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[Page 54685-54739]
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[[Page 54685]]

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 101

Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease; Interim Final Rule

[[Page 54686]]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket Nos. 00P-1275 and 00P-1276]

Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule.

SUMMARY: The Food and Drug Administration (FDA) is authorizing the use, on food labels and in food labeling, of health claims on the association between plant sterol/stanol esters and reduced risk of

coronary heart disease (CHD). FDA is taking this action in response to a petition filed by Lipton (plant sterol esters petitioner) and a petition filed by McNeil Consumer Healthcare (plant stanol esters petitioner). Based on the totality of publicly available evidence, the agency has concluded that plant sterol/stanol esters may reduce the risk of CHD.

DATES: This rule is effective September 8, 2000. Submit written comments by November 22, 2000. The Director of the Office of the Federal Register approves the incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of certain publications in 21 CFR 101.83(c)(2)(ii)(A)(2) and (c)(2)(ii)(B)(2), as of September 8, 2000.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Sharon A. Ross, Center for Food Safety and Applied Nutrition (HFS-832), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5343.

SUPPLEMENTARY INFORMATION:

I. Background

The President signed into law, on November 8, 1990, the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Public Law 101-535). This new law amended the Federal Food, Drug, and Cosmetic Act (the act) in number of important ways. One of the most notable aspects of the 1990 amendments was that they provided procedures whereby FDA is to regulate health claims on food labels and in food labeling.

In the Federal Register of January 6, 1993 (58 FR 2478), FDA issued a final rule that implemented the health claim provisions of the act for conventional foods (hereinafter referred to as the 1993 health claims final rule). In that final rule, FDA adopted Sec. 101.14 (21 CFR 101.14), which sets out the rules for the authorization of health claims by regulation and prescribes general requirements for the use of health claims. Additionally, Sec. 101.70 (21 CFR 101.70) establishes a process for petitioning the agency to authorize health claims about a substance-disease relationship (Sec. 101.70(a)) and sets out the types of information that any such petition must include (Sec. 101.70(d)). On January 4, 1994 (59 FR 395), FDA issued a final rule applying the requirements of Secs. 101.14 and 101.70 to health claims for dietary supplements.

FDA also conducted an extensive review of the evidence on 10 substance-disease relationships listed in the 1990 amendments. As a result of its review, FDA authorized claims for 8 of these 10 relationships, one of which focused on the relationship between dietary saturated fat and cholesterol and reduced risk of CHD. CHD is the most common, most frequently reported, and most serious form of cardiovascular disease (CVD) (58 FR 2739, January 6, 1993). Further, while the agency denied the use on food labeling of health claims relating dietary fiber to reduced risk of CVD (58 FR 2552, January 6, 1993), it authorized a health claim relating fiber-containing fruits, vegetables, and grain products to a reduced risk of CHD.

In the proposed rule entitled "Health Claims and Label Statements; Lipids and Cardiovascular Disease" (56 FR 60727 at 60727, 60728, and 60732, November 27, 1991), FDA set out the criteria for evaluating evidence on diet and CVD relationships, including the relationship

between diet and CHD. FDA noted that, because of the public health importance of CHD, identification of "modifiable" risk factors for CHD had been the subject of considerable research and public policy attention. The agency also noted that there is general agreement that elevated blood cholesterol levels are one of the major modifiable risk factors in the development of CHD. FDA cited Federal Government and other reviews that concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total and low density lipoprotein (LDL) cholesterol are a cause of atherosclerosis (inadequate blood circulation due to narrowing of the arteries) and represent major contributors to CHD. Further, factors that decrease total blood cholesterol and LDL cholesterol will also decrease the risk of CHD. FDA concluded that it is generally accepted that blood total and LDL cholesterol levels are major risk factors for CHD, and that dietary factors affecting blood cholesterol levels affect the risk of CHD. High intakes of dietary saturated fat and, to a lesser degree, of dietary cholesterol are consistently associated with elevated blood cholesterol levels. FDA concluded that the publicly available data supported an association between diets low in saturated fat and cholesterol and reduced risk of CHD (58 FR 2739 at 2751).

The agency has authorized other health claims for reducing the risk of CHD using the aforementioned criteria. In the final rule entitled "Health Claims; Dietary Fiber and Cardiovascular Disease" (58 FR 2552), FDA concluded that the publicly available scientific information supported an association between fruits, vegetables, and grain products (i.e., foods that are low in saturated fat and cholesterol and that are good sources of dietary fiber) and reduced risk of CHD through the intermediate link of blood cholesterol (58 FR 2552 at 2572) (codified at Sec. 101.77)). In response to two petitions documenting that dietary consumption of soluble fiber from beta-glucan from oat products and psyllium seed husk significantly reduced blood cholesterol levels, FDA authorized health claims for soluble fiber from certain foods and reduced risk of CHD in Sec. 101.81 (21 CFR 101.81) (62 FR 3584 at 3600, January 23, 1997, and amended at 62 FR 15343 at 15344, March 31, 1997, pertaining to beta-glucan from oat products, and 63 FR 8103 at 8119, February 18, 1998 pertaining to psyllium seed husk). More recently, FDA authorized a health claim for soy protein and reduced risk of CHD in Sec. 101.82 (21 CFR 101.82) (64 FR 57700, October 26, 1999). In the final rule authorizing the claim, the agency concluded, based on the totality of publicly available scientific evidence, that there is significant scientific agreement that soy protein, included at a level of 25 grams (g) per day (d) in a diet low in saturated fat and cholesterol, can help reduce total and LDL cholesterol levels, and that such reductions may reduce the risk of CHD (64 FR 57700 at 57713). The dietary fiber and CVD (56 FR 60582 at 60583 and 60587, November 27, 1991), soluble fiber from beta-glucan from oat products and CHD (61 FR 296 at 298, January 4, 1996), soluble fiber from psyllium seed husk and CHD (62 FR 28234 at 28236 and 28237, May 22, 1997), and soy protein and CHD (63 FR 62977 at 62979 and 62980, November 10, 1998) health claim reviews in the proposed rules were conducted in accordance with the

[[Page 54687]]

1991 criteria for evaluating the evidence between diet and CHD (56 FR 60727 at 60727, 60728, and 60732).

The present rulemaking is in response to two health claim petitions. One health claim petition concerns the relationship between plant sterol esters and the risk of CHD, and the other concerns the relationship between plant stanol esters and the risk of CHD. Although the plant sterol esters petition characterizes the petitioned substance

as vegetable oil sterol esters, FDA believes it is more accurately characterized as plant sterol esters. The petition states that vegetable oil sterol esters consist of esterified plant sterols (Ref. 1, page 3). The petition also mentions that canola oil is one of the oils used as a source for the sterol component of vegetable oil sterol esters (Ref. 1, page 82). Canola oil is derived from a seed (rapeseed). Although seeds are clearly part of the plant kingdom, they are not ordinarily thought of as vegetables. Therefore, FDA is concerned that the term "vegetable oil sterol esters" may not be understood to cover esterified sterols from sources like canola oil. Accordingly, the agency is using the term "plant sterol esters" throughout this document. For purposes of this rule, plant sterol esters and plant stanol esters will be referred to collectively as "plant sterol/stanol esters."

II. Petitions for Plant Sterol/Stanol Esters and Reduced Risk of CHD

A. Background

Lipton submitted a health claim petition to FDA on February 1, 2000, requesting that the agency authorize a health claim on the relationship between consumption of certain plant sterol ester-containing foods and the risk of CHD (Refs. 1 through 4). Specifically, Lipton requested that spreads and dressings for salad\1\ containing at least 1.6 grams of plant sterol esters per reference amount customarily consumed be authorized to bear a health claim about reduced risk of CHD. On May 11, 2000, the agency sent this petitioner a letter stating that FDA had decided to file the petition for further review (Ref. 5). On June 26, 2000, Lipton submitted a request asking FDA to exercise its authority under section 403(r)(7) of the act (21 U.S.C. 343(r)(7)) to make any proposed regulation for its petitioned health claim effective upon publication, pending consideration of public comment and publication of a final rule (Ref. 6). If the agency does not act, by either denying the petition or issuing a proposed regulation to authorize the health claim, within 90 days of the date of filing, the petition is deemed to be denied unless an extension is mutually agreed upon by the agency and the petitioner (section 403(r)(4)(a)(i) of the act and 21 CFR 101.70(j)(3)(iii)). On August 2, 2000, FDA and the plant sterol ester petitioner agreed to an extension of 30 days, until September 6, 2000 (Ref. 7).

\1\ The agency is using the term "dressings for salad" throughout this document in lieu of the term "salad dressing" used by the petitioners because the standard of identity for "salad dressing" in Sec. 169.150 (21 CFR 164.150) refers to a limited class of dressings for salad, i.e., those that contain egg yolk and meet certain other specifications. "Salad dressing" as defined in Sec. 169.150 does not include a number of common types of dressings for salad, such as Italian dressing.

On February 15, 2000, McNeil Consumer Healthcare submitted a health claim petition to FDA requesting that the agency authorize a health claim on the relationship between consumption of plant stanol ester-containing foods and dietary supplements and the risk of CHD (Refs. 8 through 14). On May 25, 2000, the agency sent this petitioner a letter stating that FDA had decided to file the petition for further review (Ref. 15). On June 14, 2000, McNeil Consumer Healthcare submitted a

request asking FDA to exercise its authority under section 403(r)(7) of the act to make any proposed regulation for its petitioned health claim effective upon publication, pending consideration of public comment and publication of a final rule (Ref. 16). On July 17, 2000, FDA and the plant stanol ester petitioner agreed to an extension of the deadline to publish a proposed regulation until September 6, 2000 (Ref. 17).

In this interim final rule, the agency concludes that a health claim about plant sterol/stanol esters and reduced risk of CHD should be authorized under the standard in section 403(r)(3)(B)(i) of the act and Sec. 101.14(c) of FDA's regulations and should be made effective upon publication under section 403(r)(7) of the act, pending consideration of public comment and publication of a final regulation. The agency is requesting comments on this interim final rule. Firms should be aware that a final rule on this health claim may differ from this interim final rule and that they would be required to revise their labels to conform to any changes adopted in the final rule.

B. Review of Preliminary Requirements for a Health Claim

1. The Substances Are Associated With a Disease for Which the U.S. Population Is at Risk

Several previous rules establish that CHD is a disease for which the U.S. population is at risk. These include rules authorizing claims for dietary saturated fat and cholesterol and risk of CHD (Sec. 101.75 (21 CFR 101.75)); fiber-containing fruits, vegetables, and grain products and risk of CHD (Sec. 101.77); soluble fiber from certain foods and risk of CHD (Sec. 101.81); and soy protein and risk of CHD (Sec. 101.82). FDA stated in these rules that CHD remains a major public health problem and the number one cause of death in the United States. Despite the decline in deaths from CHD over the past 30 years, this disease is still exacting a tremendous toll in morbidity (illness and disability) and mortality (premature deaths) (Refs. 18 through 20). There are more than 500,000 deaths each year for which CHD is the primary cause, and another 250,000 deaths for which CHD is a contributing cause. About 20 percent of adults (male and female; black and white) ages 20 to 74 years have blood total cholesterol (or serum cholesterol) levels in the "high risk" category (total cholesterol greater than (>) 240 milligrams (mg) / deciliter (dL) and LDL cholesterol > 160mg/dL) (Ref. 21). Another 31 percent have "borderline high" cholesterol levels (total cholesterol between 200 and 239 mg/dL and LDL cholesterol between 130 and 159 mg/dL) in combination with two or more other risk factors for CHD.

CHD has a significant effect on health care costs. In 1999, total direct costs related to CHD were estimated at \$53.1 billion, and indirect costs from loss of productivity due to illness, disability, and premature deaths from this disease were an estimated \$46.7 billion (Ref. 22). Based on these facts, FDA concludes that, as required in Sec. 101.14(b)(1), CHD is a disease for which the U.S. population is at risk.

2. The Substances Are Food

The substances that are the subject of this interim final rule are plant sterol esters and plant stanol esters (Refs. 1 through 4 and 8 through 14).

a. Plant sterol esters. The substance that is the subject of the plant sterol ester petition is a mixture of plant sterols esterified to food-grade fatty acids. The sterols are primarily (beta-sitosterol, campesterol, and stigmasterol and are extracted from plant sources (Ref. 1, page 6). Plant sterols occur widely throughout the plant kingdom

[[Page 54688]]

and are present in many edible fruits, vegetables, nuts, seeds, cereals, and legumes (Refs. 23 and 24). The plant sterols in foods may occur as either the free sterol or esterified with a fatty acid.

