanols are analyzed by gas-liquid chromatography.

Brief Procedure: Sample corresponding to 15 mg phytosterols is weighed into an Erlenmeyer flask. Four (4) mL of an internal stock standard solution (IS-S) containing 13 mg of 5-α-cholestane are pipetted into the sample. Fifty (50) ml of toluene and 50 ml distilled water are added to the flask. The flask is closed with a stopper and stirred (magnetic stirrer) for 15 minutes. The mixture is transferred quantitatively into a separatory funnel. The flask is washed with few mL of toluene and which is also transferred to the separatory funnel. The aqueous phase is separated and reextracted as before in a second separatory funnel containing 40 mL toluene. The aqueous layer is rejected. The toluene layers are combined in the first separatory funnel, the second separatory funnel is washed with few mL of toluene and this washing also transferred into the first separatory funnel. The unified toluene layers are washed at least twice with 20 ml distilled water and at least once with 20 ml sodium chloride solution (saturated). The toluene extracts are quantitatively transferred through a filter containing about 10 grams of sodium sulfate and into a 250 mL round bottom flask. The separatory funnel and the sodium sulfate are washed with small quantities of toluene. The toluene is evaporated to dryness under nitrogen on a steam bath.

The dry residue is dissolved in 3 mL pyridine and transferred with small quantities (3 x 1 ml) of toluene quantitatively into a 10 mL reaction vial. BSTFA, 600 µl, is added, the reaction vial closed tightly and warmed to 90 °C for 1 hour. The vial is cooled to room temperature and the solution transferred quantitatively with small portions of toluene into a 25 mL volumetric flask and diluted to volume with toluene.

$$\text{g phytosterols / 100 g} = \frac{\text{int. std. wt} \times \Sigma A_S}{\text{sample wt} \times A_{std} \times 10}$$

int. std. wt = Weight of internal standard, mg
ΣA_S = Sum of peak areas of the sterols and stanols in sample solution
sample wt = Weight of sample, g

A_{std} = Area of the internal standard peak
10 = Conversion factor to percent (i.e., g /100 g)

Specificity:

Representative base (placebo) formulations of bar, cereal and beverage were analyzed using the method. There are no significant levels of interference from the bar, beverage and cereal matrices as shown in table 1.

Table 1: Base Matrix Analysis:

Base Matrix	Phytosterols
Bar (# 2000120259)	0.01%
Beverage (# 2000120249)	No Detectable Levels Present
Cereal – Clusters (# 2001010048)	0.002%
Cereal – Flakes (# 2001010049)	0.008%

The method is specific for the determination of phytosterols in bars, beverages and cereals.

Accuracy:

Method # 210 to determine the total sterols and stanols in various food matrices is accurate as confirmed by spike recovery studies. Known amounts of the phytosterol reference mixture at 50%, 100% and 150% of the formulation target were added to matrix blanks. The phytosterol content of this reference mixture was determined prior to conducting these spike recovery studies.

This reference mixture delivers about 0.6 gram phytosterols/ serving. The serving size of bar and cereal is 40 gram and for beverage it is 240 gram. The cereal this is made up of clusters and flakes. Phytosterols added to the clusters only which make up about 25% of the final product. Hence for spike recovery studies, phytosterol was added to cluster base matrix. Phytosterol was added at the same level to flakes to establish any effect flakes may have on the recovery of phytosterols from clusters in the final mixed product.

Table 2: Percent of Phytosterol Reference Mixture Added to Various Products

Spiking Levels	Bars	Beverage	Cereal Clusters	Cereal Flakes
50% Spike	0.75%	0.13%	3.0%	3.0%
100% Spike	1.5 %	0.25%	6.0%	6.0%
150% Spike	2.25%	0.38%	9.0%	9.0%

Table 3: Phytosterol Recovery from Various Food Matrices

Product	50% Spike - % Recovery	100% Spike - % Recovery	150% Spike - % Recovery
Bar	102.4	100.0	97.7
Beverage	94.0	97.7	97.7
Cereal Clusters	99.6	98.9	98.8
Cereal Flakes	101.5	96.8	99.7

Linearity:

The total of sterols and stanols is linear in the studied food products (bar, beverage and cereal) containing 50 – 150% of the formulation levels of phytosterols. Linearity of the analytical method for all three products was determined by performing linear regression analysis of the assayed total phytosterol concentration and the theoretical phytosterol concentration. Regression Parameters are tabulated below:

Table 4: Results of Regression Analysis

Product	Slope	Intercept	R^2
Bar	0.953	0.6049	0.9998
Beverage	0.9954	-0.3824	0.9999
Cereal Clusters	0.9863	0.0679	1.000
Cereal Flakes	0.9877	0.0395	0.9984

Precision:

Method # 210 has a high degree of precision as determined by %RSD (Table 5).

