Final

Request for scientific evaluation of "Substantial Equivalence" for Cargill, Incorporated phytosterols/phytostanols intended to be used in specified foods

With a view to support a notification under the procedure laid down in Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients

August 13, 2004

Principal Contact:
Fred L. Shinnick, Ph.D.
Manager, Regulatory & Scientific Affairs
Cargill, Incorporated
Health & Food Technologies
15407 McGinty Rd. W. MS110
Wayzata, MN 55391
USA

Telephone +1 952-742-4517
Fax +1 952-742-7573
fred_shinnick@cargill.com

Final

Request for scientific evaluation of "Substantial Equivalence" for Cargill phytosterols/phytostanols intended to be used in specified foods, with a view to support a notification under the procedure laid down in Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients

Table of Contents

List of Tables

List of Appendices

Final

Request for scientific evaluation of "Substantial Equivalence" for Cargill phytosterols/phytostanols intended to be used in specified foods, with a view to support a notification under the procedure laid down in Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients

1. Background to "Substantial Equivalence"

Regulation No 258/97[1] covers a number of classes of foods and food ingredients that have not been exposed to a significant degree to the EU population prior to May 1997.

However, Article 3 (4) states "By way of derogation from paragraph 2 (which refers to sections on the full application procedure), the procedure laid down in Article 5 shall apply to foods or food ingredients referred to in Article 1 (2) (b) (d) and (e) which, on the basis of the scientific evidence available and generally recognized or on the basis of an opinion delivered by one of the competent bodies (Member State) are substantially equivalent to existing foods as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained within."

Article 5 states "…the applicant shall notify the Commission of the placing on the market when he does so. Such notification shall be accompanied by the relevant details provided for in Article 3 (4). The Commission shall forward to Member States a copy of that notification within 60 days and, at the request of a Member State, a copy of the relevant details."

2. Introduction

Commission Decision 2004/334/EC of 31 March 2004 authorising the placing on the market of yellow fat spreads, milk type products, yoghurt type products, and spicy sauces with added phytosterols/phytostanols as novel foods or novel food ingredients under Regulation (EC) No 258/97 of the European Parliament and of the Council[2] has recently been addressed to Pharmaconsult Oy Ltd (formerly Multibene Health Oy Ltd) or "Pharmaconsult". Whilst the latter company had originally applied for the use of specific tall oil phytosterols/phytostanols, the approval decision itself took into consideration the Scientific Committee on Food (SCF) Opinion on Applications for Approval of a Variety of Plant Sterol-Enriched Foods (expressed on 5 March 2003)[13]. Consequently, a generalised specification for phytosterol/phytostanol products has now been adopted for Pharmaconsult, and indeed all new phytosterol/phytostanol product approvals[4,5,6] based on the recommendations of this Opinion. This generalised specification does not specify the source of the phytosterols/phytostanols.

3. Objective

It is the understanding of Cargill, Incorporated ("Cargill") that foods as mentioned under part 7 (intended uses) in which the phytosterols/phytostanols of Cargill would be added meet the condition of substantial equivalence defined in article " (4) of Regulation *(EC) No 258/97* above mentioned, on the following grounds:
1/ the food categories in which the phytosterols/phytostanols of Cargill are to be used are the same food categories in which phytosterols/phytostanols have been so far permitted by the decisions of the Commission Nr 2004/333 to 2004/336.
2/ the phytosterols/phytostanols ingredient of Cargill is substantially equivalent to the phytosterols/phytostanols ingredients permitted by the decisions of the Commission Nr

2004/333 to 2004/336, in particular, but not exclusively, to the phytosterols/phytostanols ingredient of Pharmaconsult.

The opinion of the Novel Food Expert Committee of Finland is sought in accordance with Article 3(4) of regulation 258/97/EEC. According to this article, an opinion of a national competent body should support notifications based on substantial equivalence.
The opinion of the Finnish competent body will be used to support notification to be made either by Cargill, on its own name or for the benefit of its future customers, or to support notifications by its customers.

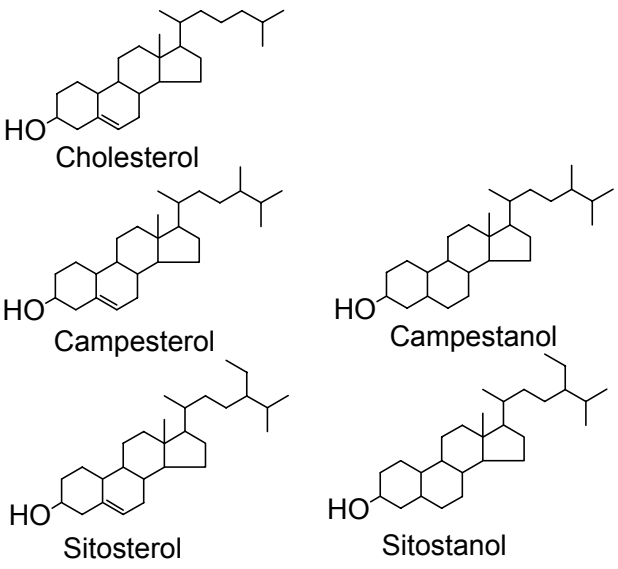
Consequently, we will provide a comparison between the ingredient of Cargill and its intended uses, and submissions previously approved, in particular the application of Pharmaconsult for the following parameters:

