notice would provide that any person may, within the period specified therein, submit to the Commission any information that relates to the Commission action requested in the application. The notice also would indicate the earliest date on which the Commission would take final action on the application, but in no event would such action be taken earlier than 25 days following publication of the notice in the **Federal Register**.

(h) The Commission may, in its sole discretion, schedule a hearing on the matter addressed by the application.

By the Commission.

Dated: February 5, 1998.

Margaret H. McFarland,

Deputy Secretary.

[FR Doc. 98–3931 Filed 2–17–98; 8:45 am]

BILLING CODE 8010–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 96P–0338]

Food Labeling: Health Claims; Soluble Fiber From Certain Foods and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing its decision to authorize the use, on food labels and in food labeling, of health claims on the association between soluble fiber from psyllium seed husk and reduced risk of coronary heart disease (CHD). Based on its review of evidence submitted with comments to the proposal, as well as evidence described in the proposal, the agency has concluded that soluble fiber from psyllium seed husk, similar to beta (β)-glucan soluble fiber from whole oats, when included as part of a diet low in saturated fat and cholesterol, may reduce the risk of CHD by lowering blood cholesterol levels. The agency has concluded, based on the totality of publicly available scientific evidence, that there is significant scientific agreement among qualified experts to support the relationship between soluble fiber in psyllium seed husk and CHD. Therefore, the agency has decided to amend the regulation that authorized a health claim on soluble fiber from whole oats and the risk of CHD to include soluble fiber from psyllium seed husk. FDA has determined that label statements alerting consumers to the need to consume adequate amounts of liquids with products containing dry or incompletely hydrated psyllium will be required on products bearing the health claim. FDA is announcing this action in response to a petition filed by the Kellogg Co. (the petitioner).

DATES: This regulation is effective February 18, 1998. The Director of the Office of the Federal Register approves of the incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of certain publications in 21 CFR 101.81(c)(2)(ii)(B), effective February 18, 1998.

FOR FURTHER INFORMATION CONTACT: Virginia L. Wilkening, Center for Food Safety and Applied Nutrition (HFS–165), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–5483.

SUPPLEMENTARY INFORMATION:

I. Background

On November 8, 1990, the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Pub. L. 101–535) was signed into law. This new law amended the Federal Food, Drug, and Cosmetic Act (the act) in a number of important ways. One of the most notable aspects of the 1990 amendments was that they confirmed FDA's authority to regulate health claims on food labels and in food labeling. FDA published final rules implementing the 1990 amendments on January 6, 1993 (58 FR 2478). In those final rules, FDA adopted § 101.14 (21 CFR 101.14), which sets out the rules for the authorization and use of health claims. The agency also adopted § 101.70 (21 CFR 101.70), which establishes a process for petitioning the agency to authorize health claims about a substance-disease relationship and sets out the types of information that any such petition must include.

In addition, FDA conducted an extensive review of the evidence on the 10 substance disease relationships listed in the 1990 amendments. As a result of its review, FDA authorized a health claim in § 101.77 (21 CFR 101.77) on the association between diets low in saturated fat and cholesterol and high in vegetables, fruits, and grain products that contain soluble fiber and a reduced risk of heart disease (58 FR 2552, January 6, 1993). In that rulemaking, FDA reviewed the evidence relating dietary fiber to heart disease and concluded that it was difficult to determine the relationship because dietary fiber comprises a diverse group of chemical substances that may be associated with different physiological functions (58 FR 2552 at 2572). Chemically and physiologically, cellulose, lignin, hemicellulose, pectin, and alginate (all relatively purified fiber types) behave differently from one another. Likewise, wheat bran, oat bran, and rice bran are not similar in composition. The agency noted that the available evidence made it difficult to correlate the role of specific fiber components to health effects.

However, in its final rule, FDA noted that hypocholesterolemic properties may be documented for specific food fibers (58 FR 2552 at 2567). Further, the agency stated that if manufacturers could document, through appropriate studies, that dietary consumption of the soluble fiber in their particular food has the effect of lowering low density lipoprotein (LDL)-cholesterol, and has no adverse effects on other heart disease risk factors (e.g., high density lipoprotein (HDL)-cholesterol), they should petition for a health claim for their particular product.

In accordance with the petition procedure in § 101.70, FDA published a final rule on the relationship between soluble fiber from whole oats and reduced risk of heart disease (the soluble fiber from whole oats final rule), § 101.81 (21 CFR 101.81) (62 FR 3584, January 23, 1997 and modified at 62 FR 15343, March 31, 1997). In that document, the agency concluded that, based on the totality of publicly available scientific evidence, there is significant scientific agreement among qualified experts to support the relationship between soluble fiber in whole oats and reduced risk of CHD. FDA also concluded that the type of soluble fiber in whole oats, β-glucan soluble fiber, is the primary component responsible for the lowering of blood total- and LDL-cholesterol associated with consumption of whole oat products when part of a diet low in saturated fat and cholesterol. The rule specified the chemical nature of the specific fiber and methods for measuring its presence in foods.

In the soluble fiber from whole oats final rule, the agency acknowledged the likelihood that consumption of β-glucan soluble fiber from sources other than whole oats, as well as soluble fiber from other sources, will affect blood lipid levels and thus the risk of heart disease (62 FR 3584 at 3587). At that time, FDA considered structuring the final rule as an umbrella regulation authorizing the use of a claim for "soluble fiber from certain foods" and risk of CHD. Such action would have allowed flexibility in expanding the claim to other specific food sources of soluble fiber when

consumption of those foods has been demonstrated to help reduce risk of heart disease. However, the agency concluded that it was premature to do so inasmuch as FDA had not reviewed the totality of evidence on other, nonwhole oat sources of soluble fiber (62 FR 3584 at 3588). Instead, the agency stated that because soluble fiber is a family of very heterogeneous substances that vary greatly in their effect on risk of CHD, a case-by-case approach is necessary as documentation is developed through appropriate studies that a soluble fiber product has an effect on blood total- and LDL-cholesterol levels and can therefore be useful in reducing risk of CHD. To this end, FDA structured § 101.81 in such a way that, while the regulation covered β-glucan soluble fiber from whole oats, it could easily be amended as evidence becomes available to support the use of the claim for other sources of soluble fiber.

In the soluble fiber from whole oats final rule, FDA emphasized the importance of the dietary component of the health claim, i.e., the necessity for the whole oat product to be consumed as part of a low saturated fat, low cholesterol diet, for a complete understanding of the claim (62 FR 3684 at 3594). FDA stated that diets low in saturated fat and cholesterol are considered by expert groups to be the most effective dietary means of reducing heart disease risk, and that, while soluble fiber from whole oats could contribute to this effect, its role is generally recognized as being of smaller magnitude.

In the **Federal Register** of May 22, 1997 (62 FR 28234), and in response to a petition filed under § 101.70, the agency proposed to amend § 101.81 by adding psyllium seed husk as an additional source of soluble fiber, thereby providing for health claims on the association between soluble fiber from psyllium seed husk and reduced risk of CHD (the psyllium husk proposed rule). In this proposed rule, FDA considered the relevant scientific studies and data presented in the petition as part of its review of the scientific literature on soluble fiber from psyllium seed husk and heart disease. The agency summarized this evidence in the proposed rule (62 FR 28234).

The psyllium husk proposed rule included qualifying criteria for the purpose of identifying psyllium-containing foods eligible to bear the proposed health claim. The proposal also specified mandatory content and label information for health claim statements and provided model health claims.

Section 101.81(c)(2)(ii) of the soluble fiber from whole oats health claim regulation lists the sources of β-glucan soluble fiber for which FDA has evaluated data pertaining to effects on blood cholesterol levels and has concluded that significant scientific agreement exists regarding a relationship between soluble fiber in whole oats and the risk of CHD. In the psyllium husk proposed rule, FDA proposed to add new § 101.81(c)(2)(ii)(B) to specify psyllium husk as a source of soluble fiber eligible to be the subject of this claim. Proposed § 101.81(c)(2)(ii)(B)(*1*) identifies psyllium husk as the dried seed coat (epidermis) of the seed of *Plantago ovata*, known as blond or Indian *psyllium*, *P. indica*, or *P. psyllium*, and specifies that the purity of the psyllium husk shall be no less than 95 percent, such that it has 3 percent or less protein content, 4.5 percent or less of light extraneous matter, and 0.5 percent or less of heavy extraneous matter, but in no case may the combined extraneous matter exceed 4.9 percent, as determined by U.S. Pharmacopeia (USP) methods.