Method precision was determined by conducting replicate analyses of a beverage sample containing phytosterols.

Assays in this context are independent analyses of samples that have been carried through the complete analytical procedure from sample preparation to final result.

Table 5 : Precision of the Method # 210

Analyte	Replicate Analysis of Beverage Sample					Mean	%RSD
	1	2	3	4	5		
Phytosterol (mg/serving)*	506.4	504.0	492.0	513.6	505.9	505.9	1.8

*Serving Size of Beverage is 240 grams.

Ruggedness:

Inter-analysts data in Table 6 show that method # 210 is rugged.
Method ruggedness was determined by comparing the results obtained by two different analysts. The absolute percent difference between two analysts is 1.0%.

Assays in this context are independent analyses of samples that have been carried through the complete analytical procedure from sample preparation to final result.

Table 6 : Method Ruggedness

Analyst 1:

Analyte	Replicate Analysis of Beverage Sample					Mean	%RSD
	1	2	3	4	5		
Phytosterol (mg/serving)	506.4	504.0	492.0	513.6	505.9	505.9	1.8

Analyst 2:

Analyte	Replicate Analysis of Beverage Sample					Mean	%RSD
	1	2	3	4	5		
Phytosterol (mg/serving)	506.4	501.6	501.6	492.0	501.6	500.6	1.1

Mean of Analyst 1: 505.9 mg/serving Phytosterol
Mean of Analyst 2: 500.6 mg/serving Phytosterol
Percent Difference: 1.0

Stability:

Final GC preparations of the 100% spiked sample solutions were analyzed initially and the same preparation reanalyzed after 24 and 48 hours. Data in Table 7 shows that the GC preparations are stable at room temperature for at least 48 hours.

Table 7: Stability of Phytosterol in Final GC Sample Preparations

Solution Analyzed	mg of Phytosterol in Solutions		
	0	24 hrs	48 hrs
Beverage	15.05	14.94	15.03
Bar	15.40	15.44	15.45
Cereal Clusters	14.90	14.95	15.17
Cereal Flakes	15.23	15.29	15.28

QUAKER

COMPUTER CODE: PHYSTGC **STANDARD METHOD NO. 210**

THE QUAKER OATS COMPANY
RESEARCH LABORATORIES
BARRINGTON, ILLINOIS

Original: **January 05, 2001**
Revised:
Effective: **January 05, 2001**

DETERMINATION OF STEROLS AND STANOLS IN FOODS BY GC

INTRODUCTION

This method quantitatively determines β-sitosterol, campesterol, sitostanol and campestanol in food products by GC. The products analyzed by this method are food bars, beverages and ready-to-eat cereals. This method has been validated for all these products. Accuracy of this method as determined by spike recovery studies is between 94.0 – 102.0%. The precision as determined by percent RSD is better than 2.0%.

PRINCIPLE:

This method determines free sterols and stanols in food products by GC. Free stanols and sterols are extracted from samples with toluene. Toluene is evaporated and the free stanols and sterols are silylated with BSTFA [N,O-Bis(trimethylsilyl)trifluoroacetamide] in pyridine. The silylated sterols and stanols are determined by GC using 5-α-cholestane as an internal standard.

SCOPE:

This method has been validated for food products Bars, Beverages, Cereal Clusters and Cereal Flakes.

APPARATUS

1. Gas Chromatograph (GC) equipped with flame ionization detector, an autosampler and data system.
2. Chromatographic column: DB-5, 30 m length X 0.25 mm i.d. X .25 μm film thickness (HP cat # 122-5032) or equivalent.
3. GC Liners: split/splitless glass wool deactivated, 990 (L volume, (HP cat # 19251-60540) or equivalent
4. Autosampler vials / caps, Hewlett Packard or equivalent.
5. Volumetric flasks, Erlenmeyer flasks and pipettes.
6. Separatory funnels, 250 mL with stopcock.
7. 10 ml reaction vial.
8. Heat block: (VWR cat # 13259-005) or equivalent.
9. Standard laboratory equipment.