Several studies have estimated dietary plant sterol intake. From a population in the Los Angeles area, Nair et al. (Ref. 25) found that plant sterol (beta-sitosterol and stigmasterol) intake ranged from 77.9 mg/d in the general population to 343.6 mg/d in lacto-ovo vegetarians. The 1991 British diet was estimated to contain about 158 mg/d of sterols (beta-sitosterol, stigmasterol, and campesterol) (Ref. 26). Scandinavian vegetarians consume, on average, 513 mg/d and nonvegetarians 398 mg/d (Ref. 27). Plant sterol intake in the Japanese diet has been estimated at 373 mg/d (Ref. 28). In an analysis of diets of participants in the Seven Countries Study, deVries et al. (Ref. 29) found plant sterol intake (sitosterol, stigmasterol and campesterol) to range from 170 mg/d among U.S. railroad workers to 358 mg/d in Corfu, Greece. In a review, Ling and Jones (Ref. 30) estimated average U.S. intake at 250 mg/d; it was speculated that this level was doubled among vegetarians. Thus, plant sterols are a constituent of the diet for Americans and other population groups.

According to the plant sterol ester petitioner, the solubility of free sterols in oil is only 2 percent, but the solubility of sterol esters in oil exceeds 20 percent (Ref. 1, pages 14 and 99). Therefore, the free plant sterols are esterified with fatty acids from sunflower to improve solubility. The petitioner also notes that improved solubility of plant sterols creates a palatable product and is associated with more uniform distribution in the product and in the gastrointestinal tract (Ref. 1, page 14). In vegetable oils, typically between 25 and 80 percent of the sterol is in the ester form (Refs. 31 through 34). One gram of plant sterols is equivalent to about 1.6 g of plant sterol esters (Refs. 35 and 36).

Under Sec. 101.14(b)(3)(i), the substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in Sec. 170.3(o) (21 CFR 170.3(o)), to the food and must retain that attribute when consumed at the levels that are necessary to justify a claim. Plant sterol esters do not contribute taste, aroma, or any other technical effect listed in Sec. 170.3(o), and thus the plant sterol esters must contribute nutritive value to meet the requirement in Sec. 101.14(b)(3)(i).

The term 'nutritive value' is defined in Sec. 101.14(a)(3) as 'value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy.' In the proposed rule entitled 'Labeling; General Requirements for Health Claims for Food' (56 FR 60537, November 27, 1991), FDA proposed this definition and explained its interpretation of nutritive value in the context of whether a substance is a food and thus appropriately the subject of a health claim (56 FR 60537 at 60542). The agency indicated that the definition was formulated based on the common meaning of the words that make up the term 'nutritive value.' The agency also added that use of the phrase 'such processes as' in the definition of nutritive value was intended to provide a measure of flexibility that the agency believed would be necessary in evaluating future petitions. In the final rule adopting the proposed definition, the agency noted that the evaluation of the nutritive value of substances would be done on a case-by-case basis to best ensure that the definition retains its intended flexibility (58 FR 2478 at 2488). In a subsequent final rule on health claims for dietary supplements (59 FR 395 at 407), FDA further explained that 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."

The scientific evidence suggests that the cholesterol-lowering effect of plant sterol esters is achieved through an effect on the digestive process (Ref. 1, pages 62 through 64). The digestive process is one of the metabolic processes necessary for the normal maintenance of human existence. Therefore, the agency concludes that the preliminary requirement of Sec. 101.14(b)(3)(i) is satisfied.

b. Plant stanol esters. The substance that is the subject of the plant stanol ester petition is a mixture of plant stanols esterified to food-grade fatty acids. The stanols are primarily sitostanol and campestanol and may be derived from hydrogenated plant sterol mixtures or extracted from plant sources (Ref. 8, page 18). Sitostanol and campestanol occur naturally in small quantities in the lipid fractions of cereal grains such as wheat, rye, and corn (Refs. 37 through 39) and in vegetable oils such as corn and olive oil (Refs. 40 and 41). The average western diet provides 20 to 50 mg of plant stanols daily (Ref. 42).

According to the plant stanol ester petitioner, esterification of free stanols with fatty acids renders plant stanols readily soluble in foods and makes an effective vehicle for delivery of plant stanols to the small intestine (Ref. 8, page 9). One gram of wood-derived plant stanols is equivalent to about 1.7 g of plant stanol esters (Ref. 43), and 1 g of vegetable oil plant stanols is equivalent to about 1.8 g of plant stanol esters (Ref. 43).

As discussed in section II.B.2.a of this document, the substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in Sec. 170.3(o), to the food and must retain that attribute when consumed at levels that are necessary to justify a claim (Sec. 101.14(b)(3)(i)). Plant stanol esters do not contribute taste, aroma or any other technical effect listed in Sec. 170.3(o) and thus must contribute nutritive value to meet the requirement in Sec. 101.14(b)(3)(i). The term "nutritive value" is defined in Sec. 101.14(a)(3) as "value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy."

The scientific evidence suggests that the cholesterol-lowering effect of plant stanol esters is achieved through an effect on the digestive process (Ref. 8, pages 11 through 12). As discussed in section II.B.2.a of this document and in the final rule on health claims for dietary supplements (59 FR 395 at 407), 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, such as digestive processes. Therefore, the agency concludes that the preliminary requirement of Sec. 101.14(b)(3)(i) is satisfied.

3. The Substances Are Safe and Lawful

a. Plant sterol esters. The plant sterol ester petitioner asserts that plant sterol esters are generally recognized as safe (GRAS) for certain uses. In a submission dated January 11, 1999, the petitioner informed FDA of its conclusion that plant sterol esters are GRAS for use in vegetable oil spreads at levels up to 20 percent (corresponding to 1.6 g of plant sterol esters per serving) to supplement the nutritive value of the spread, and to help structure the fat phase and reduce the fat and water content of the spread. The January 11, 1999, submission included the supporting data on which this conclusion was based. FDA responded to this submission in a letter dated April 30, 1999 (Ref. 44). In its response, the agency stated, "Based on its evaluation, the agency has no questions at this time regarding Lipton's conclusion that vegetable oil sterol esters are GRAS under the intended

conditions of use. Furthermore, FDA is not aware of any scientific evidence that

[[Page 54689]]

vegetable oil sterol esters would be harmful. The agency has not, however, made its own determination regarding the GRAS status of the subject use of vegetable oil sterol esters'' (Ref. 44). In a letter dated September 24, 1999, the petitioner informed FDA of an additional use of plant sterol esters in dressings for salad (Ref. 45). The letter contained additional safety information to support the new use.

The agency notes that authorization of a health claim for a substance should not be interpreted as affirmation that the substance is GRAS. A review of Lipton's January 11, 1999, submission and of its September 24, 1999, letter to the agency, however, reveals significant evidence supporting the safety of the use of plant sterol esters at the levels necessary to justify a health claim. Moreover, FDA is not aware of any evidence that provides a basis to reject the petitioner's position that the use of plant sterol esters in spreads and dressings for salad up to 1.6 g/serving is safe and lawful. As discussed in section V.B of this document, the level of plant sterol esters necessary to justify a claim is 1.3 g per day. Therefore, FDA concludes that the petitioner has satisfied the requirement of Sec. 101.14(b)(3)(ii) to demonstrate that the use of plant sterol esters in spreads and dressings for salad at the levels necessary to justify a claim is safe and lawful.

b. Plant stanol esters. Under the health claim petition process, FDA evaluates whether the substance is ``safe and lawful'' under the applicable food safety provisions of the act (Sec. 101.14(b)(3)(ii)). For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is GRAS, listed as a food additive, or authorized by a prior sanction issued by FDA (see Sec. 101.70(f)). Dietary ingredients in dietary supplements, however, are not subject to the food additive provisions of the act (see section 201(s)(6) of the act (21 U.S.C. 321(s)(6))). Rather, they are subject to the new dietary ingredient provisions in section 413 of the act (21 U.S.C. 350b) and the adulteration provisions in section 402 of the act (21 U.S.C. 342). The term ``dietary ingredient'' is defined in section 201(ff)(1) of the act and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding ingredients.

A ``new dietary ingredient'' is a dietary ingredient that was not marketed in the United States before October 15, 1994 (section 413(c) of the act). If a dietary supplement contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered, section 413(a)(2) of the act requires the manufacturer or distributor of the supplement to submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 413(a)(2) of the act, there must be a 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. If FDA believes that this requirement has not been met, the agency responds to the notification within 75 days from the

date of its receipt. Otherwise, no response is sent. If a new dietary ingredient notification has been submitted and a history of use or other evidence of safety exists that establishes a reasonable expectation of safety, the new dietary ingredient may be lawfully marketed in dietary supplements 75 days after the notification is submitted.

As previously noted, the plant stanol ester petitioner requested authorization to make a health claim about plant stanol esters and the risk of CHD in the labeling of both conventional foods and dietary supplements. Because the standards under which the safety and legality of conventional foods and dietary supplements are evaluated differ, the agency is discussing these two proposed uses separately.

i. Conventional foods. The plant stanol ester petitioner asserts that plant stanol esters are GRAS. In a submission dated February 18, 1999, the petitioner informed FDA of its conclusion that plant stanol esters are GRAS for use as a nutrient in spreads at a level of 1.7g of plant stanol esters per serving of spread. The February 18, 1999, submission included the supporting data on which this conclusion was based. FDA responded to this submission in a letter dated May 17, 1999 (Ref. 46). In its response, the agency stated, "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" (Ref. 46). The petitioner's GRAS determination applies to plant stanol esters whose stanol components are prepared by the hydrogenation of commercially available plant sterol blends, which are obtained as distillates from vegetable oils or as byproducts of the kraft paper pulping process (Ref. 46). In letters dated July 21, 1999, and October 13, 1999, the petitioner informed FDA of additional uses of plant stanol esters in dressings for salad and snack bars (Refs. 47 and 48).

The agency notes that authorization of a health claim for a substance should not be interpreted as affirmation that the substance is GRAS. A review of McNeil's February 18, 1999, submission, however, reveals significant evidence supporting the safety of the use of plant stanol esters at the levels necessary to justify a health claim. Moreover, FDA is not aware of any evidence that provides a basis to reject the petitioner's position that the use of plant stanol esters in spreads, dressings for salad, snack bars, and other foods is safe and lawful. FDA therefore concludes that the petitioner has satisfied the requirement of Sec. 101.14(b)(3)(ii) to demonstrate that the use of plant stanol esters in conventional foods at the levels necessary to justify a claim is safe and lawful.

ii. Dietary supplements. The petitioner submitted a new dietary ingredient notification for plant stanol esters on August 19, 1999. The new dietary ingredient notification contained several papers that reported the results of studies conducted in humans to test hypocholesterolemic effects of plant stanol esters as well as a reference to the plant stanol ester petitioner's GRAS submission of February 18, 1999, and the agency's response to this submission in a letter dated May 17, 1999 (Ref. 46). In FDA's judgment, the studies submitted in the plant stanol esters new dietary ingredient notification and GRAS submission appeared to provide an adequate basis that a dietary

[[Page 54690]]

supplement containing plant stanol esters would reasonably be expected

to be safe. Therefore, the agency did not respond to the new dietary ingredient notification. Because the safety standard in section 413(a)(2) of the act has been met and the new dietary ingredient notification was submitted more than 75 days ago, plant stanol esters may now be lawfully marketed as dietary ingredients in dietary supplements. Therefore, FDA concludes that the petitioner has satisfied the requirement of Sec. 101.14(b)(3)(ii) to demonstrate that the use of plant stanol esters in dietary supplements at the levels necessary to justify a claim is safe and lawful.

\2\ The notification states that McNeil does not believe plant stanol esters to be a new dietary ingredient requiring submission of a premarket notification, but that McNeil is voluntarily submitting the information that would be required as part of such a notification for the purpose of providing the Food and Drug Administration with advance notice concerning its dietary ingredient'' (Ref. 49).

III. Review of Scientific Evidence of the Substance-Disease Relationship

A. Basis for Evaluating the Relationship Between Plant Sterol/Stanol Esters and CHD

FDA's review examined the relationship between plant sterol/stanol esters and CHD by focusing on the effects of dietary intake of this substance on blood cholesterol levels and on the risk of developing CHD. In the 1991 lipids-CVD and dietary fiber-CVD health claim proposals, the agency set forth the scientific basis for the relationship between dietary substances and CVD (56 FR 60727 at 60728 and 56 FR 60582 at 60583). In those documents, the agency stated that there are many risk factors that contribute to the development of CVD, and specifically CHD, one of the most serious forms of CVD and among the leading causes of death and disability. The agency also stated that there is general agreement that elevated blood cholesterol levels are one of the major modifiable risk factors in the development of CVD and, more specifically, CHD.