In its evaluation of the scientific evidence for a relationship between consumption of soluble fiber from psyllium seed husk and blood total- and LDL-cholesterol levels, the agency found no reliable data to establish a dose-response for this relationship. However, the agency did find that in placebo-controlled studies that tested an intake of 10.2 grams (g) of psyllium seed husk per day as a part of a diet low in saturated fat and cholesterol, there were consistently significant effects of psyllium husk on blood total- and LDL-cholesterol levels. Therefore, the agency proposed to base the qualifying level of soluble fiber from psyllium seed husk on a total daily intake of 10.2 g husk (about 7 g of soluble fiber), as suggested by the petitioner. Therefore, the proposed qualifying criterion in § 101.81(c)(2)(iii)(A)(*2*) was that the food provide at least 1.7 g of soluble fiber from psyllium seed husk per reference amount customarily consumed (RACC) (i.e., 7 g divided by 4 eating occasions per day). The psyllium husk proposed rule also stated that if a manufacturer can demonstrate that a diet low in saturated fat and cholesterol that includes a blend of the eligible sources of soluble fiber listed in § 101.81(c)(2)(ii) has an effect on the risk of heart disease, the manufacturer should petition to amend § 101.81 further.

To reflect the agency's tentative decision to broaden § 101.81 to include soluble fiber from psyllium seed husk, the agency proposed to modify the section heading in § 101.81 from "Soluble fiber from whole oats and risk of coronary heart disease" to "Soluble fiber from certain foods and risk of coronary heart disease." Accordingly, the agency also proposed to revise the statement "soluble fiber from whole oats" to either "soluble fiber from certain foods" or "soluble fiber from the eligible food sources from paragraph (c)(2)(ii) of this section" where appropriate in § 101.81. The agency did not propose to modify the model claims.

II. Summary of Comments and the Agency's Responses

In response to the psyllium husk proposed rule, the agency received 19 letters, each containing one or more comments, from professional organizations, industry, consumer groups, health care professionals, and research scientists.

Approximately one-half of the comments that the agency received agreed with one or more provisions of the psyllium husk proposed rule without providing grounds for this support other than those provided by FDA in the preamble to the psyllium husk proposed rule. A few of these comments also requested modification of one or more provisions of the proposed rule. Some comments provided additional data on the relationship between psyllium husk soluble fiber and CHD. Some of the comments that disagreed with the proposed rule provided specific support for their positions. The agency has summarized and addressed the relevant issues raised in all comments in the sections of this document that follow.

A. Food Substance Associated With Reduced Risk of CHD

Health claims have two essential elements: A food substance and a disease or health-related condition (§ 101.14). The agency proposed to authorize a health claim on the relationship between consumption of soluble fiber from psyllium husk, as part of a diet low in saturated fat and cholesterol, and reduced risk of CHD. Further, the agency proposed to amend the authorized claim for soluble fiber from whole oats and CHD (§ 101.81) to include soluble fiber from psyllium husk and to broaden the subject of the claim to "soluble fiber from certain foods" and risk of CHD (62 FR 28234 at 28239).

1. Terminology (Comment 1)

Comments received in response to the proposed rule used the term "psyllium"

interchangeably with the terms "psyllium seed husk" and "psyllium husk." The agency also noticed that a few comments used the term "psyllium" when referring to the soluble fiber component of the psyllium husk. Therefore, the agency finds it important to clarify the terms that may be used in referring to the substance that is the subject of this claim as well as the common or usual name of the product that should be used in ingredient statements.

The substance that is the subject of this claim is soluble fiber of the psyllium husk, i.e., the seed coat that has been removed from the psyllium seed. It is the seed husk, rather than the seed, that is the source of soluble dietary fiber. The purity specifications suggested by the petitioner and adopted in proposed § 101.81(c)(2)(ii)(B)(*1*) refer to the extent to which psyllium husk has been separated from residual seed components.

The agency notes that in the ingredient list of the petitioner's psyllium husk-containing cereal the substance is declared as "psyllium seed husk" (Ref. 1). The agency also notes that in the USP National Formulary this substance is referred to as "psyllium husk" (Ref. 2). The agency therefore considers both "psyllium seed husk" and "psyllium husk" to be common or usual names for the soluble dietary fiber source that is the subject of this rule. In the psyllium husk proposed rule, the agency used the term "psyllium" synonymously with the term "psyllium husk" (62 FR 28234 at 28237). Upon further consideration, the agency concludes that the term "psyllium" is not sufficiently descriptive of the substance of this claim because this term is likely to be construed as inclusive of the psyllium seed. The psyllium seed includes nutrients and allergenic proteins that are not components of psyllium husk. The psyllium husk purity specifications of § 101.81(c)(2)(ii)(B)(*1*) make the presence of psyllium seed in a food a disqualifying criterion for foods eligible to bear the claim.

In this final rule, the agency is clarifying under § 101.81(c)(2) that the proper terms for the soluble fiber source which is the substance of this rule are "psyllium husk" or "psyllium seed husk." Therefore, § 101.81 (c)(2)(ii)(B)(*1*) is revised to read "psyllium seed husk, also known as psyllium husk, shall have a purity of * * *." Section 101.81 (c)(2)(ii)(B)(*1*), (c)(2)(ii)(B)(*2*), and (c)(2)(iii)(A)(*2*) are revised to read "psyllium husk" where the term "psyllium" had been used in the proposed rule.

2. Eligibility of Psyllium Seed Husk

(Comment 2)

Some comments stated that psyllium husk is not a food and is not consumed by itself. The comments stated that psyllium husk is an ingredient or additive and, therefore, should not be eligible for a health claim. One comment expressed concern that a health claim on a food additive will put more reliance on food fortification or supplementation as a strategy to improve health. The comment asserted that the psyllium proposal represents a public policy shift that may result in diverting attention from the importance of a varied selection of foods.

FDA disagrees with comments that psyllium husk, as a food ingredient, is not an appropriate substance for consideration of a health claim. As discussed in the final rule implementing the 1990 amendments on the use of health claims (58 FR 2478 at 2480, January 6, 1993), a broad range of substances are potentially subject to regulation under section 403 (r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)). Section 101.14(a)(2) was written to reflect this broad coverage. Under the general requirements for health claims, the substance that is the subject of the health claim can be either a specific food or a component of food (§ 101.14(a)(2)). Moreover, the fact that a substance may be a "food additive," within the meaning of that term in 21 CFR 170.3(g), does not preclude it from also being a "substance" under § 101.14(a)(2). Although psyllium seed husk is not consumed as a single food, it is a consumable portion of a seed grain that is, or could be, used as a component of foods (e.g., cereal, pasta, cookies, breakfast bars) and is a rich source of soluble fiber. As such, psyllium seed husk is a "substance" within the meaning of § 101.14(a)(2) and thus eligible for consideration of a health claim.

The agency also disagrees with the comment that the proposed health claim represents a public policy shift in diverting attention from the importance of a varied selection of foods by placing more reliance on food fortification or supplementation to achieve public health goals. The establishment of a health claim for soluble fiber from psyllium husk and CHD, when viewed in conjunction with existing health claims for fruits, vegetables, and grain products and CHD and for soluble fiber from whole oats and CHD, emphasizes an important role (i.e., possible reduced risk of CHD) of an even wider variety of food selections. It is important to note that the concept of formulating a food product with psyllium seed husk is no different than formulating a product with oat bran (another food ingredient supplying soluble fiber that is the subject of an authorized health claim). As with oat bran, the inclusion of psyllium husk in a food would be based on its basic functional properties in addition to its nutritional contribution or potential health benefit. The decision to include such an ingredient in a food would be considered food product development, not fortification. Therefore, the agency disagrees that the approval of this health claim represents a public policy shift on food fortification.

B. Updated Review of Scientific Evidence and Issues Related to the Evidence

Under § 101.14(c), FDA will issue a regulation authorizing a health claim only when it determines, based on the totality of publicly available scientific evidence, that there is significant scientific agreement that the claim is supported by such evidence. In its review of the psyllium petition, the agency completed a comprehensive review (see Ref. 7) of 21 human studies (Refs. 8 through 28) (62 FR 28234 at 28237). Of these, it gave particular weight to 7 studies (Refs. 13, 14, 15, 18, 22, 23, and 28) that were well designed and controlled and that reported intakes of dietary saturated fat and cholesterol.