REAGENTS

Unless otherwise specified, the term water in this method means either distilled or deionized water.

1. Standard, 5-α-Cholestane (internal standard), Reagent, Sigma Chemical, cat # C-8003 (CAS # [481-21-0]). Store in desiccator when not in use.
2. Phytrol, production reference mixture containing β-sitosterol, campesterol, sitostanol and campestanol from Novartis. Store in desiccator when not in use.
3. Standard, β-Sitosterol, Sigma Chemical, cat # S 1270 (CAS # 83-46-5). Store in freezer.
4. Standard, Campesterol, Sigma Chemical, cat # C5157 (CAS # 474-62-4). Store in freezer.
5. Standard, Stigmastanol (Sitostanol), Sigma Chemical, cat # S 4297 (CAS # 19466-47-8). Store in desiccator when not in use.
5. Standard, Campestanol is not available commercially.
6. BSTFA [N,O-bis(trimethylsilyl)trifluoroacetamide], Pierce, cat #3883022 (CAS # [25561-30-2]) Store refrigerator in a desiccator when not in use. CAUTION: FLAMMABLE. HARMFUL BY INHALATION. IRRITATING TO THE EYES, RESPIRATORY SYSTEM AND SKIN.
7. Toluene, Reagent grade. CAUTION: HIGHLY FLAMMABLE. HARMFUL BY INHALATION.
8. Pyridine, Reagent grade, low water content, (CAS # [110-86-1]). CAUTION: HIGHLY FLAMABLE. HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
9. Sodium Sulfate, anhydrous, analytical reagent.
10. Sodium Chloride, reagent grade.
11. Sodium Chloride (saturated) Solution (1:1): Add 500 gm. to 500 mL water. Mix thoroughly.

SAFETY PRECAUTIONS:

USE PROPER GLOVES AND FUME HOODS WHEN WORKING WITH ORGANIC SOLVENTS. AVOID SKIN AND EYE CONTACT WITH ORGANIC SOLVENTS. ALL HEATING STEPS SHOULD BE PERFORMED IN THE HOOD USING PYREX GLASSWARE. USE STANDARD LABORATORY SAFETY PRECAUTION. FOR ADDITIONAL SAFETY PRECAUTIONS REGARDING A PARTICULAR REAGENT, CONSULT A MATERIAL SAFETY DATA SHEET (MSDS).

INSTRUMENT PARAMETERS:

Injector Temperature:	240°C
Detector (FID) Temperature:	340°C
Column Inlet Pressure:	21.2 psi @ 230°C
Helium Carrier Gas Flow:	1.0 mL / min.
Carrier Flow Mode:	Constant Flow On
Split Ratio:	Splitless
Column Temperature:	Gradient Program
	Initial Temperature, 230°C
	Initial Hold Time, 1.0 min.
	Rate, 3°C / min.
	Final Temperature, 300°C
	Final Hold Time, 6.0 min.
	Total GC Analysis Time Per Sample, 30.3 min.
Injection Volume:	1.0 µL
Integration:	Peak Area

These conditions may be modified to obtain a separation equivalent to that shown on the standard and sample chromatograms for Phytrol Ref. and samples figures.

PROCEDURE

I. STANDARD PREPARATION:

1. Weigh 0.2600gm. ± 0.0002gm. 5-α-cholestane (internal std) into 100mL volumetric (2.6mg/mL), and make it up to volume with toluene. This is ISTD-1 stock solution for analyses of all food products.
2. Weigh 0.3250gm. ± 0.0002gm. 5-α-cholestane (internal std.) into 50mL volumetric (6.5mg/mL), make it up to volume with pyridine. This is the ISTD-2 stock solution for analyses of the phytrol production reference mixture.

Stock standard solution can be kept in refrigerator for up to 3 months. Let the stock standard solution come to room temperature prior to use.

