DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

AUG 24 1999

Date

0982 '99 SEP -7 A9:30

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Plant stanol fatty acid esters
Firm:	McNeil Consumer Healthcare
Date Received by FDA:	August 20, 1999
90-day Date:	November 2, 1999

In accordance with the requirements of section 413(a)(2) 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 number 95S-0316 after November 2, 1999

Robert J. Moore, Ph.D.

95S-0316

RPT54

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

AUG 24 1999

John C. Young
Director, Regulatory Affairs - Nutritionals
McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, Pennsylvania 19034-2299

Dear Mr. Young:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) dated August 19, 1999, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., plant stanol esters) was received by the Food and Drug Administration (FDA) on August 20, 1999. Your submission will be kept confidential for 90 days from the date of receipt, and after November 2, 1999, your submission 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 questions concerning this matter.

Sincerely,

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
Division of Programs and Enforcement Policy
Office of Special Nutritionals

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

0980 '99 SEP -7 A9:29

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

AUG 19 1999

RECEIVED 8/20/99

RE: New Dietary Ingredient Notification

Dear Sir or Madam:

McNeil Consumer Healthcare ("McNeil") submits the attached information to the Food and Drug Administration, pursuant to the provisions of Section 413(a) of Federal Food, Drug and Cosmetic Act, in anticipation of its marketing of a dietary supplement form which contains the new dietary ingredient plant stanol esters. McNeil intends to incorporate the ingredient plant stanol esters into a dietary supplement form by encapsulating it into a gelatin capsule.

On February 18, 1999, McNeil submitted to the Agency, in a format provided in proposed regulation 21 CFR 170.36 [62 FR 18938, Substances Generally Recognized as Safe (GRAS)], a summary of plant stanol ester information for use as an ingredient in food. That submission, now included in Food Master File 000626, informed the Agency of McNeil's conclusion that plant stanol esters are generally recognized as safe (GRAS) for use in food at a level of 1.7g of plant stanol esters per serving of food.

The Food and Drug Administration responded to the summary on May 17, 1999 that, at that time and based upon their evaluation of the submission and other available data, there were no questions regarding McNeil's conclusion that plant stanol esters are GRAS under the intended conditions of use. That finding, together with the scientific information relied upon and cited in that submission, forms the scientific basis on which McNeil has concluded that the stanol esters dietary supplement is safe. This conclusion meets and exceeds the statutory requirement established under section 413(a)(2) of the Federal Food, Drug and Cosmetic Act that the dietary supplement will "...reasonably be expected to be safe."

This submission is made under section 413 of the Federal Food, Drug and Cosmetic Act; therefore, we request that it be accorded the 90 day confidentiality provisions relating to public notice. McNeil further considers some of the information contained in this notification relating unpublished studies to be trade secret or confidential commercial information and, therefore, protected from public disclosure. Such information has been stamped "CONFIDENTIAL."

If you have any questions, please do not hesitate to call me at 215/273-7695.

Sincerely
MCNEIL CONSUMER HEALTHCARE

John C. Young
Director, Regulatory Affairs - Nutritionals

attach.

SECTION 1

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 supplement will be:

McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, Pennsylvania 19034

SECTION 2

SECTION 2

The name of the dietary ingredient.

The dietary ingredient is plant stanol esters ("plant stanol fatty acid esters," "stanol esters," "phytostanol fatty acid esters," or "phytostanol esters").

Plant stanol esters are made from a variety of plant sterol sources, including wood-derived oils and vegetable oils. The principal plant stanol esters are mixed fatty acid esters of the 5α-phytostanols, sitostanol and campestanol. Sitostanol[1/] (24-ethylcholestan-3β-ol, CAS No. 19466-47-8) is formed by the hydrogenation of the Δ^5-mono-unsaturated plant sterol, sitosterol (24-ethylcholestan-5-en-3β-ol, CAS No. 83-46-5) and also by the complete hydrogenation of the $\Delta^{5,22}$-di-unsaturated plant sterol, sigmasterol (24-ethylcholest-5,22-dien-3β-ol, CAS No. 83-48-7), hence the alternative name "sigmastanol." Campestanol (24-methycholestan-3β-ol) is formed by the hydrogenation of the Δ^5-mono-unsaturated plant sterol, campesterol (24-methycholest-5-en-3β-ol, CAS No. 474-62-4). Sitostanol and campestanol, in the free form and as their fatty acid esters, also occur naturally in cereal grains such as wheat, rye, corn and other foods that have for many years been part of the human diet in the United States.