1. Data Submitted With Comments

(Comment 3)

One comment to the psyllium husk proposed rule noted that FDA excluded from comprehensive review three studies (Ref. 12, 17, and 25) because they lacked evidence that the study subjects were compliant with a low saturated fat and cholesterol diet (i.e., the American Heart Association "Step 1" diet). This comment submitted reports of subsequent diet analyses of these studies indicating that study subjects were compliant with the Step 1 diet (see Docket 96P–0338, C8). This comment also noted that two unpublished studies included in the psyllium petition have since been published or submitted for publication (Refs. 12 and 25).

Another comment submitted five recently published studies for consideration (Refs. 29 through 33) and three studies for reconsideration (Refs. 14, 28, and 34). The latter were recently published revisions of material submitted in the psyllium petition. The comment stated that the published report by Jenkins et al. (Ref. 28) contains additional data not presented in the

unpublished report submitted with the petition.

FDA, in reviewing the supplemental data for Refs. 12, 17, and 25, concluded that this information shows the subjects of these three studies were compliant with the dietary protocol and made no significant changes to their diets throughout the duration of the treatment period. Therefore, these studies have been added to the seven studies to which the agency gave particular weight in evaluating the relationship of soluble fiber from psyllium husk and CHD risk in the psyllium husk proposed rule. These studies are summarized in Table 1 of this document. The results of these three additional studies support the relationship between consumption of soluble fiber from psyllium seed husk and reduced risk of heart disease.

The agency also reviewed the published version of the study by Jenkins et al. (Ref. 28) that was submitted in comments and has summarized this study accordingly in Table 1 of this document. The investigators evaluated the effect on serum lipid levels of two Step 2 metabolic diets that provided either 6 or 12 percent of energy from monounsaturated fat (MUFA), approximately 60 g per day (/d) total dietary fiber, and psyllium seed husk-containing cereal (mean intake of 11 g/d of psyllium seed husk) or wheat bran. The results showed significantly lower total- and LDL-cholesterol levels in the psyllium husk-supplemented groups compared to the control group at both MUFA levels. The saturated fat intake during the two study periods was very low (less than 6 percent of energy).

The agency did not conduct an in-depth review of five of the studies submitted with comments. The study by Jensen and co-workers (Ref. 33) does not meet the agency's criteria for study selection (62 FR 28234 at 28237) because the authors evaluated the usefulness of a soluble fiber mixture (containing psyllium, pectin, guar gum, and locust bean gum) in the long-term management of hypercholesterolemia. The results of this study do not allow an evaluation of the effects of soluble fiber from psyllium seed husk alone.

The experimental design of the study by Ganji and Kies (Ref. 32) did not meet the agency's criteria for comprehensive review. In the psyllium proposal, the agency stated that in evaluating a study, it considered whether the intervention studies had been of long enough duration to reasonably ensure stabilization of blood lipid levels (i.e., greater than or equal to 3 weeks duration) (62 FR 28234 at 28237). In this study, diets were varied in four 7-day treatment periods with no time between treatment periods. With this study design, it cannot be determined whether the subjects' blood lipids had stabilized to each diet or that there were no carryover effects from one treatment period to another. Neither did the study design have an adequate pre-intervention baseline period to ensure blood lipids had stabilized to the base diet.

The other three studies submitted in comments that were not reviewed indepth were animal studies (Refs. 29 through 31). Animal studies are useful in studying mechanisms of action. However, the agency relied primarily on the clinical studies in this rule. Such an approach is consistent with that taken by the agency in its evaluation of the relationship between soluble fiber from whole oats and risk of CHD.

A meta-analysis (Ref. 34) was conducted to determine the effect of psyllium seed husk-containing cereal products on serum lipid levels in hypercholesterolemic subjects and to estimate the magnitude of the effect among 404 subjects with mild to moderate hypercholesterolemia (total-cholesterol of about 200 to 300 milligrams per deciliter (mg/dL) who followed a low fat diet. In its review of the evidence submitted in the psyllium petition, the agency reviewed 6 of the 11 studies (Refs. 11, 13, 22 through 24, and 28) included in the meta-analysis (see tables in Ref. 7). The remaining studies used in the meta-analysis did not meet the agency's criteria for study selection (62 FR 28234 at 28237). The conclusion of the meta-analysis report was that hypercholesterolemic subjects who consumed the psyllium seed husk-containing cereal had significantly lower total-cholesterol (about 5 percent) and LDL-cholesterol (about 9 percent) compared with those subjects who consumed the control cereal (Ref. 34).

2. Totality of the Data on Soluble Fiber from Psyllium Seed Husk and CHD (Comment 4)

One comment stated that there was considerably more scientific data on psyllium seed husk presented in the petition than that reviewed by the agency. The comment noted that results of 56 studies were included in the psyllium petition. The comment expressed concern that the agency failed to consider studies published prior to 1988 and some additional evidence made available since 1988, noting that studies with soluble fiber mixtures, studies with treatment periods that were less than 3 weeks in duration, and abstracts were not selected for comprehensive review. The comment stated that the agency began its review of the scientific evidence by first considering the conclusions of the Surgeon General's report and the Food and Nutrition Board/National Academy of Sciences (FNB/NAS) report (Refs. 3 and 4) and then considered the evidence that was made available since 1988. The comment explained that neither the Surgeon General's report nor the FNB/NAS report reviewed the evidence on psyllium up to 1988; therefore, the agency improperly ignored a significant portion of the scientific evidence provided in the petition (see Ref. 35, Table 3, pages 30 and 31). Another comment noted that among the 56 studies submitted in the psyllium petition (see Ref. 35), the results of only three failed to demonstrate that consumption of psyllium-containing foods was associated with risk of CHD through a reduction in serum cholesterol. The comment stated that the totality of evidence on psyllium husk that was submitted in the petition includes data on children and the elderly.

Some comments stated that it is premature to authorize a claim on psyllium seed husk and risk of CHD because of a lack of significant scientific agreement on this nutrient/disease relationship. Some of these comments stated that the decision to propose this health claim is based on evidence from a limited number of studies that overall covered a small number of subjects, of which women were underrepresented, and on the absence of data on certain subpopulations (children and the elderly).

The agency agrees with the comment that the Surgeon General's report (Ref. 3) and the FNB/NAS report (Ref. 4) did not review of all of the psyllium studies that were publicly available prior to 1988 and identified in the petition (Ref. 35). The petition identified 16 clinical studies, published prior to 1989, of the effect of psyllium seed husk on blood cholesterol levels (see Ref. 35, Table 3). The agency had not reviewed these studies in the psyllium husk proposed rule, but in response to the comment, has subsequently considered them. Half of these studies did not meet the agency's stated criteria for selection of human studies (62 FR 28234 at 28237) in that they were conducted in special populations, were published as abstracts only, or the psyllium dose was unreported. Studies that used special population groups were excluded from review because, as explained in the psyllium husk proposed rule (62 FR 28234 at 28237), the results from such groups may not be relevant to the general healthy U.S. population. The

agency's rationale for excluding from review studies presented only in abstracts was also presented in the proposal. Abstracts do not provide sufficient detail regarding the methodology and results to allow a detailed assessment of the merits of the study. Likewise, information regarding actual amounts of psyllium administered is a key detail of the study design, without which an adequate assessment of the study cannot be made.

In each of the pre-1989 clinical studies meeting the selection criteria, there were aspects of the study design (e.g., lack of dietary data, lack of a control group) that would have precluded the results of these studies from having a major influence on the agency's conclusions. Among the pre-1989 clinical studies was one double-blind placebo-controlled psyllium husk study with dietary data (Ref. 36). However, the report contained no evidence that the study subjects were compliant with a low saturated fat and cholesterol diet. Thus, a review by FDA of pre-1989 data would not have altered the conclusions reached by the agency in the psyllium husk proposed rule nor contribute to issuing the final rule.