Several Federal agencies and scientific bodies that have reviewed the matter have concluded that there is substantial epidemiologic evidence that high blood levels of total cholesterol and LDL cholesterol are a cause of atherosclerosis and represent major contributors to CHD (56 FR 60727 at 60728, 56 FR 60582 at 60583, Refs. 18 through 20). Factors that decrease total cholesterol and LDL cholesterol will also tend to decrease the risk of CHD. High-intakes of saturated fat and, to a lesser degree, of dietary cholesterol are associated with elevated blood total and LDL cholesterol levels (56 FR 60727 at 60728). Thus, it is generally accepted that blood total cholesterol and LDL cholesterol levels can influence the risk of developing CHD, and, therefore, that dietary factors affecting these blood cholesterol levels affect the risk of CHD (Refs. 18 through 20).

When considering the effect that the diet or components of the diet have on blood (or serum) lipids, it is important to consider the effect that these factors may have on blood levels of high density lipoprotein (HDL) cholesterol. HDL cholesterol appears to have a protective effect against CHD because it is involved in the regulation of cholesterol transport out of cells and to the liver, from which it is ultimately excreted (Refs. 18 and 50).

For these reasons, the agency based its evaluation of the

relationship between consumption of plant sterol/stanol esters and the risk of CHD primarily on changes in blood total and LDL cholesterol resulting from dietary intervention with plant sterol/stanol ester-containing products. A secondary consideration was that beneficial changes in total and LDL cholesterol should not be accompanied by potentially adverse changes in HDL cholesterol. This focus is consistent with that used by the agency in deciding on the dietary saturated fat and cholesterol and CHD health claim, Sec. 101.75 (56 FR 60727 and 58 FR 2739); the fiber-containing fruits, vegetables, and grain products and CHD claim, Sec. 101.77 (56 FR 60582 and 58 FR 2552); the soluble fiber from certain foods and CHD claim, Sec. 101.81 (61 FR 296, 62 FR 3584, 62 FR 28234, and 63 FR 8119) and the soy protein and CHD claim, Sec. 101.82 (63 FR 62977 and 64 FR 57700).

B. Review of Scientific Evidence

1. Evidence Considered in Reaching the Decision

a. Plant sterol esters and CHD. The plant sterol esters petitioner submitted 15 scientific studies (Refs. 51 through 60, 61 and 62 (1 study), 63 and 64 (1 study), and 65 through 67) evaluating the relationship between plant sterol esters or plant sterols and blood cholesterol levels in humans. The studies submitted were conducted between 1953 and 2000. The petition included tables that summarized the outcome of each of the studies and a summary of the evidence.

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 a 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. Accordingly, FDA included such studies in its evaluation of the relationship between plant sterol esters and reduced risk of CHD if they met the study selection criteria specified in section III.B.2 of this document.

In several previous diet and CHD health claim rulemakings, the agency began its review of scientific evidence in support of the health claim by considering those studies that were published since 1988, the date of publication of the "Surgeon General's Report on Nutrition and Health" (Ref. 18), which is the most recent and comprehensive Federal review of the scientific evidence on dietary factors and CHD. That approach was not possible in this instance, however, as the "Surgeon General's Report on Nutrition and Health" does not discuss the effects of dietary plant sterols or plant sterol esters on blood cholesterol or CHD. A discussion of the role of dietary sterols in CHD does appear in another roughly contemporaneous source, the National Academy Press publication "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 19), which was issued in 1989. That publication states:

Long ago, plant sterols (beta-sitosterol and related compounds) were found to prevent absorption of dietary cholesterol (Best et al., 1955; Farquhar and Sokolow, 1958; Farquhar et al., 1956; Lees et al., 1977; Peterson et al., 1959), apparently by blocking absorption of cholesterol in the intestine (Davis, 1955; Grundy and Mok, 1977; Jandacek et al., 1977; Mattson et al., 1977). More recent reports indicate that these compounds may be more effective in small doses than previously believed (Mattson et al., 1982).

This discussion highlights the previous and current emphasis of

research on the topic. Investigations in the 1950's reported the effects of plant sterols on cholesterol absorption using animal models and in a few human studies; work in the 1970's examined beta-sitosterol in the form of a drug product to lower cholesterol in humans. In fact, beta-sitosterol is approved for use as a drug to lower cholesterol (Refs. 72 and 73). More recent research has focused on smaller amounts of plant sterols that are solubilized as fatty acid esters of plant sterols in food products. The agency considers the older research to be of little relevance to the petitioned health claim because it concerned forms and amounts of the substance different from those that are the subject of the

[[Page 54691]]

petition. Therefore, FDA included in its review only those studies published from 1982 (the date the National Academy Press publication refers to for the more recent research reports (Ref. 19)) to the present among those submitted by the petitioner (Refs. 51, 52, 57, 58, 61 and 62 (1 study), 63 and 64 (1 study), 65, and 67). In addition to eight studies submitted by the petitioner, FDA also considered two other studies (Refs. 74 and 75) concerning the effects of plant sterol esters on blood cholesterol. These two studies were identified by a literature search (Ref. 76) performed to verify that the totality of publicly available scientific evidence had been submitted to the agency.

In addition to the human studies previously discussed, the plant sterol esters petition also presented some findings from studies that employed animal models. Human studies are weighted most heavily in the evaluation of evidence on a diet and disease relationship; animal model studies can be considered as supporting evidence but cannot serve as the sole basis for establishing that a diet and disease relationship exists. Because there were enough well-controlled studies in humans to evaluate the relationship between plant sterol esters and CHD, FDA did not closely review the studies in animals.

b. Plant stanol esters and CHD. The plant stanol ester petitioner submitted 21 scientific studies (Refs. 63 and 64 (1 study), and 67, 77 through 80, 81 and 82 (1 study), and 83 through 96) evaluating the relationship between plant stanol esters or plant stanols and blood cholesterol levels in humans. The studies submitted were conducted between 1993 and 2000. The petition included tables that summarized the outcome of each of the studies and a summary of the evidence.

Stanol esters are hydrolyzed in the gastrointestinal tract to fatty acids and free stanols, and investigators believe there is 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 section III.B.2 of this document.

In several previous diet and CHD health claim rulemakings, the agency began its review of scientific evidence in support of the health claim by considering those studies that were published since 1988, the date of publication of the "Surgeon General's Report on Nutrition and Health" (Ref. 18), which is the most recent and comprehensive Federal review of the scientific evidence on dietary factors and CHD. The "Surgeon General's Report on Nutrition and Health," however, did not discuss the effects of dietary plant stanol esters on blood cholesterol or CHD. Although a discussion of the role of dietary sterols in CHD appears in the 1989 National Academy Press publication "Diet and

Health: Implications for Reducing Chronic Disease Risk," there is no mention of plant stanol esters in this publication (Ref. 19). In fact, research on the cholesterol-lowering capacity of plant stanol esters has been a recent development. The agency used 1992 as a starting point for its scientific evaluation, because this is the year that the earliest study evaluating the effects of plant stanol esters on blood cholesterol was published. The agency included in its review 24 studies published from 1992 to present that were submitted by the petitioner or otherwise identified (Refs. 58, 63 and 64 (1 study), 67, 74, 77 through 80, 81 and 82 (1 study), and 83 through 97). Of these, 21 studies (Refs. 63 and 64 (1 study), 67, 77 through 80, 81 and 82 (1 study), and 83 through 96) were submitted by the petitioner. Two studies (Refs. 74 and 97) were identified by a literature search (Ref. 76) performed to verify that the totality of publicly available scientific evidence had been submitted to the agency. In addition, one recently published study that was submitted in the plant sterol esters petition included administration of plant stanol esters (Ref. 58). This study was included in the plant stanol ester review.

In addition to the published studies previously discussed, the plant stanol ester petitioner submitted a summary of 10 unpublished studies (Ref. 8, pages 59 through 69). The unpublished studies did not weigh heavily in the agency's review because health claims are authorized based on the totality of publicly available scientific evidence (see section 403(r)(3)(B)(i) of the act and Sec. 101.14(c)) and because the summaries of these studies lacked sufficient detail on study design and methodologies.

2. Criteria for Selection of Human Studies on Plant Sterol/Stanol Esters and CHD

The criteria that the agency used to select the most pertinent studies in both health claim petitions were consistent with those that the agency used in evaluating the relationship between other substances and CHD. These criteria were that the studies: (1) Present data and adequate descriptions of the study design and methods; (2) be available in English; (3) include estimates of, or enough information to estimate, intakes of plant sterols or stanols and their esters; (4) include direct measurement of blood total cholesterol and other blood lipids related to CHD; and (5) be conducted in persons who represent the general U.S. population. In the case of criterion (5), these persons can be considered to be adults with blood total cholesterol levels less than 300 mg/dL, as explained below.

In a previous rulemaking (62 FR 28234 at 28238 and 63 FR 8103 at 8107), the agency concluded that hypercholesterolemic study populations were relevant to the general population because, based on data from the National Health and Nutrition Examination Surveys (NHANES) III, the prevalence of individuals with elevated blood cholesterol (i.e., 200 mg/dL or greater) is high, i.e., approximately 51 percent of adults (Ref. 21). The proportion of adults having moderately elevated blood cholesterol levels (i.e., between 200 and 239 mg/dL) was estimated to be approximately 31 percent, and the proportion of adults with high blood cholesterol levels (240 mg/dL or greater) was estimated to be approximately 20 percent (Ref. 21). It is also estimated that 52 million Americans 20 years of age and older would be candidates for dietary intervention to lower blood cholesterol (Ref. 21). As the leading cause of death in this country, CHD is a disease for which the general U.S. population is at risk. Since more than half of American adults have mildly to moderately elevated blood cholesterol levels, FDA considers studies in these populations to be representative of a large segment of the general population. Accordingly, in this rule, the agency has reviewed and considered the evidence of effects of plant sterol/stanol esters on blood cholesterol in mildly and moderately

hypercholesterolemic subjects as well as subjects with cholesterol levels in the normal range.

In selecting human studies for review, the agency excluded studies that were published in abstract form because they lacked sufficient detail on study design and methodologies, and because they lacked necessary primary data. Studies using special population groups, such as adults with very high serum cholesterol (mean greater than 300 mg/dL), children with hypercholesterolemia, and persons who had already experienced a myocardial infarction (heart attack) or

[[Page 54692]]

who had a diagnosis of noninsulin dependent diabetes mellitus, were also excluded because of questions about their relevance to the general U.S. population.

3. Criteria for Evaluating the Relationship Between Plant Sterol/Stanol Esters and CHD

The evaluation of study design, protocol, measurement, and statistical issues for individual studies serves as the starting point from which FDA determines the overall strengths and weaknesses of the data and assesses the weight of the evidence. FDA's "Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" articulates the agency's approach to evaluating studies supporting diet/disease relationships (Ref. 98). The criteria that the agency used in evaluating the studies for this rulemaking include: (1) Adequacy and clarity of the design (e.g., was the methodology used in the study clearly described and appropriate for answering the questions posed by the study?); (2) population studied (e.g., was the sample size large enough to provide sufficient statistical power to detect a significant effect?); (3) assessment of intervention or exposure and outcomes (e.g., was the dietary intervention or exposure well defined and appropriately measured?); and (4) statistical methods (e.g., were appropriate statistical analyses applied to the data?).

The general study design characteristics for which the agency looked included selection criteria for subjects, appropriateness of controls, randomization of subjects, blinding, statistical power of the studies, presence of recall bias and interviewer bias, attrition rates (including reasons for attrition), potential for misclassification of individuals with regard to dietary intakes, recognition and control of confounding factors (for example, monitoring body weight and control of weight loss), and appropriateness of statistical tests and comparisons. The agency considered whether the intervention studies that it evaluated had been of long enough duration, greater than or equal to 3 weeks duration, to ensure reasonable stabilization of blood lipids.

As discussed above, dietary saturated fat and cholesterol affect blood cholesterol levels (Refs. 19 and 20). Previous reviews by FDA and other scientific bodies have generally concluded that, in persons with relatively higher baseline levels of blood cholesterol, responses to dietary intervention tend to be of a larger magnitude than is seen in persons with more normal blood cholesterol levels (56 FR 60582 at 60587 and Refs. 19 and 20). To take into account these factors, FDA separately evaluated studies on mildly to moderately hypercholesterolemic individuals (persons with elevated blood total cholesterol levels of 200 to 300 mg/dL) and studies on normocholesterolemic individuals (persons with blood total cholesterol levels in the normal range (< 200 mg/dL)). FDA also separately evaluated studies in which the effects of plant sterol/stanol esters were evaluated as part of a "typical" American diet (approximately 37 percent of calories from fat, 13 percent of calories from saturated

fat, and more than 300 mg of cholesterol daily) and studies in which the test protocols incorporated a dietary regimen that limits fat intake such as the National Heart, Lung, and Blood Institute's National Cholesterol Education Program Step I Diet (intake of 8 to 10 percent of total calories from saturated fat, 30 percent or less of calories from total fat, and cholesterol less than 300 mg/d) (Ref. 99).