After the hydrogenation process has been completed, the mixed plant sterols are converted to the corresponding fully saturated plant stanols (sitosterol and sigmasterol to sitostanol, campesterol to campestanol). The plant stanols are thereafter converted to their fatty acid esters by an interesterification process using food grade esters from vegetable oils.

[1/] Synonyms for sitostanol are β-sitostantol, 5,6-dihydro-β-sitosterol, 24-α-ethylcholestanol, dihydrositosterin, fucostanol, spinastanol, stigmastanol. Sitosterol is often referred to in the scientific literature as β-sitostertol.

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 supplement containing the plant stanol esters dietary ingredient will be in an encapsulated gelatin form. This plant stanol esters softgel product form will be clearly labeled and promoted as a dietary supplement intended for use to reduce the absorption of cholesterol from the gastrointestinal tract. The number of gelatin capsules per serving size will be described on the label and each serving of the dietary supplement will contain 1.7g of plant stanol esters. Label directions will suggest or recommend consumption of up to 3 servings per day, resulting in maximum daily consumption of up to 5g of plant stanol esters. That level of consumption is within the level of dietary exposure considered as 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.

On February 18, 1999, McNeil submitted a summary of plant stanol esters information for use as an ingredient in food. This information formed the basis for McNeil's conclusion that plant stanol esters are safe (GRAS) for use in food when intended for use to reduce the absorption of cholesterol from the gastrointestinal tract.

The Agency responded on May 17, 1999 that, after evaluating the materials, there were no further questions regarding McNeil's conclusion that stanol esters are GRAS for use in food at a level of 1.7g of plant stanol esters per serving of food.

The materials and information submitted in support of the GRAS issue, which have been updated to include information that has become available since the February 18, 1999 submission, together with the response from FDA, form the basis for the opinion that plant stanol esters meet (and exceed) the statutory requirement under section 413(a)(2) that they are "..reasonably expected to be safe..." for use as a dietary supplement.

The information provided in support of McNeil's conclusion of safety are:

- Attachment 1 – The Agency's May 17, 1999 response to McNeil's GRAS submission.

- Attachment 2 – The updated list of scientific articles which form the basis for the opinion of safety. The references listed in **bold** have become available since the February 18, 1999 submission, or have been updated with their current publication status.

- Copies of the listed references are attached and, where appropriate, are stamped "CONFIDENTIAL."

ATTACHMENT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

May 17, 1999

M.M.B.
MAY 24 1999

Vivian A. Chester
Edward B. Nelson, MD, Ph.D.
McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Re: Food Master File 000626

Dear Ms. Chester and Dr. Nelson:

The Food and Drug Administration (FDA) is responding to the summary of information, dated February 18, 1999, that you submitted to FDA. FDA received this summary of information on February 19, 1999, and designated it as Food Master File 000626.

The subject of your submission is plant stanol esters. Your submission informs FDA of McNeil's view that plant stanol esters are generally recognized as safe (GRAS) for use as a nutrient in spread at a level of 1.7 grams of plant stanol esters per serving of spread. According to your submission, plant stanol esters are intended for use as nutrients in food to reduce the absorption of cholesterol from the gastrointestinal tract. The basis for McNeil's view that this use of plant stanol esters is GRAS is through scientific procedures (21 CFR 170.30(b)). The submission states that the determination that plant stanol esters are GRAS has been made through the deliberations of a panel of individuals (Raisio's GRAS panel) who were convened by Raisio Benecol Ltd. McNeil considers the members of Raisio's GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food.