The agency disagrees with the comments that there is not significant scientific agreement that soluble fiber from psyllium husk may help reduce the risk of CHD through its action on blood total- and LDL-cholesterol levels. Some of the comments incorrectly suggested that the agency's decision on this nutrient/disease relationship was based solely on the results of the seven studies in Table 1 of the psyllium husk proposed rule (62 FR 28234 at 28244). As stated previously, the agency reviewed 21 human studies on psyllium (Refs. 8 through 28) that were submitted with the petition and met the agency's criteria for consideration (Ref. 7). Of these, the agency gave particular weight to seven studies. As stated in the psyllium husk proposed rule, the results of the seven studies (Refs. 13 through 15, 18, 22, 23, and 28), and now three additional studies (Refs. 12, 17, and 25) (see comment 3 in section II.B.1 of this document), strongly support the relationship between soluble fiber from psyllium husk and risk of CHD in mild to moderate hypercholesterolemic adults (62 FR 28234 at 28238). Moreover, the results of the remaining clinical studies (Refs. 8 through 11, 16, 19 through 21, 24, and 26) that were given less weight in the psyllium husk proposed rule were consistent in showing an effect of soluble fiber from psyllium husk on serum lipid levels. These studies included both men and women subjects and adults of all ages, including the elderly. It is on the totality of this evidence and conclusions from the 1989 Life Sciences Research Office (LSRO) report on health consequences of dietary fiber (Ref. 5) that the agency is basing its conclusion to authorize a health claim on psyllium seed husk.

3. Psyllium Consumed as a Bulk Laxative

In the psyllium husk proposed rule, the agency included in its evaluation the results of studies of this nutrient/disease relationship in which psyllium was administered as a product marketed as a bulk-forming fiber laxative. (Comment 5)

Some comments were opposed to the consideration of studies in which psyllium husk was supplied as a bulk-forming fiber laxative. One comment stated that the use of studies in which psyllium seed husk was consumed in different forms makes meaningful comparisons difficult. Other comments had no objection to the agency's use of this evidence. One comment stated that consuming psyllium husk as a bulk-forming fiber laxative at mealtime is functionally equivalent to consuming a psyllium husk-enriched food at mealtime. Another comment stated that clinical studies evaluating psyllium seed husk administered as a bulk-forming fiber laxative were conducted in a fashion similar to studies conducted with food products, including consuming the substance at mealtime, dietary counseling, and patient selection criteria. The comment stated that both compliance with the regimen and efficacy were comparable for food and laxative studies.

In the psyllium husk proposed rule, the agency tentatively decided that including, in its comprehensive review, the three studies in which psyllium seed husk was administered in the form used as a laxative (Refs. 13, 15, and 18) was appropriate. In these studies, the psyllium seed husk was consumed in concentrations similar to those at which psyllium husk was incorporated into conventional foods in the other studies selected for comprehensive review (Refs. 14, 22, 23, and 28) (62 FR 28234 at 28238). The agency further noted that the magnitude of the effect of soluble fiber from psyllium husk on the change in serum lipid levels reported in the studies in which this substance was consumed in conventional foods (Refs. 14, 22, 23, and 28) was similar to that observed in the studies (Refs. 13, 15, and 18) in which it was consumed as a bulk laxative. Therefore, the agency stated that the results of the studies suggest that the form in which psyllium husk is consumed is not significant when evaluating the effect of psyllium husk on serum lipid levels (62 FR 28234 at 28238). Comments that were opposed to reliance on studies which used a psyllium husk bulk-forming laxative provided no new data to support their position. Therefore, the agency is not persuaded that it is inappropriate to rely on this evidence and concludes that studies that used a psyllium husk bulk-forming laxative are appropriate in the evaluation of this nutrient/disease relationship.

4. Studies in Subjects With Borderline to High Blood Cholesterol Levels

The subject populations in the studies reviewed in the psyllium proposed rule (see Table 1, 62 FR 28234 at 28244) had borderline to high blood total-cholesterol levels (i.e., average baseline cholesterol values in the studies were between 225 and 275 mg/dL). The agency tentatively concluded in the psyllium proposed rule that the studies with hypercholesterolemic subjects are relevant to the general U.S. population (62 FR 28234 at 28238) and requested comments on this issue. (Comment 6)

Some comments agreed with the agency's view that studies of populations with elevated blood cholesterol are relevant to the general population. These comments cited current statistics of the incidence of elevated blood cholesterol in the U.S. population, and noted that the CHD risk factor that is the target of the proposed health claim is elevated blood cholesterol. Other comments disagreed with the view that the results of studies in hypercholesterolemics can be generalized to the general population. One comment stated that because hypercholesterolemic individuals are generally more responsive to dietary intervention that normocholesterolemic individuals, it is questionable whether normocholesterolemic persons would respond to psyllium at all.

As the leading cause of death in this country, CHD is a disease for which the general U.S. population is at risk. The risk of dying from CHD is related to serum cholesterol levels in a continuous and positive manner, increasing slowly for levels between 150 mg/dl and 200 mg/dl and more rapidly when the cholesterol level exceeds 200 mg/dl (Ref. 37). The public health policy elucidated by the National Cholesterol Education Program (NCEP), National Heart, Lung, and Blood Institute, is to extend the benefits of cholesterol lowering to the population as a whole by promoting adoption of eating patterns that can help lower the blood cholesterol levels of most Americans

(Ref. 37). A dietary intervention that lowers blood cholesterol levels only in persons with high levels would, like an intervention that lowers cholesterol levels across the entire population range, cause a shift in the population distribution of blood cholesterol levels resulting in a decrease in the mean value for the blood cholesterol level in the general population (Ref. 37). The anticipated effect of such a shift would be to reduce the morbidity from CHD and to produce a continued or accelerated decline in the CHD mortality rate in the United States. The agency is persuaded by the evidence it has reviewed in this rulemaking that the consumption of psyllium seed husk, as part of a low saturated fat and cholesterol diet, can be a prudent public health measure to assist in the national policy of promoting eating patterns that will help in achieving or maintaining desirable blood cholesterol levels in the general population. Therefore, it concludes that the health claim is relevant to the general population and should not be limited to a subpopulation of hypercholesterolemic individuals. In addition, consistent with the agency's conclusions in rulemaking on the dietary saturated fat and cholesterol/CHD claim (58 FR 2739 at 2745, January 6, 1993), the wording of the health claim as "may' or might' reduce the risk of heart disease" adequately represents the fact that not all persons will realize the same magnitude of benefit from adopting the dietary change.

C. Issues Relative to Amending § 101.81 to Include Soluble Fiber From Psyllium Seed Husk

In the psyllium husk proposed rule, the agency tentatively concluded that the soluble fiber in psyllium husk, like β-glucan soluble fiber from whole oats, when consumed as part of a diet low in saturated fat and cholesterol, may help reduce the risk of heart disease. Therefore, the agency proposed to amend the authorized claim for β-glucan soluble fiber from whole oats and risk of CHD (§ 101.81) to include soluble fiber from psyllium husk and to broaden the subject of the claim to "soluble fiber from certain foods" and risk of CHD.

(Comment 7)

One comment stated that § 101.81 should not be expanded to include soluble fiber from psyllium husk because the eligible sources of β-glucan soluble fiber are whole grain foods that provide nutrients in addition to soluble fiber, whereas psyllium seed husk, which offers only soluble fiber, is neither a food nor a whole grain. The comment also stated that psyllium seed husk should not be added to § 101.81 because the husk soluble fiber is separated from the whole seed, whereas β-glucan soluble fiber extracted from the whole oat grain is not eligible for a claim. Two comments suggested that if the claim must be structured as a soluble fiber claim, then only those soluble fiber sources that elicit clinically significant reductions in serum cholesterol via the same mechanism should be eligible to be included in the claim.

FDA disagrees with the comment that substances qualifying for a health claim under § 101.81 must be whole grains similar to the whole oats that are listed under § 101.81(c)(2)(ii)(A). The subject of the claim is soluble fiber and the food source of β-glucan soluble fiber is whole oats. There is no scientific basis to require that only soluble fiber from whole grain foods can qualify for a claim. The soluble fiber in psyllium seed is concentrated in the outer husk. This is the opposite from whole oats where the soluble fiber is concentrated in the inner portion of the oat groat. Moreover, purified β-glucan soluble fiber was not included as a substance eligible to bear the claim because, as discussed in the whole oat final rule, the hypocholesterolemic properties of β-glucan fiber extracts are affected by processing. Therefore, before an extract of β-glucan fiber could qualify for the claim, it would have to be characterized so as to identify the processed form of the soluble fiber that maintains its hypocholesterolemic properties. The data on psyllium husk soluble fiber are associated with reduced risk of CHD via its documented hypocholesterolemic properties. As discussed previously (see comment 2 in section II.A.2 of this document), psyllium seed husk is a "substance" eligible for consideration of a health claim within the meaning of that term in § 101.14(a)(2). Therefore, the agency finds it appropriate to consider soluble fiber from psyllium seed husk as a source of soluble fiber that is eligible to be included in § 101.81.