C. Review of Human Studies

1. Studies Evaluating the Effects of Plant Sterol Esters on Blood Cholesterol

As discussed in section III. B.1.a of this document, FDA reviewed 10 human clinical studies on plant sterol esters or other plant sterols (Refs. 51, 52, 57, 58, 61 and 62 (1 study), 63 and 64 (1 study), 65, 67, and 74 and 75). Of these, nine met the selection criteria listed in section III.B.2 of this document (Refs. 51, 57, 58, 61 and 62 (1 study), 63 and 64 (1 study), 65, 67 and 74 and 75). These studies are summarized in table 1 at the end of this document and discussed below. The remaining study (Ref. 52) failed to meet the inclusion criteria because the population studied (children with familial hypercholesterolemia) was not representative of the general U.S. population. As supporting evidence, the results of one research synthesis study (Ref. 100) that included a number of the plant sterol ester studies submitted in the petition are discussed in section III.C.1.d of this document.

Studies typically report the amount of free plant sterol consumed rather than the amount of plant sterol ester administered. Where possible, we report both the amount of plant sterol ester and the equivalent free sterol.

(a) Hypercholesterolemics (serum cholesterol 300 mg/dL): low saturated fat and cholesterol diets. One study was submitted as a draft in the plant sterol esters petition because it has been submitted for publication, but has not yet been published other than in abstract form (Ref. 62). FDA reviewed this study but considers the results preliminary until a full report of the study has been published. The preliminary results in this study (Refs. 61 and 62 (1 study)) showed a cholesterol-reducing effect of plant sterol esters in hypercholesterolemic subjects who consumed soybean oil sterol esters as part of a low saturated fat and low cholesterol diet. In this study, 224 men and women with mild-to-moderate hypercholesterolemia instructed to follow a National Cholesterol Education Program Step I diet were randomly assigned to one of three groups: (1) control reduced-fat spread, (2) reduced-fat spread containing 1.76 g/d of plant sterol esters (1.1 g/d free plant sterols) (low intake group), or (3) reduced-fat spread containing 3.52 g/d of plant sterol esters (2.2 g/d free plant sterols) (high-intake test group). All subjects consumed 14 g/d of spread in two 7 g servings/day, with food. Subjects in the low- and high-intake groups who consumed 80 percent of scheduled servings had decreases in serum total cholesterol of 5.2 and 6.6 percent, and LDL cholesterol of 7.6 and 8.1 percent, respectively, versus control (p<0.001). The difference between the two test groups with regard to serum total and LDL cholesterol levels was not statistically significant. HDL cholesterol responses did not differ among the groups. These preliminary results indicate that a plant sterol ester-containing reduced-fat spread, in a diet low in saturated fat and cholesterol, can reduce cholesterol.

(b) Hypercholesterolemics (serum cholesterol 300 mg/dL): "typical" or "usual" diets. Four studies (Refs. 57, 58, 67, and 74) show a relationship between consumption of plant sterols and reduced blood cholesterol in hypercholesterolemic subjects consuming diets

within the range of a typical American diet. A fifth study (Refs. 63 and 64 (1 study)) shows inconclusive results.

Jones et al. (Ref. 58) conducted a controlled feeding crossover study in which diets were based on a fixed-food North American diet formulated to meet Canadian recommended nutrient intakes. This study reported significantly lower plasma total cholesterol (9.1 percent, $p < 0.005$) and LDL cholesterol (13.2 percent, $p < 0.02$) in male subjects consuming 2.94 g/d vegetable oil sterol esters (1.84 g/d free plant sterols delivered in 23 g of margarine each day; daily margarine doses were divided into three equal

[[Page 54693]]

portions and added to each meal) for 21 days compared to 21 days on control margarine. Plasma HDL cholesterol did not differ across groups and there was no significant weight change shown by the subjects while consuming any of the margarine mixtures.

Hendriks et al. (Ref. 57) reported the effects of feeding three different levels of vegetable oil sterol esters (1.33, 2.58, and 5.18 g/d corresponding to 0.83, 1.61, and 3.24 g/d free plant sterols, respectively) incorporated in spreads (25 g/d of spread replaced an equivalent amount of the spread(s) habitually used; one-half was consumed at lunch, one-half at dinner) in apparently healthy normocholesterolemic and mildly hypercholesterolemic subjects using a randomized, double-blind placebo-controlled balanced incomplete Latin square design with five treatments and four periods. The vegetable oil sterols were esterified to sunflower oil and the degree of esterification was 82 percent. Blood total and LDL cholesterol levels were reduced compared to the control spread ($p < 0.001$) after 3.5 weeks. Blood total cholesterol decreased by 4.9, 5.9, and 6.8 percent for daily consumption of 1.33, 2.58, and 5.18 g/d plant sterol esters, respectively. For LDL cholesterol these decreases were 6.7, 8.5, and 9.9 percent. No significant differences in cholesterol-lowering effect between the three levels of plant sterol esters could be detected. There were no effects on HDL cholesterol. The subjects' body weight differed after daily consumption of 2.58 and 5.18 g plant sterol esters by 0.3 kilogram (kg) ($p < 0.01$), but this small difference in body weight probably did not affect the study findings.

Another study by Jones et al. (Ref. 74) investigated the effects of a mixture of plant sterols and plant stanols. The plant stanol compound sitostanol made up about 20 percent of the mixture by weight. The remaining sterol component of the mixture was composed mostly of the plant sterols sitosterol and campesterol from tall oil (derived from pine wood). The investigators evaluated the cholesterol-lowering properties of this nonesterified plant sterol/stanol mixture in a controlled feeding regimen based on a "prudent," fixed-food North American diet formulated to meet Canadian recommended nutrient intakes. Thirty-two hypercholesterolemic men were fed either a diet of prepared foods alone or the same diet plus 1.7 g per d of the plant sterol/stanol mixture (in 30 g/d of margarine, consumed during 3 meals) for 30 days in a parallel study design. The plant sterol/stanol mixture had no statistically significant effect on plasma total cholesterol concentrations. However, LDL cholesterol concentrations on day 30 had decreased by 8.9 percent ($p < 0.01$) and 24.4 percent ($p < 0.001$) with the control and plant sterol/stanol-enriched diets, respectively. On day 30, LDL cholesterol concentrations were significantly lower ($p < 0.05$) by 15.5 percent in the group consuming the plant sterol/stanol mixture compared to the control group. HDL cholesterol concentrations did not change significantly during the study.

Weststrate and Meijer (Ref. 67) evaluated the effects of different

plant sterols on plasma total and LDL cholesterol in normocholesterolemic and mildly hypercholesterolemic subjects consuming their usual diets with the addition of a test or placebo margarine. A randomized double-blind placebo-controlled balanced incomplete Latin square design with five treatments and four periods of 3.5 weeks was utilized to compare the effect of margarines (30 g/d) with added sterol esters from soybean oil (4.8 g/d; 3 g/d free plant sterol), sheanut oil (2.9 g/d) or ricebran oil (1.6 g/d) or with plant stanol esters (4.6 g/d; 2.7 g/d free plant stanols) to a placebo margarine. The sterol esters from soybean oil were mainly esters from sitosterol, campesterol, and stigmasterol. Plasma total and LDL cholesterol concentrations were significantly reduced, by 8.3 and 13.0 percent (p 0.05), respectively, compared to control, in the soybean oil sterol ester margarine group. Similar reductions were reported in the plant stanol ester margarine group (see discussion of this study in section III. C.2.b of this document). Sterols from sheanut oil and rice bran oil did not have a significant effect on cholesterol levels. No effects on HDL cholesterol concentrations were reported in either the control or any of the test groups. The cholesterol-lowering effects of ingestion of plant sterol/stanol esters on blood cholesterol did not differ between normocholesterolemic and mildly hypercholesterolemic subjects. The authors concluded that both the margarine with plant stanol esters and the margarine with sterol esters from soybean oil were effective in lowering blood total and LDL cholesterol levels without affecting HDL cholesterol concentrations. The authors further suggested that incorporating such substances in edible fat-containing products may substantially reduce the risk of cardiovascular disease in the population.

Two reports of apparently the same study (Refs. 63 and 64) gave inconclusive results regarding the relationship between plant sterol consumption and blood cholesterol levels. Interpretation of this study is complicated by design issues such as concerns about sample size and level of plant sterol administered, but both reports are discussed here and summarized in table 1 of this document because they provide information to assist in determining the minimum level of plant sterol esters necessary to provide a health benefit.

Miettinen and Vanhanen (Refs. 63 and 64 (1 study)) reported the effect of small amounts of sitosterol (700 mg/d free sterols) and sitostanol (700 mg/d free stanols) dissolved in 50 g rapeseed oil (RSO) mayonnaise on serum cholesterol in 31 subjects with hypercholesterolemia for 9 weeks. Subjects did not change their diets except for replacing 50 g/d of dietary fat with the 50 g/d of RSO mayonnaise. It appears that these authors later conducted another 9-week phase of the study using sitostanol esters (1.36 g/d plant stanol esters or 800 mg/d free stanols) dissolved in 50 g RSO mayonnaise. The results of this later phase were reported in the Miettinen reference (Ref. 63), together with the earlier results. The Vanhanen reference (Ref. 64) reports only the earlier results for sitosterol and sitostanol. The Vanhanen reference (Ref. 64) reports reduced serum total cholesterol concentrations (8.5 percent) during the RSO mayonnaise run-in period (stabilization period before the intervention begins) compared to values before the run-in period when combining all subjects. Continuation of RSO mayonnaise in the RSO mayonnaise control group (n=8) during the experimental period had no further effect on blood cholesterol (Refs. 63 and 64). ('N' refers to the number of subjects.) Neither sitosterol (n=9) nor sitostanol (n=7) significantly altered serum total cholesterol or LDL cholesterol concentrations compared to the RSO control group (n=8) during the experimental period (Refs. 63 and 64). Sitostanol ester (n=7), however, significantly reduced serum total and LDL cholesterol levels compared to the RSO

control group (Ref. 63). Furthermore, serum total cholesterol was significantly reduced by 4 percent ($p = 0.05$) during the experimental period in an analysis, which compared the combined plant sterol/stanol groups (sitostanol, sitosterol, and sitostanol ester groups; $n=23$) to the RSO control group ($n=8$) (Ref. 63). HDL cholesterol did not change in the plant sterol group compared to the RSO control group (Ref. 63).

The agency notes that it is difficult to decipher from the descriptions in these

[[Page 54694]]

reports the amount of plant sterol that was consumed and the level of cholesterol-lowering that was observed. For the sitosterol group, as an example, the method section states that 722 mg/d of sitosterol was added to the RSO mayonnaise, yet the abstract mentions that the RSO mayonnaise contained an additional 625 mg/d of sitosterol (Ref. 64). The results section of the Miettinen reference (Ref. 63) notes that in the combined plant sterol/stanol groups, total and LDL cholesterol levels were slightly but significantly decreased up to 4 percent, yet the abstract states that serum total cholesterol was reduced by about 5 percent in the combined plant sterol/stanol groups. Therefore, FDA considers the results in these reports inconclusive because of inconsistencies in the descriptions of methods and results.

(c) Normocholesterolemics: ``typical'' or ``usual'' diets. The results of three studies (Refs. 51, 65, and 75) support a cholesterol-lowering effect of plant sterols in subjects with normal cholesterol values.

Ayesh et al. (Ref. 51), in a controlled feeding study, reported significantly lower serum total cholesterol (18 percent, $p = 0.0001$) and LDL cholesterol (23 percent, $p = 0.0001$) in subjects consuming 13.8 g/d vegetable oil sterol esters (8.6 g/d free plant sterols delivered in 40 g of margarine each day consumed with breakfast and dinner under supervision) for 21 days in males and 28 days in females, compared to subjects consuming a control margarine. These results were calculated as the difference from baseline to days 21 for male and 28 for female; analysis of covariance was adjusted for gender. There was no significant difference in effect on HDL cholesterol between control and plant sterol groups.

In a double-blind crossover study, Sierksma et al. (Ref. 75) showed that daily consumption of 25 g of a spread enriched with free soybean oil sterols (0.8 g/d) for 3 weeks lowered plasma total and LDL cholesterol concentrations respectively by 3.8 percent ($p = 0.05$) and 6 percent ($p = 0.05$) compared with a placebo spread. No effect on plasma HDL cholesterol was found. Subjects followed their usual diets, except that they replaced their usual spread with the test or placebo spread. The investigators also tested sheanut-oil sterols (3.3 g/d) in 25 g of spread and found that the sheanut-oil spread did not lower plasma total and LDL cholesterol levels. The sheanut-oil sterols were primarily phenolic acid esters of 4,4-dimethyl sterols, whereas the soybean-oil product contained 4-desmethyl sterols (the class of sterols containing no methyl group at the carbon 4 atom). The structure of 4-desmethyl sterols is more similar to cholesterol than the structure of 4,4-dimethyl sterols. The investigators stated that soybean-oil sterol structural similarity to cholesterol may offer increased competition with cholesterol for incorporation in mixed micelles, the most likely mechanism for the blood cholesterol-lowering action of plant sterols.