II. SAMPLE PREPARATION

(A) PRODUCTION REFERENCE MIXTURE

1. For Phytrol production reference mixture weigh 0.35 g ± 0.1 mg into a 50 mL volumetric flask and make it up to volume with pyridine. This is the stock solution.
1. Pipette 2 mL of the stock solution and 2 mL of the stock internal standard solution (ISTD-2) in to a 10 mL reaction vial.
2. Add 600 µL of BSTFA, close the reaction vial tightly and warm to 90 °C for 1 hour.
3. Cool to room temperature and transfer the solution quantitatively with small portions of toluene into a 25 ml volumetric flask. Dilute to volume with toluene.

(B) FOOD PRODUCTS

4. Weigh an amount of sample corresponding to 15 mg phytrol in an Erlenmeyer flask (250 mL). Sample weights for products tested are::

Product / g Phytrol per serving size	Sample Wt.
Bars / 0.6 per 40 g	1 ± 0.005 g
Beverages / 0.6 per 240 g	6 ± 0.005 g
Ccreal / 0.6 per 40 g	1 ± 0.005 g

2. Pipette 5 mL. of stock internal standard (ISTD-1) to Erlenmeyer flask with sample.
3. With a graduate cylinder add approximately 50mL toluene and 50mL water to the flasks.
4. Stopper and stir (magnetic stirrer) for 15 min.
5. Transfer the mixture quantitatively into a separatory funnel. Wash the Erlenmeyer flask with few mL of toluene and transfer to the separatory funnel.
6. Allow the layers to separate and reextract the aqueous phase in a second separatory funnel containing 40 mL toluene, discard the aqueous (lower) layer.
7. Unify the toluene layers in the first separatory funnel and wash the second separatory funnel with few mL of toluene and transfer these washings also in to the first separatory funnel.
8. Wash the unified toluene layers with 20 ml distilled water, allow the layers to separate, discard the aqueous (lower) layer.
9. Repeat step 8 at least one more time.
10. Wash the unified toluene layers with 20 ml sodium chloride solution (saturated), allow the layers to separate, discard the aqueous (lower) layer. Repeat if emulsion remains.
11. Swirl to force water down, discard all traces of water.
12. Quantitatively transfer the toluene extract to a funnel containing filter paper and about 10 grams of sodium sulfate and into a 250 mL boiling flask. Rinse stopper, separatory funnel and the sodium sulfate with small quantities of toluene.

13. Evaporate to dryness under nitrogen on a steam bath..
14. Dissolve the dry residue in 3 ml pyridine and transfer the solution with small quantities (3 x 1 ml) of toluene quantitatively into a 10 ml reaction vial.
15. Add 600 µL of BSTFA, close the reaction vial tightly and warm to 90 °C for 1 hour.
16. Cool to room temperature and transfer the solution quantitatively with small portions of toluene into a 25 ml volumetric flask. Dilute to volume with toluene.

III. ANALYSIS:

1. Set up the GC system using the operating conditions in the instrument parameter section. Initialize the method file for the GC and data systems and allow the baseline to stabilize.
2. Inject the standard solutions for peak identification.
3. Inject the phytrol production reference mixture into the GC.
4. Inject the sample solutions twice into the GC.
5. Examine the chromatograms to make sure the peaks of interest are being identified and integrated correctly and consistently. Average the peak area results of at least two acceptable injections of each sample solutions.

CALCULATIONS:

$$\text{g Phytosterols / 100 g} = \frac{\text{int. std. wt} \times \Sigma A_S}{\text{sample wt} \times A_{std} \times 10}$$

int. std. wt	= Weight of internal standard, mg
ΣA_S	= Sum of peak areas of the sterols and stanols in sample solution
sample wt	= Weight of sample, g
A_{std}	= Area of the internal standard peak
10	= Conversion factor to percent (i.e., g /100 g)

STATISTICAL EVALUATION:

Typical precision of the method is <2.0% RSD.

REFERENCES:

1) Quaker Lab Notebook No. NV0044 #5
2) 210 Notes
3) Novartis Nutrition Research AG Analytical Services Method
4) Sterol Content in Saw Palmetto by Gas Chromatography, INA Methods Validation Program.

REASONS FOR REVISION:

New Method

ATTACHED FIGURES:

Figure 1: Typical chromatogram of standard (sitosterol & campesterol & sitostanol)
Figure 2: Typical chromatogram of Reference Mixture
Figure 3: Typical chromatogram of Bar
Figure 4: Typical chromatogram of Beverage
Figure 5: Typical chromatogram of Cereal Clusters
Figure 6: GC Print out of the method

SIGNATURES

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