The agency also disagrees with the comment that a soluble fiber source should not be included in § 101.81 unless it elicits reductions in serum cholesterol via the same mechanism as the β-glucan soluble fiber in whole oats. There is no scientific basis to require soluble fibers to have the same mechanism of action for lowering serum cholesterol in order to be eligible for a health claim under § 101.81, nor did the comments provide such a basis. In the whole oat final rule, the agency stated that if a manufacturer can document that a soluble fiber product has an effect on blood lipid levels, and thereby can be useful in reducing the risk of CHD, the manufacturer may petition to amend § 101.81 to include that type of soluble fiber-containing product as an eligible food source (62 FR 3584 at 3588). In this rulemaking, the agency has concluded that consumption of soluble fiber from psyllium seed husk has an effect of lowering blood total- and LDL-cholesterol levels, and therefore an amendment to § 101.81 to include psyllium seed husk as a soluble fiber source is eligible for a health claim under § 101.81.

D. Specifications for Psyllium Seed Husk

Based upon information provided by the petitioner, the agency proposed a minimum psyllium husk purity specification as a qualifying criterion for eligible sources of soluble fiber from psyllium. Proposed § 101.81(c)(2)(ii)(B)(1) stated that psyllium husk shall have a purity of:

> no less than 95 percent, such that it contains 3 percent or less protein, 4.5 percent or less of light extraneous matter, and 0.5 percent or less of heavy extraneous matter, but in no case may the combined extraneous matter exceed 4.9 percent * * *.

(62 FR 28234 at 28243).

1. Issues Relative to Psyllium Seed Husk Specifications

(Comment 8)

One comment noted that there are no assurances that food manufacturers other than the petitioner will be able to meet the petitioner's product specifications and therefore a compliance monitoring program needs to be developed prior to authorization of the health claim. A comment noted that due to natural variability in psyllium seed husk and analytical variation, a "94 percent purity" specification would better represent the practical limit of commercially-available "95 percent purity" psyllium. Accordingly, this comment urged FDA to adopt a minimum psyllium husk purity of 94 percent with 5.0 percent or less of light extraneous matter and 1.0 percent or less of heavy extraneous matter. One comment expressed concern that the purification of psyllium husk may render psyllium inactive as a hypocholesterolemic agent. This comment also urged FDA to determine whether the purification process described by the petitioner should serve as the approved purification technique for psyllium.

The agency disagrees with the comment that a specific compliance monitoring system is needed for psyllium seed husk. The monitoring and

verification of compliance with current good manufacturing practice in the manufacture of human food is a routine FDA activity. The comment urging the agency to change the psyllium husk purity specification to "no less than 94 percent" provided no data to substantiate that commercial supplies of psyllium seed husk do not routinely meet the 95 percent purity specification and the agency sees no compelling reason to revise the proposed purity specifications. Accordingly, the agency is adopting the specifications proposed in § 101.81(c)(2)(ii)(B)(*1*).

The agency notes that evidence provided in the petition and in comments indicates that the psyllium seed husk in the food and bulk laxative products used in the clinical studies, which were discussed in the psyllium husk proposed rule, had a purity of at least 95 percent. The blood cholesterol lowering effect of psyllium seed husk is attributed to the soluble fiber content of the husk and not to the seed components. As such, the concern that the process of separating the psyllium husk from residual seed components would alter the effectiveness of psyllium husk in lowering blood cholesterol level is unfounded. The agency further notes that it has proposed to adopt a psyllium husk purity specification only, and not a purification process.

E. Nature of the Food Eligible to Bear the Claim

In the proposal, the agency determined a qualifying level of psyllium husk for foods eligible to bear a soluble fiber and CHD claim based on a daily intake of approximately 7 g of soluble fiber from psyllium seed husk (62 FR 28234 at 28240). The agency stated that the level of daily intake of soluble fiber from psyllium seed husk (7 g/d was not based on the results of data from a dose-response study, but was the amount shown in clinical studies to be consistently associated with significant reductions in serum lipids in conjunction with a diet low in saturated fat and cholesterol. Therefore, the agency proposed that the qualifying level of soluble fiber for foods to bear a soluble fiber and CHD claim be 1.7 g of soluble fiber from psyllium seed husk per RACC (7 g divided by 4 eating occasions per day) (62 FR 28234 at 28240). The agency asked for comments on whether this approach for establishing a qualifying soluble fiber level for psyllium husk-containing products is appropriate or for data to support another qualifying level for psyllium husk.

1. Qualifying Criteria for Psyllium Seed Husks

(Comment 9)

Some comments stated that it is premature to authorize this health claim because of the limited data regarding an appropriate dose-response curve. One comment stated that the qualifying level for psyllium should be based on an intake level that will elicit a clinically significant 5 percent reduction in blood cholesterol. The comment stated that results from dose-response and meta-analysis studies would assuage concerns that the proposed qualifying level of soluble fiber from psyllium seed husk may not be an effective cholesterol-lowering dose. Other comments agreed with the proposed qualifying level for psyllium-containing foods. One comment stated that the revised report of the dose-response study by Davidson et al. (Ref. 14), that was submitted with the comment, supports the effectiveness of 10.2 g psyllium husk daily intake in significantly lowering cholesterol levels. In an analysis of data from subjects who completed the protocol (197 of 286 subjects), LDL-cholesterol levels of the group with 10.2 g psyllium husk daily intake was reported to be 5 percent lower than the control group after 24 weeks. The comment also stated that the data from the meta-analysis by Olson et al. (Ref. 34), which was submitted with the comment, lends additional support to the conclusion that 10.2 g/d of psyllium is an appropriate level on which to base the qualifying criteria for this claim. One comment stated that the maximum level of daily psyllium husk consumption should be determined as part of the generally recognized as safe (GRAS) process.

FDA notes that dose-response data are not a requirement to establish the qualifying criteria for a substance that is the subject of a health claim. Under § 101.70, which describes the requirements for health claim petitions, the petition must address whether there is an optimum level of the particular substance to be consumed beyond which no benefit would be expected (§ 101.70(f)B.1.). This information may or may not be based on dose-response data. Even though the optimal or lowest effective cholesterol lowering doses can not be determined from the available data, the qualifying level (10.2 g/d of psyllium husk) has been demonstrated to be effective. The results of studies that evaluated the effect of psyllium husk intakes above 10.2 g/d showed no additional benefit on serum lipid levels (Ref. 7). Therefore, the agency disagrees with the comments stating that dose-response data are needed before the agency can authorize a health claim. The totality of scientific data, which establish a significant reduction in blood cholesterol based on an intake of 10.2 g/d of psyllium seed husk, provides an adequate basis for establishing a qualifying soluble fiber level for psyllium seed husk-containing products.

Similarly, there is no basis to require that the qualifying criteria for a substance associated with risk of CHD be based on the amount of that substance to elicit a 5 percent reduction in blood total- and LDL-cholesterol levels. The data on psyllium seed husk suggests that the magnitude of the effect on blood lipids for intakes of about 10 g/d of psyllium seed husk ranges from 4 to 6 percent for blood total-cholesterol and about 4 to 8 percent for LDL-cholesterol levels in conjunction with diets low in saturated fat and cholesterol (Ref. 7). Although modest in size, these are clinically significant reductions in blood lipids that translate to a reduced risk of CHD for individuals with hypercholesterolemia and serve as a useful adjunct to a diet already low in saturated fat and cholesterol.

In the absence of data to the contrary, the agency concludes that based on the evidence submitted in comments and on the totality of scientific data considered in its review of the petition, a daily intake of 7 g of soluble fiber from psyllium seed husk (10.2 g of psyllium seed husk) as part of a diet low in saturated fat and cholesterol may reduce the risk of CHD by lowering blood total- and LDL-cholesterol levels in individuals with mild to moderate hypercholesterolemia.

FDA finds that the comment that a maximum level of daily consumption of psyllium husk should be determined as part of the psyllium husk GRAS status is not relevant to this rulemaking.