Pelletier et al. (Ref. 65) reported reductions in blood total cholesterol (10 percent, $p = 0.001$) and LDL cholesterol (15 percent, $p = 0.001$), compared to a control period, in subjects consuming 740 mg/d of soybean oil sterols (nonesterified) in 50 g/d of butter for 4 weeks.

These results were obtained in a crossover experiment in 12 normocholesterolemic men consuming a controlled, but "normal" diet. The total fat intake as a percent of energy was 36.4 percent during both the control and the plant sterol-feeding period. The cholesterol intake during the control period was 436 mg/d; it was 410 mg/d during the plant sterol-feeding period. The diets were designed to have a plant sterol to cholesterol ratio of 2.0, which has repeatedly been shown to affect cholesterol levels in various animal models. There was no significant difference in effect on HDL cholesterol between control and plant sterol groups.

(d) Other studies: research synthesis study. FDA considered the results of a March 25, 2000, research synthesis study by Law (Ref. 100) of the effect of plant sterols and stanols on serum cholesterol concentrations. While evaluation of research synthesis studies, including meta-analyses, is of interest, the appropriateness of such analytical techniques in establishing substance/disease relationships has not been determined. There are ongoing efforts to identify criteria and critical factors to consider in both conducting and using such analyses, but standardization of this methodology is still emerging. Therefore, this research synthesis study was considered as supporting evidence but did not weigh heavily within the body of evidence on the relationship between plant sterol/stanol esters and CHD.

Law performed a research synthesis analysis of the effect of plant sterols and stanols on serum cholesterol concentrations by pooling data from randomized trials identified by a Medline search using the term "plant sterols." Law obtained additional data for analysis from other studies cited in papers and review articles. A total of 14 studies that employed either a parallel or crossover design were incorporated in the analysis, consisting of 20 dose comparisons of either plant sterols or plant stanols to a control vehicle. The data described the effects on serum LDL cholesterol concentrations obtained from using spreads (or in some cases, mayonnaise, olive oil, or butter) with and without added plant sterols or stanols. Studies that included children with familial hypercholesterolemia were excluded from the research synthesis analysis. Law included in the research synthesis analysis study populations with severe hypercholesterolemia (mean serum total cholesterol greater than 300 mg/dL) and study populations with previous myocardial infarction or noninsulin dependent diabetes mellitus, as well as study populations with mildly and moderately hypercholesterolemic and/or normal cholesterol concentrations.

Based on the placebo-adjusted reduction in serum LDL cholesterol, the analysis indicated that 2 g of plant sterol (equivalent to 3.2 g/d of plant sterol esters) or plant stanol (equivalent to 3.4 g/d of plant stanol esters) added to a daily intake of spread (or mayonnaise, olive oil, or butter) reduces serum concentrations of LDL cholesterol by an average of 20.9 mg/dL (0.54 millimole per liter (mmol/l)) in people aged 50 to 59 ($p=0.005$), 16.6 mg/dL (0.43 mmol/l) in those aged 40 to 49 ($p=0.005$), and 12.8 mg/dL (0.33 mmol/l) in those aged 30 to 39 ($p=0.005$). The results indicated that the reduction in the concentration of LDL cholesterol at each dose is significantly greater in older people versus younger people. The reductions in blood total cholesterol concentrations were similar to the LDL cholesterol reductions and there was little change in serum concentrations of HDL cholesterol. The results of this analysis also suggested that doses greater than about 2 g of plant sterol (3.2 g/d of plant sterol esters) or stanol (3.4 g/d of plant stanol esters) per day would not result in further reduction in LDL cholesterol (Ref. 100).

Observational studies and randomized trials concerning the relationship between serum cholesterol and the risk of heart disease (Ref. 101) indicate that for people aged 50 to 59, a reduction in LDL

cholesterol of about 19.4 mg/dL (0.5 mmol/l) translates into a 25 percent reduction in the risk of heart disease after about 2 years. Studies administering plant sterols and stanols have demonstrated the potential to provide this protection. According to Law, the cholesterol-lowering capacity of plant sterols and stanols is even larger than the effect that could be expected to occur if people ate less animal fat (or saturated fat) (Ref. 100).

[[Page 54695]]

(e) Summary. In one preliminary report of hypercholesterolemic subjects consuming a low saturated fat and low cholesterol diet (Refs. 61 and 62 (1 study)), plant sterol ester intake was associated with statistically significant decreases in serum total and LDL cholesterol levels. Levels of HDL cholesterol did not change during plant sterol consumption compared to controls. Levels of plant sterol ester found to be effective in lowering serum total and LDL cholesterol levels, in the context of a diet low in saturated fat and cholesterol, were reported to be 1.76 and 3.52 g/d (1.1 and 2.2 g/d of free plant sterol) (Refs. 61 and 62 (1 study)).

In four (Refs. 57, 58, 67, and 74) of five (Refs. 57, 58, 67, 74, and 63 and 64 (1 study)) studies of hypercholesterolemic subjects consuming "usual" diets that were generally high in total fat, saturated fat and cholesterol, plant sterol intake was associated with statistically significant decreases in blood total and/or LDL cholesterol levels. Levels of HDL cholesterol were found to be unchanged by consumption of diets containing plant sterol (Refs. 57, 58, 67, 74, and 63 and 64 (1 study)). Levels of plant sterol ester found to be effective in lowering blood total and/or LDL cholesterol levels, in the context of a usual diet, ranged in these studies from 1.33 (Ref. 57) to 5.18 g/d (Ref. 57) (equivalent to 0.83 to 3.24 g/d of free plant sterol).

The results of one study in hypercholesterolemic subjects consuming "usual" diets (Refs. 63 and 64 (1 study)) are inconclusive; this may be due to lack of statistical power (e.g., sample size too small to detect the hypothesized difference between groups) or too low a dose of plant sterols to provide an effect. As previously discussed, the descriptions of methods and results also were inconsistent and difficult to interpret. These investigators report no effect of 700 mg/d of plant sterol (equivalent to 1.12 g/d of plant sterol esters) on blood cholesterol levels. However, when the results of three test groups (700 mg/d plant sterol, 700 mg/d plant stanol, 1.36 mg/d plant stanol ester) were pooled and compared to a control group, a statistically significant effect on reducing serum total cholesterol emerged, perhaps because the increased number of subjects in this pooled analysis artificially increased the ability to detect a difference.

In three of three studies (Refs. 51, 65, and 75) of healthy adults with normal blood cholesterol levels consuming a "usual" diet, plant sterol intake was associated with statistically significant decreases in both blood total and LDL cholesterol levels. HDL cholesterol levels were not significantly affected by plant sterol intake. Levels of plant sterol found to be effective in lowering blood total and LDL cholesterol ranged in these studies from 0.74 (Ref. 65) to 8.6 g/d (equivalent to 1.2 to 13.8 g/d of plant sterol esters) (Ref. 51).

Based on these studies, FDA finds there is scientific evidence for a consistent, clinically significant effect of plant sterol esters on blood total and LDL cholesterol. The cholesterol-lowering effect of plant sterol esters is consistent in both mildly and moderately hypercholesterolemic populations and in populations with normal

cholesterol concentrations. The cholesterol-lowering effect of plant sterol esters has been reported in addition to the effects of a low saturated fat and low cholesterol diet. It has been consistently reported that plant sterols do not affect HDL cholesterol levels. These conclusions are drawn from the review of the well controlled clinical studies and are supported by the research synthesis study of Law (Ref. 100).

2. Studies Evaluating the Effects of Plant Stanol Esters on Blood Cholesterol

As discussed in section III.B.1.b of this document, FDA reviewed 24 studies (Refs. 58, 63 and 64 (1 study), 67, 74, 77 through 80, 81 and 82 (1 study), and 83 through 97) on plant stanols, including both free and esterified forms. Of these, 15 met the selection criteria listed in section III.B.2. of this document (Refs. 58, 63 and 64 (1 study), 67, 74, 77, 78, 80, 81 and 82 (1 study), 88 through 92, 94, and 97). These studies are summarized in table 2 at the end of this document and discussed below. The nine remaining studies (Refs. 79, 83 through 87, 93, 95, and 96) failed to meet the selection criteria because of insufficient information to evaluate the design and method of the study or because the populations studied were not considered representative of the general U.S. adult population. For example, some of the studies were performed in children with type II or familial hypercholesterolemia; others used adult subjects with mean serum total cholesterol levels > 300 mg/dL or subjects with preexisting disease (e.g., diabetes). As supporting evidence, the results of a community intervention study (Ref. 102) and a research synthesis study (Ref. 100) that included a number of the plant stanol ester studies submitted in the petition are discussed in section III.C.2.d of this document.

Studies typically report the amount of free plant stanol consumed, rather than the levels of stanol esters administered. Where possible, we report both the amount of plant stanol ester and the equivalent free stanol.

(a) Hypercholesterolemics (serum cholesterol 300 mg/dL): low saturated fat and cholesterol diets. Two studies (Refs. 77 and 80) showed a relationship between consumption of plant stanol esters and reduced blood cholesterol in hypercholesterolemic subjects who consumed plant stanol esters as part of a low saturated fat and low cholesterol diet.

Andersson et al. (Ref. 80) randomized subjects to receive one of three test diets: Either a low fat margarine containing 3.4 g/d plant stanol esters (2 g/d of plant stanols) with a controlled, low saturated fat, low cholesterol diet; a control low fat margarine containing no plant stanol esters with a controlled, low saturated fat, low cholesterol diet; or to continue their normal diet with the addition of the margarine containing 3.4 g/d plant stanol esters (2 g/d of plant stanols). Serum total and LDL cholesterol were reduced in all three groups after 8 weeks. The group consuming the margarine containing plant stanol esters with the low saturated fat, low cholesterol diet showed 12 percent (p 0.0035) and 15 percent (p 0.0158) reductions in serum total and LDL cholesterol levels, respectively, compared to the group that consumed a control low fat margarine with a controlled, low saturated fat, low cholesterol diet. The serum total and LDL cholesterol reductions were reported to be 4 percent (p 0.0059) and 6 percent (p 0.0034), respectively, for the group consuming the margarine containing plant stanol esters with the low saturated fat, low cholesterol diet compared to the group consuming the margarine containing plant stanol esters with a normal diet. Although a normal diet and control margarine group was not included, this study suggests that 3.4 g/d of plant stanol esters in conjunction with a normal or controlled, low saturated fat, low cholesterol diet can significantly

lower serum cholesterol levels. There was no change in HDL cholesterol levels in the normal diet, plant stanol ester margarine group. The study results suggest that the reduction in serum cholesterol levels is significantly greater when the plant stanol esters are consumed as part of a diet low in saturated fat and cholesterol. HDL cholesterol was decreased, however, in subjects in both low saturated fat, low cholesterol diet groups, and this result was statistically significant in the group that consumed the plant stanol ester margarine in conjunction with this diet.

[[Page 54696]]

Hallikainen et al. (Ref. 77) randomly assigned 55 mildly hypercholesterolemic subjects, after a 4-week high fat diet (36 to 38 percent of energy from fat), to one of three low fat margarine groups: a 3.9 g/d (2.31 g/d of free plant stanols) wood stanol ester-containing margarine, a 3.9 g/d (2.16 g/d of free plant stanols) vegetable oil stanol ester-containing margarine, or a control margarine group. The groups consumed the margarines for 8 weeks as part of a diet resembling that of the National Heart, Lung, and Blood Institute's National Cholesterol Education Program Step II diet (a diet in which saturated fat intake is less than 7 percent of calories and cholesterol is less than 200 mg/d) (Ref. 99). During the experimental period, the serum total cholesterol reduction was significantly greater in the wood stanol ester-containing margarine (10.6 percent, $p = 0.001$) and vegetable oil stanol ester-containing margarine (8.1 percent, $p = 0.05$) groups than in the control group, but no significant differences were found between the wood stanol ester-containing margarine and vegetable oil stanol ester-containing margarine groups. The LDL cholesterol reduction was significantly greater in the wood stanol ester-containing margarine (13.7 percent $p = 0.01$) group than in the control group. For the vegetable oil stanol ester-containing margarine group, the LDL cholesterol reduction was 8.6 percent greater than in the control, but the difference was not statistically significant ($p = 0.072$). However, there were no significant differences reported between the wood stanol ester-containing margarine and vegetable oil stanol ester-containing margarine groups for LDL cholesterol. HDL cholesterol concentrations did not change during the study. The authors state, ``* * * that plant stanols can reduce serum cholesterol concentrations, even in conjunction with a markedly low dietary cholesterol intake, indicates that plant stanols must inhibit not only the absorption of dietary cholesterol but also that of biliary cholesterol.''