Section 4. Composition
Section 5. Nutritional Value
Section 6. Metabolism
Section 7. Intended Use
Section 8. Level of Undesirable Substances

4. Comparison of Composition

4.1 Molecular Structure

The structures of the major plant sterols derived from tall oil and cholesterol are shown below:



4.2 Source Material

Cargill phytosterols/phytostanols are derived from tall oil soap. Annex 2 of Decisions 2004/333[4], 2004/334[2], 2004/335[5] and 2004/336[6] states "Phytosterols/phytostanols are sterols and stanols that are extracted from plants and may be presented as free sterols and stanols or esterified with food grade fatty acids".

The ingredient of Pharmaconsult, as well as the ingredient of Teriaka, are also derived from tall oil soap.

4.3 Extraction/Refining/Purification Process

Volatile compounds are first removed by fractional distillation. The resulting tall oil pitch is treated with alkali to hydrolyze the phytosterol esters present. The resulting material is subjected to two-stage distillation. The distillate is then dissolved in methanol/ methylethylketone and the phytosterol crystals produced are recovered by filtration, washed with solvent and dried.

This process is in substance the same as used by Pharmaconsult (description in the SCF opinion of 4 April 2003):
Wood extractives from wood chips (pine, spruce and birch) are dissolved into the heated alkaline liquor as a soap fraction. Neutral components (unsaponifiables as sterols) are separated from the soap (fatty- and resin acid soaps) by liquid extraction. Sterols are separated by crystallization from other neutral components; the sterol crystals are collected by centrifugation and washed. After a second purification step with pure solvent the formed crystals are filtered and the product dried in a vacuum drier and packed in drums.

4.4 Specification

Annex 2 of Decisions 2004/333[4], 2004/334[2], 2004/335[5] and 2004/336[6] defines the "Specifications of phytosterols and phytostanols for the additions to foods and food ingredients". This specification is reproduced in column 2 of Table 1 below and compared to specifications for the Cargill ingredient.

The ingredient of Cargill shall meet the EU specifications as defined in decisions 2004/333 to 336.

Table 1 Comparison of EU *vs.* Cargill *vs.* Pharmaconsult Oy Ltd (Multibene) specifications for phytosterols/phytostanols for the addition to foods and food ingredients

Composition (with GC-FID or equivalent method)	**EU requirements[2,4,5,6]**	**Cargill Phytosterols/phytostanols specification**
β-sitosterol (%)	<80	<80%
β-sitostanol (%)	<93	<15%
Campesterol (%)	<40	<15%
Campestanol (%)	<35	<5%
Stigmasterol (%)	<30	<30
Brassicasterol (%)	<3	<3
Other sterols/stanols (%)	<3	<3%
Total sterols (%)	>99	>99%

Analysis results shown in Table 2 below compare the composition of four lots of Cargill phytosterols/phytostanols to the specifications submitted by Pharmaconsult to the Finnish competent authority. These data demonstrate that the composition of the product from the Cargill manufacturing process is consistent with EU requirements and substantially equivalent to the approved Pharmaconsult tall oil ingredient.

Table 2 Comparison of batch analysis results of Cargill phytosterol and phytostanols to EU specifications for phytosterols/phytostanols for the addition to foods and food ingredients

Composition (with GC-FID or equivalent method)	Specification submitted by Pharmaconsult in its initial submission to the Finnish Competent Authority (24 Sept 2001)	Cargill Batch P1180 9304	Cargill Batch P1190 9604	Cargill Batch P1200 9904	Cargill Batch P1211 0204
β-sitosterol (%)	75-80%	79.1	79.2	79.3	79.1
β-sitostanol (%)	10-14	9.2	9.1	9.1	9.3
Campesterol (%)	6-10	7.0	7.0	7.0	7.0
Campestanol (%)	0-2	1.08	1.07	1.08	1.09
Stigmasterol (%)	<30	0.8	0.8	0.8	0.8
Brassicasterol (%)	<3	0.03	0.04	0.03	0.04
Other sterols/stanols (%)	0-2.5	2.12	2.06	2.05	2.08
Total sterols (%)	>95	99.4	99.3	99.4	99.4

5. Nutritional Value

The SCF *Opinion on the general view on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on ß-carotene of 26 September 2002*[3] indicated that there was no evidence of additional benefit at intakes greater than 3 g/day of phytosterols/phytostanols. Further, it was stated that high intakes might induce undesirable effects and that it was therefore prudent to avoid plant sterol intakes exceeding 3 g/day. Furthermore, the SCF, in its opinion on Pharmaconsult (as Multibene) for approval of plant sterol-enriched foods of 4 April 2003[7] concluded that the addition of phytosterols is safe, provided that the daily consumption does not exceed 3 g.

The above consideration would apply equally to Cargill phytosterols/phytostanols and products made thereof.