2. Issues Relative to Four Eating Occasions Per Day

(Comment 10)

The proposed qualifying level of soluble fiber from psyllium husk was based on the assumption that individuals will consume four servings of psyllium husk-containing foods a day. Some comments questioned whether it is realistic to assume that consumers will consume four servings per day of psyllium husk-containing foods. One comment stated that the majority of Americans never consume any psyllium husk-containing foods and that there is no evidence that a health claim would convince them to consume up to four servings of these foods daily. Other comments stated that the proposed rule would provide consumers

with an increased selection of foods containing soluble fiber in sufficient quantities to have a potentially beneficial influence on CHD risk and thus have a positive public health impact.

FDA acknowledges that foods containing psyllium seed husk are not widely available; e.g., the petitioner currently produces only one product, a breakfast cereal, containing psyllium. However, the agency disagrees with the comments that it is unrealistic to consider that consumers could consume psyllium-containing foods four times a day. Two studies (Refs. 8 and 14) that were reviewed by the agency tested psyllium seed husk incorporated into a variety of foods that were consumed during the day. These products included cereal, fruit drinks, peanut butter, cookies, muffins, bread, pasta, and snack bars. In addition to these products, the petitioner identified other food products in which psyllium could be used, such as toaster pastries, rolls, biscuits, tortillas, waffles, pancakes, pizza crust, stuffing, breakfast bars, and a variety of ready-to-eat cereals (Ref. 35, pp. 90 and 91). Authorization of a claim on soluble fiber from psyllium seed husk will be an incentive for manufacturers to expand product lines to provide consumers with additional soluble fiber-containing products that can be part of a heart healthy diet. Based on these facts, the agency finds that a factual predicate exists to support the contention that psyllium husk-containing foods could be consumed at four eating occasions a day and, therefore, finds that the comments that questioned whether such consumption was realistic are without support.

The agency notes that the approach used to determine the qualifying level of soluble fiber from psyllium husk (i.e., dividing the amount shown to provide a significant reduction in blood lipid levels by 4 eating occasions per day) is consistent with that used to determine the qualifying level of β-glucan soluble fiber from whole oats in the soluble fiber from whole oats final rule. In that document, the agency pointed out that the approach used to derive the qualifying level of soluble fiber from whole oats is somewhat different from that used in authorizing other health claims. It stated:

> Specifically, the guiding principle for other health claims is to use the established definition for "good source" or "high" which characterizes the amount of a nutrient, based on a percentage of the Daily Value (DV) for the nutrient, in a serving of food. In this way, products that qualify to bear the claim contain a meaningful level of the substance per serving compared to the recommended intake of the substance from all food sources. In the case of this final rule, there is no DV for β-glucan soluble fiber or soluble fiber. (62 FR 3584 at 3592).

The agency had also indicated in the soluble fiber from whole oat final rule that it intends to propose to establish a Daily Reference Value (DRV) for soluble fiber (62 FR 3584 at 3588). The establishment of a DRV for soluble fiber would not only permit claims for "good source" and "high" in soluble fiber, but would allow the agency to consider amendments to § 101.81 to establish a single qualifying level for soluble fiber from all eligible soluble fiber sources that would be effective in lowering cholesterol. Available scientific evidence suggests that there are a variety of soluble fibers in foods that may demonstrate the benefit. Thus, smaller dietary contributions from any one source could be appropriate given the potential for multiple sources of such fibers.

A DRV for soluble fiber would establish a qualifying level for soluble fiber blends in a food that would be effective in lowering cholesterol in hypercholesterolemic individuals. However, in the absence of a DRV for soluble fiber, the qualifying criteria for the eligible sources of soluble fiber in this health claim must be based on the scientific evidence specific for each soluble fiber source. The agency intends to amend § 101.81 to revise the qualifying levels of soluble fibers when a DRV for soluble dietary fiber has been established.

The agency notes that existing § 101.81(d)(6) provides for an optional statement informing consumers of the level of daily intake of β-glucan from whole oats that may help reduce the risk of CHD and the contribution that one serving of the product makes to this specified intake level. However, when issuing the soluble fiber from whole oats and reduced risk of CHD health claim, FDA inadvertently overlooked the requirement in § 101.14(d)(2)(vii) of the general requirements for health claims. That section states that if the claim is about the effects of consuming the substance at other than decreased levels, and if no definition for "high" has been established (e.g., where the claim pertains to a food either as a whole food or as an ingredient in another food), the claim must specify the daily dietary intake necessary to achieve the claimed effect, as established in the regulation authorizing the claim.

As stated, FDA has not established a DRV for soluble fiber. As a result, the term "high" is not defined for soluble fiber. Therefore, consistent with § 101.14(d)(2)(vii), a claim for soluble fiber from whole oats requires specification of the daily dietary intake from whole oats (3 g or more per day of β-glucan soluble fiber from whole oats) necessary to achieve a reduction in the risk of CHD. This requirement is independent of the optional statement provided in § 101.81(d)(6).

When discussing the optional statement under § 101.81(d)(6) in the soluble fiber from whole oats final rule, FDA stated that when the amount of soluble fiber to be consumed per day is stated, the amount per serving is also needed so that consumers would not be misled to believe that a serving of the food contributes the full daily amount (62 FR 3584 at 3596). Therefore, to be consistent with the current regulation in § 101.14(d)(2)(vii) and with the need to specify the amount of soluble fiber that a serving of food contributes when the daily dietary intake is specified in the claim, the agency is requiring, under § 101.81(c)(2)(i)(G), that this information be included in a health claim for both whole oats and psyllium husk soluble fiber claims. However, because FDA did not note this requirement in the soluble fiber from whole oats final rule, firms currently marketing foods that bear the health claim for whole oats may wait until the next printing of their food labels and labeling for such foods to incorporate this added information.

Therefore, the agency is adding § 101.81(c)(2)(i)(G) in this final rule to clarify current regulatory requirements. Existing § 101.81(d)(6), which provides for the same information for whole oats as an optional statement, is being removed. Accordingly, § 101.81(c)(2)(i)(G) states that the claim shall specify that an intake of 7 g or more per day of soluble fiber from psyllium seed husk, or an intake of 3 g or more per day of β-glucan soluble fiber from whole oats may help reduce the risk of CHD. Such a claim must be accompanied by information on the contribution that one serving of the product makes to the specified daily dietary intake level. Any foods containing psyllium seed husk, or whole oats, and bearing the health claim are required to include this information as part of the claim.

3. Blends of Eligible Soluble Fibers

In the psyllium husk proposed rule, the agency noted that foods might be produced with a blend of the eligible soluble fibers listed in § 101.81(c)(2)(ii) and stated that it would be willing to consider whether such foods should be eligible to bear the health claim (62 FR 28234 at 28240). However, the agency stated that it does not have the data from which to evaluate the relationship between consumption of foods

containing both psyllium and whole oats and risk of heart disease, and cannot assume that foods containing a blend of these grains would have the same ability to affect blood total- and LDL-cholesterol levels when compared to a product containing either whole oats or psyllium. In the proposal, the agency encouraged manufacturers to petition to amend § 101.81 further if it can be demonstrated that a diet that is low in saturated fat and cholesterol that includes a blend of the eligible soluble fibers listed in § 101.81(c)(2)(ii) has an effect on the risk of heart disease. (Comment 11)

One comment agreed with the agency's tentative conclusion not to include blends of the eligible soluble fibers at this time. The comment stated that data should be submitted to verify the effectiveness of any soluble fiber blend.

The agency agrees that data are needed to verify the effectiveness of blends of soluble fiber. In the absence of a review of such data, FDA is not including the option of a blend of the eligible soluble fibers listed in § 101.81(c)(2)(ii) in this final rule. While some studies submitted to the agency did evaluate the usefulness of soluble fiber mixtures in lowering blood cholesterol levels, they were outside the scope of this rulemaking, which pertains to the effects of soluble fiber from psyllium alone. As a result, time and resource constraints did not allow for an indepth review of how blends of eligible soluble fibers might work in synergy with one another. Such a task would better be addressed as a part of rulemaking to establish a DRV for soluble fiber and a review of qualifying levels.