The results of another study (Ref. 97) did not show a relationship between consumption of plant stanols and blood cholesterol in hypercholesterolemic subjects who consumed plant stanols as part of a low saturated fat and low cholesterol diet. In this study, Denke (Ref. 97) tested the cholesterol-lowering effects of dietary supplementation with plant stanols (3 g/d suspended in safflower oil and packed into gelatin capsules) in 33 men with moderate hypercholesterolemia who were consuming a Step 1 diet. Plant stanol consumption did not significantly lower plasma total cholesterol or LDL cholesterol compared with the Step 1 diet alone. HDL cholesterol levels were also unchanged. The authors state that although previous reports suggested that low dose plant stanol consumption is an effective means of reducing plasma cholesterol concentrations, its effectiveness may be attenuated when the diet is low in cholesterol. The agency notes that, unlike several of the studies submitted with the petition, this study was not a randomized, placebo-controlled, double-blind study, but rather a fixed sequence design. One result of this design was that during the plant stanol dietary supplement phase the subjects consumed an additional 12

g of fat that they did not consume in other phases because each dietary supplement contained 1g of safflower oil and subjects were instructed to consume 4 capsules per meal (subjects were to consume a total of 12 capsules (3000 mg) in three divided doses during three meals). The agency does not give as much weight to this study as it does the studies in which subjects were randomly assigned to placebo or plant stanol arms of a study with all else being equal among the participants.

(b) Hypercholesterolemics (serum cholesterol 300 mg/dL): ``typical'' or ``usual'' diets. Eight studies (Refs. 63 and 64 (1 study), 67, 78, 81 and 82 (1 study), 88 through 90, and 94) show a relationship between consumption of plant stanols and reduced blood total and LDL cholesterol in hypercholesterolemic subjects consuming diets within the range of a typical American diet. Two studies (Refs. 58 and 74) show a relationship between consumption of plant stanols and reduced LDL cholesterol, but not blood total cholesterol, in the same category of subjects consuming diets within the range of a typical American diet.

Hallikainen et al. (Ref. 88) conducted a single-blind, crossover study in which 22 hypercholesterolemic subjects consumed margarine containing four different doses of plant stanol esters, including 1.4, 2.7, 4.1, and 5.4 g/d (0.8, 1.6, 2.4, and 3.2 g/d of free plant stanols) for 4 weeks each. These test margarine phases were compared to a control margarine phase, also 4 weeks long. All subjects followed the same standardized diet throughout the study, and the order of the margarine phases was randomized. Serum total cholesterol concentration decreased (calculated in reference to control) by 2.8 percent for the 1.4 g/d dose ($p=0.384$), 6.8 percent for the 2.7 g/d dose ($p=0.001$), 10.3 percent for the 4.1 g/d dose ($p=0.001$) and 11.3 percent ($p=0.001$) for the 5.4 g/d dose of plant stanol esters. The respective decreases for LDL cholesterol were 1.7 percent ($p=0.892$), 5.6 percent ($p=0.05$), 9.7 percent ($p=0.001$) and 10.4 percent ($p=0.001$). Although decreases were numerically greater with 4.1 and 5.4 g doses than with the 2.7 g dose, these differences were not statistically significant ($p=0.054-0.516$). This study demonstrates that at least 2.7 g/d of plant stanol esters can significantly reduce both serum total cholesterol and LDL cholesterol levels by at least 5.6 percent compared to control. No statistically significant changes in HDL cholesterol were observed with any of the plant stanol ester margarines.

Gylling and Miettinen (Ref. 78) reported the serum cholesterol-lowering effects of feeding different campestanol/sitostanol mixtures in margarine or butter in 23 postmenopausal women using a double-blind crossover design. The participants were randomly allocated to study periods where they consumed 25 g/d of plant stanol-containing rapeseed oil margarine with either 5.4 g sitostanol ester-rich (3.18 g of free plant stanols; wood-derived plant stanol esters with a campestanol to sitostanol ratio 1:11) plant stanol esters or 5.7 g campestanol ester-rich (3.16 g of free plant stanols; vegetable oil-derived plant stanol esters with a campestanol to sitostanol ratio 1:2) plant stanol esters. After 6 weeks, subjects consumed the other margarine for an additional 6 weeks. Following an 8 week home diet wash-out period, 21 of the subjects were randomly assigned to consume either 25 g of butter or 4.1 g/d plant stanol esters (2.43 g/d of free plant stanols with a campestanol to sitostanol ratio 1:1) in 25 g of butter for an additional 5 weeks. Throughout the study, subjects consumed their usual diets, except that they were instructed to substitute the 25 g/d of butter or margarine consumed as part of the study for 25 g of their normal daily fat intake. Both the wood and vegetable stanol ester margarines lowered serum total cholesterol by 4 and 6 percent, respectively, compared to baseline ($p=0.05$ for both). LDL cholesterol

was reduced by 8 and 10 percent with the wood and vegetable stanol ester margarines, respectively, versus baseline (p 0.05 for both). Furthermore, HDL cholesterol was increased by 6 and 5 percent (p 0.05) with the wood and vegetable stanol ester margarines, respectively, versus baseline, so the LDL/HDL cholesterol ratio was reduced by 15 percent (p

[[Page 54697]]

0.05 for both). The two plant stanol mixtures in margarine appeared equally effective in reducing serum cholesterol. Butter alone increased serum total and LDL cholesterol by 4 percent (p 0.05 for total cholesterol, not statistically significant for LDL cholesterol). Although the plant stanol ester butter did not significantly reduce serum total and LDL cholesterol compared to baseline, the plant stanol ester butter was found to decrease serum total cholesterol by 8 percent and LDL cholesterol by 12 percent (p 0.05 for both) compared to butter alone. There was no significant change in HDL cholesterol between the two butter groups. The study reported that plant stanol esters are able to decrease serum total and LDL cholesterol in a saturated environment, i.e., when plant stanol ester is consumed in butter, a high saturated-fat food, and compared to the effects of butter without plant stanol esters. The observation that the plant stanol ester butter did not reduce blood cholesterol levels compared to baseline suggests that plant stanol esters do not completely counteract the impact of a high saturated-fat diet on blood cholesterol levels.

Nguyen et al. (Ref. 90) examined the blood cholesterol-lowering effects in subjects consuming either a European spread containing 5.1 g/d plant stanol esters (3 g/d free plant stanols), a U.S.-reformulated spread containing 5.1 g/d plant stanol esters (3 g/d free plant stanols), a U.S.-reformulated spread containing 3.4 g/d plant stanol esters (2 g/d of free plant stanols), or a U.S.-reformulated spread without plant stanol esters for 8 weeks. The subjects consumed a total of 24 g of spread in three 8 g servings a day, but made no other dietary changes. Serum total cholesterol (p 0.001) and LDL cholesterol (p 0.02) levels were significantly reduced in all three test groups compared with the placebo group at all time points during the ingredient phase. The U.S. spread containing 5.1 g/d plant stanol esters lowered serum total and LDL cholesterol by 6.4 and 10.1 percent, respectively, when compared to baseline (p 0.001). Subjects consuming the 5.1 g/d plant stanol esters European spread achieved a 4.7 percent reduction in serum total cholesterol and a 5.2 percent reduction in LDL cholesterol compared to baseline (p 0.001). The 3.4 g/d plant stanol ester U.S. spread group showed a 4.1 percent reduction in both serum total and LDL cholesterol levels compared to baseline (p 0.001). HDL cholesterol levels were unchanged throughout the study.

Weststrate and Meijer (Ref. 67) evaluated the effects of different plant sterols and stanols on plasma total and LDL cholesterol in normocholesterolemic and mildly hypercholesterolemic subjects. The subjects consumed their usual diets with the addition of a test or placebo margarine. A randomized double-blind placebo-controlled balanced incomplete Latin square design with five treatments and four periods of 3.5 weeks was utilized to compare the effect of margarines (30 g/d) with added plant stanol esters (4.6 g/d; 2.7 g/d free plant stanols), or with added plant sterol esters from sheanut oil (2.9 g/d), ricebran oil (1.6 g/d), or soybean oil (4.8 g/d; 3 g/d free plant sterol) to a placebo margarine. Plasma total and LDL cholesterol concentrations were significantly reduced by 7.3 and 13.0 percent (p 0.05), respectively, compared to control, in the plant stanol ester margarine group. Similar reductions were reported in the soybean oil

sterol ester margarine group (see discussion of this study in section III.C.1.b of this document). No effect on HDL cholesterol concentrations was reported during the study.

In a long term study conducted in Finland (Ref. 89), 153 mildly hypercholesterolemic subjects were instructed to consume 24 g/d of canola oil margarine or the same margarine with added plant stanol esters for a targeted consumption of 5.1 g/d plant stanol esters (3 g/d free plant stanols), without other dietary changes. At the end of 6 months, those consuming plant stanol esters were randomly assigned either to continue the test margarine with a targeted intake of 5.1 g/d plant stanol esters or to switch to a targeted intake of 3.4 g/d plant stanol esters (2 g/d free plant stanols) for an additional 6 months. The control group also continued for another 6 months. Based on measured margarine consumption, average plant stanol ester intakes were 4.4 g/d (in the 5.1 g/d target group) and 3.1 g/d (in the 3.4 g/d target group). The mean 1 year reduction in serum total cholesterol was 10.2 percent in the 4.4 g/d plant stanol ester group, as compared with an increase of 0.1 percent in the control group. The difference in the change in serum total cholesterol concentration between the two groups was -24 mg/dL (p 0.01). The respective reductions in LDL cholesterol were 14.1 percent in the 4.4 g/d plant stanol ester group and 1.1 percent in the control group. The differences in the change in LDL cholesterol concentration between the two groups was -21 mg/dL (p 0.001). Significant reductions in serum total and LDL cholesterol were also reported after consuming plant stanol esters for 6 months. Unlike the group consuming 4.4 g/d of plant stanol esters for 12 months, where continued reductions in serum total and LDL cholesterol were observed from 6 to 12 months, the reduction in plant stanol ester intake to 3.1 g/d at 6 months was not followed by any further decrease in the serum total and LDL cholesterol concentrations. Serum HDL cholesterol concentrations were not affected by plant stanol esters.

Vanhanen et al. (Ref. 94) reported the hypocholesterolemic effects of 1.36 g/d of plant stanol esters (800 mg/d of free plant stanols) in RSO mayonnaise for 9 weeks followed by 6 weeks of consumption of 3.4 g/d of plant stanol esters (2 g/d of free plant stanols) in RSO mayonnaise compared to a group receiving RSO mayonnaise alone. Subjects consumed their usual diets, except that they were instructed to substitute the RSO mayonnaise for 50 g/d of their normal daily fat intake. After 9 weeks of consumption of the lower dose plant stanol ester mayonnaise, the changes in serum levels of total and LDL cholesterol were -4.1 percent (p 0.05) and -10.3 percent (not statistically significant), respectively, as compared to the control. Greater reductions in both serum total and LDL cholesterol were observed after consumption of 3.4 g/d of plant stanol esters for an additional 6 weeks (p 0.05). The changes in serum levels of total and LDL cholesterol were -9.3 percent and -15.2 percent, respectively, for subjects consuming 3.4 g/d of plant stanol esters as compared to control. Plant stanol ester consumption in RSO mayonnaise did not change HDL cholesterol levels compared to control RSO mayonnaise.

Blomqvist et al. (Ref. 81) and Vanhanen et al. (Ref. 82) separately reported the results of another study showing plasma cholesterol-lowering effects of plant stanol esters dissolved in RSO mayonnaise. After subjects replaced 50 g of their daily fat intake by 50 g of RSO mayonnaise for 4 weeks, they were randomized into two groups, one that continued with the original RSO mayonnaise (control group) and the other with RSO mayonnaise in which 5.8 g of plant stanol ester was dissolved (3.4 g/d of free plant stanols in 50 g of mayonnaise preparation). After 6 weeks on the plant stanol ester-enriched diet, plasma total and LDL cholesterol were reduced from 225 <plus-minus> 27 (control group) to 2- <plus-minus> 34 mg/dL (plant stanol ester group)

(p 0.001) and from 134 <plus-minus> 18 (control group) to 124 <plus-minus> 32 mg/dL (plant stanol ester) (p 0.01), respectively (Ref. 81). In the report by

[[Page 54698]]

Blomqvist (Ref. 81), HDL cholesterol was reported to be significantly lower in the plant stanol ester group compared to the control group. Using the same data, with the exception that the number of control subjects utilized in the analysis was 33 rather than 32 as in the Blomqvist report, HDL cholesterol was reported to be unchanged in the report by Vanhanen (Ref. 82). The agency does not give as much weight to this study because the two reports lacked sufficient detail on the reason for the varying number of control subjects.