McNeil's submission describes the manufacturing process for plant stanol esters and proposes food grade specifications. According to McNeil, sitostanol and campestanol are the main stanol components of plant stanol esters. These stanols are prepared by the hydrogenation of commercially available plant sterol blends, which are obtained as distillates from vegetable oils and as byproducts of the kraft paper pulping industry. These stanols are transesterified with fatty acid esters that are obtained from food-grade refined, bleached and deodorized vegetable oils, fats, or their blends (e.g., canola oil, sunflower oil, safflower oil, or corn oil). The transesterification of plant stanols improves their solubility in fat and allows them to be properly distributed in the fat phase in the gut prior to digestion.

Based on the use of plant stanol esters in regular and reduced fat spreads at a level of 1.7 gram per 8 gram spread (packaged in single-serving units) or at a level of 1.7 gram per 15 gram spread (packaged in a tub), and the consumption of three servings per day, McNeil estimates that consumer exposure to plant stanol esters would be approximately 5.1 g/person/day, which corresponds to an estimated dietary exposure to plant stanols of approximately 3 g/person/day (i.e., approximately 43 mg/kg body weight/day for a 70 kg adult). McNeil estimates that the current dietary exposure to plant stanols from naturally occurring sources is in the range of 20 to 30 mg/person/day.

McNeil describes published and unpublished absorption, distribution, metabolism, and excretion studies in animals and humans. Based on these studies, which show that 97% or more of stanol esters that are administered to humans is excreted quantitatively and unchanged in feces, McNeil concludes that plant stanol esters are hydrolyzed to free stanols in the gastrointestinal tract, that there is no evidence of further metabolism of the plant stanols that are absorbed, and that plant stanols from the blood and liver are excreted in the bile and eliminated in the feces intact.

McNeil describes published and unpublished human studies that were conducted in support of the safety and efficacy of plant stanols or plant stanol esters in reducing serum cholesterol levels. The populations described in these studies include adults with elevated serum cholesterol levels, adults with normal cholesterol levels, adults with coronary heart disease, adults consuming cholesterol lowering drugs, adults with non-insulin dependent diabetes mellitus, children with elevated cholesterol, and children with normal cholesterol. According to McNeil, approximately 2000 people have consumed plant stanol or plant stanol ester-containing products for periods of up to one year in human studies at ingestion rates that range from 1.2 to 17 grams of plant stanol esters per day, with most studies using an ingestion rate in the range of 3.4 to 5.1 grams of plant stanol esters per day.

McNeil states that no serious adverse events have been reported in either the published or the unpublished human studies and that stanol ester containing products have been well tolerated by the study populations. According to McNeil, extensive clinical laboratory monitoring in subjects fed stanol ester spreads demonstrated no systemic abnormalities related to glycemic control, liver enzymes, or kidney function. McNeil conducted an in-depth follow-up with the clinical investigators to determine the nature and extent of safety data collections and to corroborate the safety conclusions reported in the publications. In addition, McNeil reports that a survey conducted by the government of Finland provides information that almost 140,000 adults in Finland consume commercially available plant stanol ester-containing spread on a daily basis. According to McNeil, the Finnish survey does not identify any association between consumption of plant stanol esters and any health conditions.

The minimal absorption of plant stanol esters, coupled with their lipophilic nature, raises the question of the potential effect of plant stanol esters on the uptake of fat-soluble vitamins (Vitamins A, D, E, and K). McNeil's submission separately addresses the potential effect of plant stanol esters on each of these vitamins. For Vitamins A, D, and E, McNeil describes (1) the results of published and unpublished human studies that included measurements or observations bearing on the potential effect of plant stanol esters on vitamin status; and (2) scientific symposia and other scientific meetings where the results of these human studies were discussed by the scientific community. For Vitamin K, McNeil (1) describes the results of human studies, which

have been discussed at scientific symposia and other scientific meetings, that included measurements or observations bearing on the potential effect of plant stanol esters on Vitamin K status; and (2) reasons that any serious impairment of Vitamin K function would result in readily observable side effects, such as bruising or bleeding, that would have been noticed during studies of the quality and duration of the published human studies. For each of the fat-soluble vitamins, McNeil notes that widespread use of plant stanol esters in Finland for more than three years, with follow-up in the form of a public health survey conducted by the Finnish government, revealed no issues related to vitamin deficiency. Finally, for each of the fat-soluble vitamins, McNeil states that Raisio's GRAS panel assessed the available published and unpublished data and concluded that ingestion of plant stanol esters does not affect vitamin status. McNeil concludes that ingestion of plant stanol esters has not been accompanied by clinically significant changes in fat soluble nutrient status.