F. Soluble Fiber From Certain Foods and From Eligible Food Sources

In the psyllium husk proposed rule, the agency proposed to modify the section heading of § 101.81 from "Soluble fiber from whole oats and risk of coronary heart disease" to "Soluble fiber from certain foods and risk of coronary heart disease" (62 FR 28234 at 28241). The agency stated that:

> "soluble fiber from certain foods" reflects the fact that the subject of the claim is no longer a specific source of soluble fiber, i.e., beta-glucan from whole oats, but rather a broader class of substances that includes those sources of soluble fiber for which there is significant scientific agreement that they may help to reduce the risk of heart disease. (62 FR 28234 at 28241).

The agency also proposed to revise the statement "soluble fiber from whole oats" in § 101.81(a), (a)(3), (b), (b)(2), (c)(2)(i), (c)(2)(i)(A), (d)(3), and (e) to state "soluble fiber from certain foods," and in § 101.81(c)(2)(i)(E), (c)(2)(i)(F), and (d)(2) to read "soluble fiber from the eligible food sources from paragraph (c)(2)(ii) of this section" (62 FR 28234 at 28241).

(Comment 12)

The agency received one comment that raised issues relative to the agency's decision to modify the soluble fiber from whole oats and CHD rule to a claim on soluble fiber from certain foods. This comment argued that the final rule for § 101.81 inappropriately refocused this claim from "whole oats" to "soluble fiber from whole oats" and heart disease. The comment asserted that β-glucan was included in the whole oats proposed rule only as a quantitative measure of whole oats for compliance purposes. This comment further argued that because the eligible source of β-glucan soluble fiber is whole oat products whereas the eligible source of psyllium soluble fiber is an isolated fiber-rich fraction (e.g., husk) separated from the whole psyllium seed, these substances should not be combined in one regulation.

The agency disagrees that the focus of § 101.81 should be whole oats. The rationale for positioning this claim as a soluble fiber claim was explained in the soluble fiber from whole oats final rule (62 FR 3584 at 3585).

G. Issues Relative to the Safety of Psyllium Seed Husk

Prior to submitting the health claim petition, the petitioner had petitioned FDA to affirm that the use of psyllium seed husk in grain-based foods is GRAS (55 FR 4481, February 8, 1990). In the psyllium husk proposed rule, the agency noted that although FDA has reached no decision on the GRAS affirmation for the use of this substance, the petition appears to contain evidence that the use of psyllium seed husk at levels necessary to justify a claim is safe and lawful, as required by § 101.14(b)(3)(ii) (62 FR 28234 at 28236). However, the agency indicated that there are some public safety concerns with the consumption of psyllium seed husk (e.g., colonic epithelial cell proliferation, allergenicity, and gastrointestinal obstruction). The agency asked for comments on whether these concerns would be a basis for not authorizing the proposed health claim. The agency also recognized that an increase in psyllium consumption is likely if the proposed health claim is authorized (62 FR 28234 at 28236). Therefore, the agency asked for comments on what type of actions may be necessary to ensure that long-term consumption of psyllium seed husk will be at safe levels, e.g., limiting psyllium husk content of foods or the kinds of foods that can bear a claim.

1. Restrictions on Psyllium Husk Content of Foods or on Types of Foods That Can Bear a Claim.

(Comment 13)

FDA received several comments regarding the safety of psyllium husk-containing foods. Some comments stated that psyllium husk has a long history of safe human consumption as a laxative product at the intake level upon which the qualifying food level of psyllium husk is based. Furthermore, the comments noted that prior authoritative reviews of the safety of psyllium husk in food, such as the 1993 LSRO evaluation of the safety of psyllium seed husk as a food ingredient (Ref. 39), concluded that there were no grounds to suggest that consumption of as much as 25 g/d of psyllium husk would be a hazard to the public. These comments argued that therefore it is unnecessary for FDA to restrict the types of psyllium husk-containing food products, the amount of psyllium husk that may be in a food product, or the amount of psyllium husk that should be consumed per day as conditions for use of the soluble fiber from psyllium husk health claim. Other comments asserted that there is inadequate information about limits of how much psyllium husk can be incorporated into foods, or about safe levels of intake for long-term consumption. These comments argued that there should be limits placed on permissible levels of psyllium husk in foods and types of foods to which psyllium husk may be added. One comment suggested that psyllium husk-containing foods be required to bear a label statement warning consumers of the maximum amount of psyllium husk that should be consumed per day.

FDA agrees that there is a history of human oral consumption of psyllium husk, both in food and over-the-counter (OTC) products, at the daily intake level contemplated for this health claim. The daily intake of psyllium husk that FDA has concluded is effective in reducing CHD risk (10.2 g psyllium husk, which is the amount of psyllium husk that is necessary to provide 7 g of soluble fiber) is well below the daily intake level that the 1993 LSRO psyllium husk report (Ref. 39) concluded was safe (i.e., 25 g psyllium husk). FDA does not expect authorization of the health claim to result in potential psyllium husk consumption exceeding this safe level.

The 1993 LSRO report based its calculation of the potential daily intake of psyllium husk, for a consumer preferentially selecting products containing psyllium husk, on the

selection of four servings of psyllium husk-containing foods per day. FDA considers four servings per day to be a reasonable estimate of consumption for several reasons.

First, consumers who are looking for foods that are identified as useful in reducing risk of CHD need not seek only psyllium-husk containing foods. They will also be able to select from foods that use the health claims approved for foods low in saturated fat and cholesterol (§ 101.75 (21 CFR 101.75)); for fruits, vegetables, and grain products that contain fiber, particularly soluble fiber (§ 101.77); and for foods containing soluble fiber from whole oats (§ 101.81).

Second, many types of frequently-consumed foods will not offer psyllium husk-containing alternatives. For example, foods such as raw meat, fish, and poultry; eggs; fats and oils; nuts and seeds; and raw fruits and vegetables are not suitable candidates for the addition of psyllium husk. In addition, technological or organoleptic effects of the use of psyllium husk at levels needed to make a health claim will limit its use in other categories of foods.

Third, because the subject health claim is only allowed on foods that are low in fat, saturated fat, and cholesterol, not all foods to which psyllium husk could be feasibly be added would be eligible to bear a health claim. Thus, there would be no incentive for a manufacturer to add psyllium husk to such foods, other than at the small amounts that may be used for technological purposes (e.g., emulsifiers or binders).

Lastly, most of the new psyllium husk-containing foods that are expected to be developed are grain-based and as such are often used as alternates for one another in usual dietary patterns (e.g., cereals, breakfast bars, toaster pastries, rolls, biscuits, pancakes, or waffles served at breakfast).

For the mentioned reasons, FDA, in evaluating this health claim, considers the selection of four servings of psyllium husk-containing foods per day to be a reasonable expectation of consumption when considering the possible use of psyllium husk in all food categories.

Estimation of the potential daily intake of psyllium husk is also dependent upon the amount of the ingredient in each food. In the 1993 LSRO report, maximum levels of use were reported as designated by the Kellogg Co. at 7.5 percent by weight for bread-based products (e.g., bread, rolls, muffins, doughnuts, biscuits, tortillas, waffles, pancakes, pizza crust and stuffing), pasta, and toaster pastries. In addition, the maximum levels of use were reported to be 10 percent by weight for breakfast bars, and 15 percent by weight for ready-to-eat cereals (Ref. 39). Assuming the highest maximum level of use, 15 percent in ready-to-eat cereals, the consumption of four 30 g servings (i.e., the reference amount customarily consumed for high fiber cereals (§ 101.12(b) Table 2)) would result in a daily intake of 18 g (30 g multiplied by 15 percent = 4.5 g/serving, multiply by 4 servings = 18 g/d). Moreover, any technological uses of psyllium husk in foods are at such low levels (e.g., 0.5 percent in frozen desserts) that they are not likely to have a notable impact on total daily intake.

A total daily intake of 18 g is within the range of intakes considered safe in the 1993 LSRO report (i.e., up to 25 g/d) (Ref. 39). However, FDA expects that actual consumption will be less than this amount because the maximum use levels were designated prior to the agency's establishment of the health claim qualifying level. FDA expects that manufacturers who develop new psyllium husk-containing foods would do so to make use of the health claim. As such, the health claim qualifying level (i.e., 2.6 g per reference amount) would be a major factor in determining the amount of psyllium husk to include in new psyllium husk-containing foods.