Two reports of apparently the same study (Refs. 63 and 64) gave inconclusive results regarding the relationship between plant stanol ester consumption and blood cholesterol levels. Interpretation of this study is complicated by design issues such as concerns about sample size and level of plant sterol/stanol administered, but both reports are discussed here and summarized in table 2 of this document because they provide information to assist in determining the minimum level of plant stanol esters necessary to provide a health benefit.

Miettinen and Vanhanen (Refs. 63 and 64 (1 study)) reported the effect of small amounts of sitosterol (700 mg/d free sterols) and sitostanol (700 mg/d free stanols) dissolved in 50 g RSO mayonnaise on serum cholesterol in 31 subjects with hypercholesterolemia for 9 weeks. Subjects did not change their diets except for replacing 50 g/d of dietary fat with the 50 g/d of RSO mayonnaise. It appears that these authors later conducted another 9-week phase of the study using sitostanol esters (1.36 g/d plant stanol esters or 800 mg/d free stanols) dissolved in 50 g RSO mayonnaise. The results of this later phase were reported in the Miettinen reference (Ref. 63), together with the earlier results. The Vanhanen reference (Ref. 64) reports only the earlier results for sitosterol and sitostanol. The Vanhanen reference (Ref. 64) reports reduced serum total cholesterol (8.5 percent) concentrations during the RSO mayonnaise run-in period compared to values before the run-in period when combining all subjects. Continuation of RSO mayonnaise in the RSO mayonnaise control group (n=8) during the experimental period had no further effect on blood cholesterol (Refs. 63 and 64). Free sitostanol (n=7) did not significantly alter serum total cholesterol or LDL cholesterol compared to the RSO control group during the experimental period (Refs. 63 and 64). HDL cholesterol also did not change in the free sitostanol group (Ref. 63). Serum total and LDL cholesterol were significantly reduced in the sitostanol ester group (n=7), however (Ref. 63). The mean change in serum total cholesterol from baseline was -7.4 mg/dL in the sitostanol ester group, compared to +4.6 mg/dL in the control group (p 0.05). The mean change in LDL cholesterol from baseline was -7.7 mg/dL in the sitostanol ester group compared to +3.1 mg/dL in the control group (p 0.05). A statistically significant increase in HDL cholesterol from baseline, however, was reported in the sitostanol ester-treated group (Ref. 63).

The agency notes that it is difficult to decipher from the descriptions in these reports the amount of plant stanol ester that was consumed and the level of cholesterol-lowering that was observed. For the sitostanol ester group, as an example, the experimental design section states that 800 mg/d of sitostanol transesterified with RSO fatty acids was added to the RSO mayonnaise, yet table 1 of this document shows that the amount of sitostanol ester in the RSO mayonnaise was 830 mg (Ref. 63). Since the conversion factor to obtain

the stanol ester equivalent of a given amount of free stanol is 1.7, the amounts of sitostanol and sitostanol ester given in the experimental design section and table 1 cannot both be correct. Based on information in the results section of the Miettinen reference (Ref. 63), serum total cholesterol reduction in the sitostanol ester group can be calculated to be approximately 18 percent as compared to control, yet the abstract of the Vanhanen reference mentions that sitostanol ester reduced serum total cholesterol by 7 percent (Ref. 63). Therefore, FDA considers the results in these reports inconclusive because of inconsistencies in the descriptions of methods and results.

Two studies (Refs. 58 and 74) show a relationship between consumption of plant stanols and reduced LDL cholesterol, but not blood total cholesterol, in subjects consuming a diet within the range of a typical American diet, although the diet was a controlled feeding regimen formulated to meet Canadian recommended nutrient intakes.

Jones et al. (Ref. 58) reported the effects of consuming 2.94 g/d of plant sterol esters in 23 g of margarine, 3.31 g/d of plant stanol esters in 23 g of margarine (1.84 g/d free plant stanols; daily margarine doses were divided into three equal portions and added to each meal) and 23 g/d of control margarine for 21 days each, using a controlled feeding crossover study design. During the experimental period, subjects consumed a fixed-food North American diet formulated to meet Canadian recommended nutrient intakes. The results from consumption of the plant sterol ester margarine are discussed in section III.C.1.b of this document. Plasma LDL cholesterol levels were reduced by 6.4 percent ($p = 0.02$) in the plant stanol ester group compared to the control group. Plasma total cholesterol was not significantly reduced in the plant stanol ester group. Plasma HDL cholesterol did not differ across groups, and there was no significant weight change shown by the subjects while consuming any of the margarine mixtures.

Jones et al. (Ref. 74) evaluated the effects of a mixture of plant stanols and plant sterols. The plant stanol compound sitostanol made up about 20 percent of the mixture by weight. The remaining sterol component of the mixture was mostly composed of the plant sterols sitosterol and campesterol. These investigators evaluated the cholesterol-lowering properties of this nonesterified plant sterol/stanol mixture in a controlled feeding regimen based on a "prudent," fixed-food North American diet formulated to meet Canadian recommended nutrient intakes. Thirty-two hypercholesterolemic men were fed either a diet of prepared foods alone or the same diet plus 1.7 g/d of the plant sterol/stanol mixture (in 30 g/d of margarine, consumed during 3 meals) for 30 days in a parallel study design. The plant sterol/stanol mixture had no statistically significant effect on plasma total cholesterol concentrations. However, LDL cholesterol concentrations on day 30 had decreased by 8.9 percent ($p = 0.01$) and 24.4 percent ($p = 0.001$) with the control and plant sterol/stanol-enriched diets, respectively. On day 30, LDL cholesterol concentrations were significantly lower ($p = 0.05$) by 15.5 percent in the group consuming the plant sterol/stanol mixture compared to the control group. HDL cholesterol concentrations did not change significantly during the study.

(c) Normocholesterolemics: "typical" or "usual" diets. Two studies (Refs. 91 and 92) show a relationship between consumption of plant stanols and reduced blood cholesterol in subjects with normal cholesterol concentrations consuming a typical American diet.

Plat and Mensink (Ref. 92) examined the effects of two plant stanol ester preparations in healthy subjects with normal serum cholesterol levels. During a 4 week run-in period, 112 subjects consumed a rapeseed oil margarine (20 g/d) and shortening (10 g/d). For the next 8 weeks, 42 subjects continued with these products, while the other

[[Page 54699]]

subjects received margarine (20 g/d) and shortening (10 g/d) with a vegetable oil-based stanol ester mixture (6.8 g/d plant stanol esters or 3.8 g/d free plant stanols) or pine wood-based stanol ester mixture (6.8 g/d plant stanol ester or 4 g/d plant stanol). Subjects did not change their diets except for replacing 30 g/d of dietary fat with the 30 g/d of test margarine and shortening. In the vegetable oil plant stanol ester group, the mean change in serum total cholesterol from baseline was -16.6 mg/dL, compared to -1.6 mg/dL in the control group (p 0.001). In the pine wood stanol ester group, the mean change in serum total cholesterol from baseline was -16.3 mg/dL compared to -1.6 mg/dL in the control group (p 0.001). Compared to consumption of a control margarine and shortening, consumption of 6.8 g/d of vegetable oil-based stanol esters lowered LDL cholesterol by 14.6 <plus-minus> 8.0 percent (p 0.001). Consumption of 6.8 g/d of the pine wood-based stanol esters showed a comparable decrease of 12.8 <plus-minus> 11.2 percent (p 0.001) in comparison to control margarine consumption. Decreases in LDL cholesterol were not significantly different between the two experimental groups (p= 0.793). Serum HDL cholesterol did not change during the study.

Niinikoski et al. (Ref. 91) randomly assigned 24 subjects with normal serum cholesterol levels to use either a plant stanol ester margarine (5.1 g/d plant stanol esters; 3 g/d of free plant stanols) or ordinary rapeseed oil margarine (control) for 5 weeks. Subjects followed their normal diets, except for substituting the test or control margarine for normal dietary fat intake. During the study period the mean plus/minus standard deviation for serum total cholesterol decreased more in the plant stanol ester spread group (-31 plus/minus 19.4) compared to the ordinary rapeseed oil spread group (-11.6 plus/minus 19.4) (p 0.05). Serum non-HDL (LDL plus very low density lipoprotein) cholesterol also decreased more in the plant stanol ester group (-31 plus/minus 23) compared to the control group (-11.6 plus/minus 19.4) (p 0.05), but the plant stanol ester spread did not influence HDL cholesterol concentration (p= 0.71 between groups).

(d) Other studies: research synthesis study. As discussed in section III.C.1.d of this document, the agency considered the results of a March 25, 2000, research synthesis study (Ref. 100) of the effect of plant sterols and plant stanols on serum cholesterol concentrations as supporting evidence on the relationship between plant sterol/stanol esters and CHD. In this research synthesis study, the combined effect of plant sterols and stanols on serum cholesterol concentrations was analyzed by pooling data from 14 randomized trials that employed either a parallel or crossover design, consisting of 20 dose comparisons of either plant sterols or plant stanols to a control vehicle. The data described the effects on serum LDL cholesterol concentrations obtained from using spreads (or, in some cases, mayonnaise, olive oil, or butter) with and without added plant sterols or stanols.

Based on the placebo-adjusted reduction in serum LDL cholesterol, the analysis indicated that 2 g of plant sterol (equivalent to 3.2 g/d of plant sterol esters) or plant stanol (equivalent to 3.4 g/d of plant stanol esters) added to a daily intake of spread (or mayonnaise, olive oil, or butter) reduces serum concentrations of LDL cholesterol by an average of 20.9 mg/dL in people aged 50 to 59 (p=0.005), 16.6 mg/dL in those aged 40 to 49 (p=0.005), and 12.8 mg/dL in those aged 30 to 39 (p=0.005). The results indicated that the reduction in the concentration of LDL cholesterol at each dose is significantly greater in older people versus younger people. Reductions in blood total cholesterol concentrations were similar to the LDL cholesterol

reductions and there was little change in serum concentrations of HDL cholesterol. The results of this analysis also suggested that doses greater than about 2 g of plant sterol (3.2 g/d of plant sterol esters) or stanol (3.4 g/d of plant stanol esters) per day would not result in further reduction in LDL cholesterol.

Observational studies and randomized trials concerning the relationship between serum cholesterol and the risk of heart disease (Ref. 101) indicate that for people aged 50 to 59, a reduction in LDL cholesterol of about 19.4 mg/dL (0.5 mmol/l) translates into a 25 percent reduction in the risk of heart disease after about 2 years. Studies administering plant sterols and stanols have demonstrated the potential to provide this protection. According to Law, the cholesterol-lowering capacity of plant sterols and stanols is even larger than the effect that could be expected to occur if people ate less animal fat (or saturated fat) (Ref. 100).

Community Intervention Study

The plant stanol ester petitioner also submitted a community intervention study by Puska et al. (Ref. 102) that described the relationship between consumption of plant stanol ester-containing margarine and serum total cholesterol concentrations in North Karelia, Finland. FDA considered this study as supporting evidence for the relationship between plant stanol esters and CHD. In the early 1970's, Finland had the highest cardiovascular-related mortality in the world. Since 1972, active prevention programs carried out in the framework of the North Karelia Project have reduced these high rates. A central target of these programs was promotion of dietary changes to reduce population cholesterol levels. In spite of great success in the 1970's and 1980's, cholesterol levels at the end of the 1980's remained, by international standards, relatively high in North Karelia, especially in rural areas. The Village Cholesterol Competition was introduced as an innovative method to promote further cholesterol reduction in the population. Puska et al. (Ref. 102) describe two competitions (1991 and 1997) in which serum cholesterol values of subjects ages 20 to 70 years in participating villages were measured twice during a 2 month period. The village with the greatest mean reduction in serum cholesterol was awarded a monetary prize. The 1991 competition is not relevant to this interim rule because plant stanol ester-containing spreads were not available at the time. However, the 1997 competition is relevant because plant stanol ester-containing spreads had become available and, as discussed below, were consumed by a significant number of participants. Subjects were asked to complete a questionnaire about demographic factors, risk factors, dietary changes, and physical activity. The questionnaire included specific questions on changes in use of milk, fat spreads, fat used for baking, and food preparation. Participating villages were responsible for arranging intervention activities and blood cholesterol measurements.

Sixteen villages, with a total of 1,333 participants, were included in the results. There were 8 weeks between the initial and final blood cholesterol measurements. Approximately 24 percent of the participants changed their fat spread on bread to recommended alternatives (e.g., from butter to margarine), but 57 percent did not make any changes in their choice of spread. Use of plant stanol ester-containing spread increased nearly fivefold, whereas use of butter, butter-vegetable oil mixture and normal vegetable margarine use declined. Approximately 200 participants began to use plant stanol ester spread during the competition as their fat spread on bread.