McNeil describes a series of recently published animal toxicity tests, including tests for oral toxicity, genotoxicty, developmental toxicity, reproductive toxicity, and potential for estrogenic effects. According to McNeil, the test articles used in these studies included wood-derived mixtures of plant stanol esters and vegetable oil-derived mixtures of plant stanol esters that cover the range of composition of the commercial product. Based on these studies, McNeil draws the following conclusions: (1) Based on a 13-week oral toxicity study in the rat, the no-observed-adverse-effect-level (NOAEL) for plant stanol esters derived either from wood or from vegetable oil corresponds to a daily intake of about 870 mg plant stanol esters per kg body weight in the rat (or approximately 61 grams per day for a 70 kg human); (2) plant stanol esters are not genotoxic; (3) plant stanol esters produced no indication of embryotoxic or teratogenic effects, and had no adverse effects on reproductive performance, at levels corresponding to a daily intake of about 4500 mg plant stanol esters per kg body weight in the rat (or approximately 320 grams per day for a 70 kg human); and (4) plant stanol esters demonstrated no estrogenic effects in a uterotrophic assay in the rat. McNeil also concludes that a carcinogenicity study is not needed for plant stanol esters because of their low absorption, their lack of systemic toxicity, their lack of genotoxicity, and the absence of structural features that are predictive of carcinogenic activity.

FDA has evaluated the information in McNeil's submission as well as other available data and information, including the *Cytellin* file that is available at FDA's Center for Drug Evaluation and Research. In addition, FDA went to the office of ENVIRON Corporation and evaluated certain data and information that were reviewed by Raisio's GRAS panel. Based on its evaluation, the agency has no questions at this time regarding McNeil's conclusion that plant stanol esters are GRAS under the intended conditions of use. Furthermore, FDA is not aware of any scientific evidence that plant stanol esters would be harmful. The agency has not, however, made its own determination regarding the GRAS status of the subject use of plant stanol esters. As always, it is McNeil's continuing responsibility to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

An evaluation that a use of a food ingredient is safe is a time-dependent judgment that is based on general scientific knowledge as well specific data and information about the ingredient. The intended use of plant stanol esters to reduce the absorption of cholesterol from the gastrointestinal tract exemplifies a recent trend in the food industry to develop food ingredients that have a nontraditional function. The evolving scientific knowledge about such ingredients in the context of changing dietary patterns, including long-term nutritional implications, amplifies the time-dependent nature of any safety evaluation. Accordingly, the agency believes that it would be both prudent and responsible for McNeil to continue to monitor, through scientific studies or otherwise, consumers' dietary exposure to plant stanol esters and the long-term nutritional implications for individuals in all age groups who routinely consume the ingredient. In this regard, we were pleased to receive McNeil's letter dated May 12, 1999, which (1) describes McNeil's intent to continue its clinical evaluation of plant stanol esters; (2) describes initiatives to ensure that plant stanol esters are well understood by consumers and healthcare professionals and to evaluate consumer use and understanding regarding plant stanol esters; and (3) states McNeil's commitment to provide FDA with updates on the outcome of these activities, including summaries of safety findings from McNeil's clinical program.

Finally, we have been advised by the Office of Food Labeling (OFL) in the Center for Food Safety and Applied Nutrition that the proposed claim, "Helps promote healthy cholesterol levels," falls within the purview of structure/function claims. However, as McNeil discussed with OFL on May 2, 1999, the label of Benecol® must include the percentage and type of fat, e.g., "__% vegetable oil" as part of the term "spread" where that term appears on the label, and the agency expects you to bring this aspect of your label into compliance with the applicable regulations. OFL will be sending you a separate letter discussing this issue. OFL has no other objection to your label in light of your letter dated May 3, 1999, and the commitments made therein.

Sincerely yours,

Alan M. Rulis, Ph.D.
Director
Office of Premarket Approval
Center for Food Safety
and Applied Nutrition

ATTACHMENT 2

SAFETY OF PLANT STANOL ESTERS
REFERENCES (Updated)

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