6. Proposed Labelling

Labelling will be consistent with *Commission Regulation (EC) No 608/2004 of 31 March 2004 concerning the labelling of foods and food ingredients with added phytosterols, phytosterol esters, phytostanols and/or phytostanol esters*[8].

This regulation ensures that consumers receive the necessary information in order to avoid excessive intake of additional phytosterols/phytostanols and that appropriate communication shall be made that the product is intended exclusively for people who want to lower their blood cholesterol level.

7. Intended Use

The intended uses that Cargill requests are as in decisions 2004/333-336/EC:

- Yellow fat spreads, as defined by Council Regulation (EC) No 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat.
- Salad dressings including mayonnaise (in single portions).
- Milk type products such as semi skimmed and skimmed milk type products, possibly with the addition of fruits and /or cereals, fermented milk type products such as yoghurt, soya drinks, and cheese type products (fat content $\leq$12 g per 100 g), where the milk fat and/or protein has been partly or fully replaced by vegetable fat or protein.
- Milk-based fruit drinks
- Spicy sauces (in single portions).

Yellow-fat spreads, milk type products , yoghurt-type products and spicy sauces were approved under decision 2004/334[2]. In addition, other applications for Milk-based fruit drinks, salad dressings, soya drinks and cheese-type products using the same phytosterol specifications as those for 2004/334 have been approved under decisions 2004/333/EC[4] and 2004/336/EC[6]

Decisions 2004/333-336/EC do not specify the source of the approved phytosterols. Nonetheless, phytosterols used must meet the generalized specifications in Annex 2 of the decisions. Approval of manufacturers other than Pharmaconsult (as Multibene) for the manufacture of the type of products approved in decisions 2004/333-336/EC will not increase individual exposure to phytosterols since consumers can only substitute one brand for another, not add a different food to their diets.

The presentation of the products shall be as prescribed in article 2 of the decisions 2004/33-336/EC, i.e.:

- The products shall be presented in such a manner that they can be easily divided into portions that contain either a maximum of 3 g (in case of one portion per day) or a maximum of 1 g (in case of three portions per day) of added phytosterols/ phytostanols.
- Spicy sauces and salad dressings shall be packed as single portions.
- The amount of phytosterols/phytostanols added to a container of beverages shall not exceed 3 g.

8. Levels of Undesirable Substances

Whilst the levels of undesirable substances (contaminants) are not included in the approved specification for Pharmaconsult (Multibene) it is important to show that levels in Cargill's tall oil phytosterols are acceptable to EU standards and comparable with existing approved materials. Table 3. below compares levels of undesirable substances for Cargill phytosterols/phytostanols to those reviewed by the Scientific Committee for Food for Pharmaconsult (Multibene). Full test reports can be seen within Appendix 1.

Table 3 Comparison of levels of undesirable substances for Cargill phytosterol and phytostanols to those Multibene (Pharmaconsult Oy Ltd)(additional documentation to be provided in final submission)

Undesirable Substance	Multibene SCF Opinion[7]	Cargill Batch P1180 9304	Cargill Batch P1190 9604	Cargill Batch P1200 9904	Cargill Batch P1211 0204
Heavy metals (ppm)	<20	<0.07	<0.07	<0.07	<0.07
PAH (ppb)					
Acenaphthylene	<150	<0.07	<0.07	<0.07	<0.07
Acenaphthene	NR	0.68	0.84	0.89	0.66
Fluorene	NR	0.90	1.25	1.46	0.87
Phenanthrene	NR	4.24	4.91	5.04	4.39
Anthracene	NR	0.12	0.17	0.13	0.14
Fluoranthene	NR	0.50	0.49	0.62	0.56
Pyrene	<30	0.26	0.23	0.32	0.24
Benzo[g,h,l]perylene	NR	0.18	ND	0.14	0.21
Methanol (ppm)	5000	48.7	434.9	443.3	64.2

ND=not determined NR=not reported (13 PAHs other than acenaphthylene, naphthalene, and pyrene were each reported to be less than 1-10 ppm)

Detected PAHs were below those specifically reported by PharmaConsult. Significant levels of pesticides, dioxins, furans, ethanol and heptane were not detected in any of the lots. The Cargill phytosterols meet all EU requirements for undesirable substances.

[1] OJ L 43, 14.2.1997, p.0001 – 0006
[2] OJ L 105, 14.4.2004, p.0043 - 0045
[1] http://www.europa.eu.int/comm/food/fs/sc/scf/out174_en.pdf
[3] http://www.europa.eu.int/comm/food/fs/sc/scf/out143_en.pdf
[4] OJ L 105, 14.4.2004, p.0043 - 0045
[5] OJ L 105, 14.4.2004, p.0046 - 0048
[6] OJ L 105, 14.4.2004, p.0049 – 0051
http://www.efsa.eu.int/science/nda/nda_opinions/216/opinion_nda_01_en1.pdf
[7] http://www.europa.eu.int/comm/food/fs/sc/scf/out191_en.pdf
[8] OJ L 97, 1.4.2004, p. 0044 – 0045