The winning village had an average serum total cholesterol reduction of 16 percent ($p < 0.001$). Results for each village were calculated as the mean percent reduction in individual

[[Page 54700]]

cholesterol levels. The mean reduction in serum total cholesterol of all participating villages was 9 percent (p 0.001). In 14 of 16 villages, the reduction between the initial and final blood cholesterol measurements was statistically significant (p 0.05). The investigators observed that the greater the self-reported daily use of the plant stanol ester spread, the greater the serum cholesterol reduction. Furthermore, of those who reported using more than 5 teaspoonfuls per day of plant stanol ester-containing spread, an average serum total cholesterol reduction of 21.3 percent was achieved.

(e) Summary. In two (Refs. 77 and 80) of three (Refs. 77, 80, and 97) studies of hypercholesterolemic subjects consuming low saturated fat and low cholesterol diets, plant stanol ester intake was associated with statistically significant decreases in total and LDL cholesterol levels when compared to a control group. Levels of HDL cholesterol were found to be unchanged (Refs. 77, 80, and 97).

Levels of plant stanol esters found to be effective in lowering total and LDL cholesterol levels, in the context of a diet low in saturated fat and cholesterol, were 3.4 g (Ref. 80) and 3.9 g (Ref. 77) (equivalent to 2 and 2.31 g of free plant stanols, respectively). Other results from one of these studies (Ref. 77) reported a statistically significant effect of 3.9 g/d of vegetable oil stanol esters (2.16 g/d of free plant stanols) on blood total cholesterol, but not LDL cholesterol. Dietary supplementation with 3 g of plant stanols per day (equivalent to 5.1 g/d of plant stanol esters) to hypercholesterolemic subjects consuming a low saturated fat and low cholesterol diet (Ref. 97) did not significantly lower plasma total or LDL cholesterol.

In 10 of 10 studies of hypercholesterolemic subjects consuming "usual" diets (Refs. 58, 63 and 64 (1 study), 67, 74, 78, 81 and 82 (1 study), 88 through 90, and 94), plant stanol ester intake was associated with statistically significant decreases in blood total and/or LDL cholesterol levels. In seven (Refs. 58, 67, 74, 88 through 90, and 94) of these ten studies, HDL cholesterol levels were not significantly affected by plant stanol dietary treatment. In 2 studies (Refs. 63 and 64 (1 study) and 78) of the 10 studies, plant stanol esters were reported to increase the levels of HDL cholesterol from baseline levels. Two separate published reports of another study (Refs. 81 and 82) were inconsistent in their description of effects on HDL cholesterol. One publication (Ref. 81) reported HDL cholesterol to be significantly lower in the plant stanol ester group compared to a control group, but the other publication reported that the difference in HDL cholesterol between the two groups was not significant (Ref. 82). This incongruity may be due to the difference in the number of control subjects utilized in the analysis between the two publications. The agency notes that the majority of studies do not report a statistically significant change in HDL cholesterol in the plant stanol ester groups compared to the control groups.

Levels of plant stanol esters found to be effective in lowering total and/or LDL cholesterol levels in hypercholesterolemic subjects consuming a "usual" diet ranged from 1.36 to 5.8 g/d (equivalent to 0.8 to 3.4 g/d of free plant stanols) (Refs. 58, 63 and 64 (1 study), 67, 74, 78, 81 and 82 (1 study), 88 through 90, and 94). In the study by Hallikainen et al. (Ref. 88), 1.4 g/d plant stanol ester (0.8 g/d of free plant stanol) did not significantly reduce serum cholesterol levels, but intakes of 2.7, 4.1, and 5.4 g/d of plant stanol esters (1.6, 2.4, and 3.2 g/d of free plant stanols, respectively) were found to significantly reduce both serum total and LDL cholesterol levels. In another of the 10 studies described above (Ref. 94), subjects consuming a higher dose (3.4 g/d, equivalent to 2 g/d of free plant stanols) of

plant stanol esters showed statistically significant reductions in both blood total and LDL cholesterol, but a lower dose of plant stanol esters (1.36 g/d, equivalent to 0.8 g/d of free plant stanols) showed reductions in blood total, but not in LDL cholesterol. The results of the study by Miettinen and Vanhanen (Refs. 63 and 64) are inconclusive. This may be due to lack of statistical power (e.g., sample size too small to detect the hypothesized difference between groups) or too low a dose of plant stanols to provide an effect. As previously discussed, the descriptions of methods and results also were inconsistent and difficult to interpret. Although these investigators reported (Ref. 63) a statistically significant effect of 1.36 g/d plant stanol esters (equivalent to 0.8 g/d of free plant stanols) on reducing serum total and LDL cholesterol compared to a control group, there was no effect of 700 mg/d of the free plant stanols (equivalent to 1.19 g/d of plant stanol esters) on blood cholesterol levels.

Two studies (Refs. 91 and 92) examined the effects of plant stanol esters in healthy adults with normal cholesterol levels consuming a "usual" diet. Both of these studies demonstrated significant decreases in blood total and LDL cholesterol or non-HDL cholesterol levels when compared to controls. Levels of plant stanol esters found to be effective were 6.8 g/d (vegetable oil stanol esters; 3.8 g/d of free plant stanols) (Ref. 92), 6.8 g/d (pine wood stanol esters; 4 g/d of free plant stanols) (Ref. 92), and 5.1 g/d (source unreported; approximately 3 g/d of free plant stanols) (Ref. 91). HDL cholesterol levels were not significantly affected by plant stanol consumption in these reports.

Based on these studies, FDA finds there is scientific evidence for a consistent, clinically significant effect of plant stanol esters on blood total and LDL cholesterol. The cholesterol-lowering effect of plant stanol esters is consistent in both mildly and moderately hypercholesterolemic populations and in populations with normal cholesterol concentrations. The cholesterol-lowering effect of plant stanol esters has been reported in addition to the effects of a low saturated fat and low cholesterol diet. Most studies also report that plant stanols do not affect HDL cholesterol levels. These conclusions are drawn from the review of the well controlled clinical studies and are supported by the research synthesis study of Law (Ref. 100) and the community intervention trial of Puska et al. (Ref. 102).

IV. Decision to Authorize a Health Claim Relating Plant Sterol/ Stanol Esters to Reduction in Risk of CHD

A. Relationship Between Plant Sterol Esters and CHD

The plant sterol esters petition provided information on pertinent human studies that evaluated the effects on serum total cholesterol and LDL cholesterol levels from dietary intervention with plant sterols or plant sterol esters in subjects with normal to mildly or moderately elevated serum cholesterol levels. FDA reviewed the information in the petition as well as other pertinent studies identified by the agency's literature search.

FDA concludes that, based on the totality of publicly available scientific evidence, there is significant scientific agreement to support a relationship between consumption of plant sterol esters and the risk of CHD. The evidence that plant sterol esters affect the risk of CHD is provided by studies that measured the effect of plant sterol ester consumption on the two major risk factors for CHD, serum total and LDL cholesterol.

In most intervention trials in subjects with mildly to moderately elevated cholesterol levels (total cholesterol 300 mg/dL), plant sterol

esters were found to

[[Page 54701]]

reduce blood total and/or LDL cholesterol levels to a significant degree (Refs. 57, 58, 61 and 62 (1 study), 67, and 74). Moreover, HDL cholesterol levels were unchanged (Refs. 57, 58, 61 and 62 (1 study), 67, and 74). Results in normocholesterolemic subjects (Refs. 51, 65, and 75) were similar to the results in mildly to moderately hypercholesterolemic subjects.

Most of the studies in subjects with mildly to moderately elevated cholesterol levels used "usual" diets in either a controlled feeding (Refs. 58 and 74) or free-living (Refs. 57, 63 and 64 (1 study), and 67) situation, but one study used a low saturated fat, low cholesterol diet during the study (Refs. 61 and 62 (1 study)). All three of the studies in subjects with normal blood cholesterol levels used "usual" diets in either a controlled feeding (Refs. 51 and 65) or free-living (Ref. 75) situation. Plant sterol esters have been reported to lower blood cholesterol levels in subjects with mildly to moderately elevated cholesterol consuming either a "usual" diet or low saturated fat, low cholesterol diet and in subjects with normal blood cholesterol levels consuming "usual" diets. Therefore, the evidence suggests that the blood cholesterol-lowering response occurs regardless of the type of background diet subjects consume.

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. Given the variability of amounts and of food carriers in which plant sterols and plant sterol esters were provided in the diets studied, the response of blood cholesterol levels to plant sterols appears to be consistent and substantial, except for plant sterols from sheanut oil and ricebran oil (Refs. 67 and 75).

Based on the totality of the publicly available scientific evidence, the agency concludes that there is significant scientific agreement that plant sterol esters from certain sources will help reduce serum cholesterol and that such reductions may reduce the risk of CHD. Section 101.83(c)(2)(ii)(A)(1) (discussed in section V.C of this document) specifies the plant sterol esters that have been demonstrated to have a relationship to the risk of CHD. In the majority of clinical studies evaluating plant sterols or plant sterol esters, blood total and LDL cholesterol were the lipid fractions shown to be the most affected by plant sterol intervention. As discussed in section I of this document, reviews by Federal agencies and other scientific bodies have concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total cholesterol and LDL cholesterol represent major contributors to CHD and that dietary factors that decrease blood total cholesterol and LDL cholesterol will affect the risk of CHD (56 FR 60727 at 60728, and Refs. 18 through 21).

Given all of this evidence, the agency is authorizing a health claim on the relationship between plant sterol esters and reduced risk of CHD.

B. Relationship Between Plant Stanol Esters and CHD

The plant stanol esters petition provided information on pertinent human studies that evaluated the effects on serum total cholesterol and LDL cholesterol levels from dietary intervention with plant stanols or plant stanol esters in subjects with normal to mildly or moderately elevated serum cholesterol levels. FDA reviewed the information in the plant stanol esters petition as well as other pertinent studies from

the plant sterol esters petition and from the studies identified by the agency's literature search.

FDA concludes that, based on the totality of publicly available scientific evidence, there is significant scientific agreement to support a relationship between consumption of plant stanol esters and the risk of CHD. The evidence that plant stanol esters affect the risk of CHD is provided by studies that measured the effect of plant stanol ester consumption on the two major risk factors for CHD, serum total and LDL cholesterol.

In most intervention trials in subjects with mildly to moderately elevated cholesterol levels (total cholesterol 300 mg/dL), plant stanol esters were found to reduce blood total and/or LDL cholesterol levels to a significant degree (Refs. 58, 63 and 64 (1 study), 67, 74, 77, 78, 80, 81 and 82 (1 study), 88 through 90, and 94). Moreover, HDL cholesterol levels were unchanged in most intervention studies (Refs. 58, 67, 74, 77, 80, 88 through 90, and 94). Results in normocholesterolemic subjects (Refs. 91 and 92) were similar to the results in mildly to moderately hypercholesterolemic subjects.

Most of the studies in subjects with mildly to moderately elevated cholesterol levels used "usual" diets in either a controlled feeding (Refs. 58 and 74) or free-living (Refs. 63 and 64 (1 study), 67, 78, 81 and 82 (1 study), 88 through 90, and 94) situation, but three studies used a low saturated fat, low cholesterol diet during the study (Refs. 77, 80 and 97). Both of the studies in subjects with normal blood cholesterol levels (Refs. 91 and 92) used "usual" diets in a free-living situation. Plant stanol esters have been reported to lower blood cholesterol levels in subjects with mildly to moderately elevated cholesterol consuming either a "usual" diet or low saturated fat, low cholesterol diet and in subjects with normal blood cholesterol levels consuming "usual" diets. Therefore, the evidence suggests that the blood cholesterol-lowering response occurs regardless of the type of background diet subjects consume.

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 techniques. Given the variability of amounts and food carriers in which plant stanol esters were provided in the diets studied, the response of blood cholesterol levels appears to be consistent and substantial.

Based on the totality of the publicly available scientific evidence, the agency concludes that there is significant scientific agreement that plant stanol esters will help reduce blood cholesterol and that such reductions may reduce the risk of CHD. Section 101.83(c)(2)(ii)(B)(1) (discussed in section V.C of this document) specifies the plant stanol esters that have been demonstrated to have a relationship to the risk of CHD. In the majority of clinical studies evaluating plant stanol esters, blood total and LDL cholesterol were the lipid fractions shown to be the most affected by plant stanol intervention. As discussed in section I of this document, reviews by Federal agencies and other scientific bodies have concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total cholesterol and LDL cholesterol represent major contributors to CHD and that dietary factors that decrease blood total cholesterol and LDL cholesterol will affect the risk of CHD (56 FR 60727 at 60728, and Refs. 18 through 21).

Given all of this evidence, the agency is authorizing a health claim on the relationship between plant stanol esters and reduced risk of CHD.

V. Description and Rationale for Components of Health Claim