Based on these considerations, the agency disagrees with the comments that argued that limits should be placed on permissible levels of psyllium husk in foods or on the types of foods to which psyllium husk may be added. Therefore, no changes are being made to § 101.81(c)(iii)(A)(*2*) that describes the nature of the food.

As noted in the psyllium husk proposed rule (62 FR 28234 at 28235), a preliminary review of the petitioner's GRAS affirmation petition revealed that it contains significant evidence supporting the safety of the consumption of up to 25 g/d of psyllium husk in a variety of food categories (i.e., types of foods). This amount is well in excess of the levels necessary to justify a health claim (i.e., 10.2 g/d) and the amounts that would reasonably be expected to be consumed in a day. Accordingly, based on the totality of the evidence, FDA is not at this time taking issue with the petitioner's view that the use of psyllium husk is safe and lawful. Therefore, the agency concludes that the petitioner has provided evidence that satisfies the requirements in § 101.14(b)(3)(ii) that psyllium seed husk at the levels necessary to justify a claim is safe and lawful.

(Comment 14)

Several comments discussed evidence from animal studies suggesting that the relationship between effects of dietary fiber on rodent colonic mucosal proliferation and the development of neoplasia is unclear. These comments stated that colonic epithelial cell proliferation is not a significant issue relative to the safety of psyllium seed husk as there is no consensus as to whether epithelial cell proliferation in rodent colonic mucosa is relevant to risk of colon cancer. Some comments noted that colonic epithelial cell proliferation is an issue of concern that needs additional research.

The agency agrees that colonic epithelial proliferation is not sufficiently validated as a reliable endpoint for prediction of colon tumorigenesis. While the rate of epithelial cell proliferation in the rodent gastrointestinal tract has been reported to be increased by some soluble dietary fibers and decreased by some insoluble dietary fibers, there is no evidence upon which to conclude that the influence of dietary fiber on the rate of epithelial proliferation is either adverse or beneficial. Whether psyllium husk influences colonic epithelial cell proliferation in humans as it does in rodents is unknown. Although enhanced cellular proliferation is associated with the neoplastic process, proliferation rates have been reported to be variably influenced by a number of dietary constituents and other exogenous and endogenous factors, and a significant overlap in proliferation rates between subjects at high and low risk of colon cancer has been observed (Ref. 40). Therefore, the agency concludes that the issue of epithelial cell proliferation is not a basis on which to deny this health claim.

2. Allergic Potential of Psyllium Husk

In the psyllium husk proposed rule, the agency acknowledged reports of allergic reactions from consumption of psyllium husk-containing food. The majority of these reports involved ingestion of a cereal made with psyllium husk of less than 95 percent

purity. Because information provided by the petitioner suggested that the purity of the psyllium husk is inversely related to its allergenicity, FDA proposed a purity criterion for psyllium husk to be eligible for the claim. Under comment 8 in section II.D.1 of this document, the agency stated that psyllium husk purity specifications of proposed § 101.81(c)(2)(ii)(B)(*1*) are being adopted in the final rule.

(Comment 15)

Two comments stated that the declaration of an ingredient in the ingredient list of the food label is sufficient labeling to alert consumers to the presence of allergenic components in foods and that additional labeling is unnecessary. Other comments stated that in consideration of the allergic potential of psyllium, the presence of psyllium husk in a food should be declared on the principal display panel in addition to the ingredient declaration.

Some comments agreed with the proposed husk purity specifications as an adequate means of reducing the potential for allergic responses. One comment explained that the major source of allergenic proteins in psyllium seed husk is from residual portions of the whole seed. The comment stated that the removal of the inner seed portions leaves a very low level of residual protein in 95 percent purity psyllium husk and thus, the potential for serious allergic reactions would be rare. However, the comment also suggested that a label statement with an appropriate caution as to the risk for allergic reactions would provide added assurances for consumers. Still other comments argued that the proposed purity standards for psyllium seed husk will not eliminate the risk for allergic reactions to psyllium husk-containing foods and as such, a cautionary statement alerting consumers to the risk of allergic reactions should be required labeling. None of the comments provided data.

The agency is not convinced by these comments that labeling, other than declaration in the ingredient statement when psyllium husk is added as a food ingredient, is necessary because of psyllium's allergic potential. The agency recognizes the possibility of isolated cases of allergic reactions to ingested allergenic substances in foods or food components, including psyllium seed husk. However, the agency believes that the declaration of the allergenic substance in the ingredient list on the food label provides adequate information for consumers regarding the presence of allergenic ingredients in food products. Psyllium seed husk is required to be declared in the ingredient statement of a food to which it is added. The agency has no basis for concluding that additional labeling requirements for the use of this health claim would have an impact on reducing the potential for allergic reactions from consumption of psyllium husk-containing foods. The agency would not object to any additional truthful, nonmisleading information regarding allergenicity that a manufacturer may wish to include on the food label.

3. Gastrointestinal Obstruction

In the psyllium proposed rule, the agency discussed the potential for esophageal and gastrointestinal obstructions to occur following consumption of psyllium seed husk when not consumed with sufficient liquid (62 FR 28234 at 28236). The agency noted that the LSRO expert panel (Ref. 39) reported that esophageal and gastrointestinal obstruction due to psyllium seed husk was associated almost exclusively with consumption without proper hydration of bulk-forming fiber laxatives and not with consumption of psyllium-containing cereal consumed with milk (62 FR 28234 at 28236). Comments were requested on whether psyllium husk-containing foods should carry a statement advising that the product be consumed with liquids, or whether the potential for blockage is not an issue of concern for psyllium husk-containing food (62 FR 28234 at 28236).

(Comment 16)

Several comments discussed the potential for esophageal and gastrointestinal obstructions from consumption of psyllium husk without sufficient liquid. These comments recommended that the agency adopt labeling requirements for psyllium husk-containing foods advising consumers to drink adequate fluids when consuming such foods. Some of these comments suggested that such statements be similar to those required under § 201.319 (21 CFR 201.319) (Warning Statements Required for Over-the-Counter Drugs Containing Water-Soluble Gums as Active Ingredients (58 FR 45194, August 26, 1993)) for OTC products to ensure consumers are aware of the consequences of inadequate hydration. In general, these comments justified their recommendations on the basis that authorization of the proposed health claim would encourage incorporation of psyllium seed husk into additional types of foods, and that these new food products containing significant amounts of psyllium seed husk will not necessarily be intended to be consumed with liquids. One comment asserted that a label statement advising the consumption of the psyllium husk-containing food with liquids is unnecessary because psyllium husk-containing foods would be consumed at meals when it is likely that sufficient liquid would also be consumed. The comment argued that the soluble fiber in psyllium husk-containing foods is already hydrated, which would reduce its ability to swell in the gastrointestinal tract. This comment further noted that the 1993 LSRO report on the safety of using psyllium seed husk as a food ingredient (Ref. 39) found no safety issues in this regard. None of the comments provided data.

The agency agrees with comments suggesting that authorization of a claim for soluble fiber from psyllium husk and risk of CHD may lead to an increase in the number and type of foods containing psyllium husk. Moreover, the agency agrees that there are no assurances that new psyllium husk-containing foods are likely to be consumed at meals or with liquids. Foods such as cookies, breakfast bars, and toaster pastries may be consumed as snacks at times when a liquid is not consumed. Psyllium husk could also be incorporated into dietary supplement products that may be consumed apart from meals. The comment that stated that the psyllium seed husk in foods is already hydrated, which would affect its ability to swell in the gastrointestinal tract, provided no data to document or with which to evaluate differences in the swell volume and rate of swelling of different psyllium husk-containing foods.

The LSRO expert panel that considered the safety of psyllium seed husk used as a food ingredient (Ref. 39) concluded that the moderate amounts of psyllium seed husk that are likely to be used in toaster pastries, bread-based products, breakfast bars, pasta, and cereals would not be expected to cause gastrointestinal obstruction. However, this panel further concluded that the possibility of obstruction would be reduced by suitable suggestions that these products be consumed with fluids.

The agency addressed the risk of esophageal obstruction by water soluble gums (including psyllium husk) in an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug products (40 FR 12902, March 21, 1975). The agency discussed in the final rule the evidence of at least 191 cases of esophageal obstruction and 8 cases of asphyxia, resulting in 18 deaths, associated with orally-administered OTC laxative and weight control products containing a variety of

water soluble gums (58 FR 45194 at 45195). The agency concluded that there is a risk that these types of products will swell to form a viscous adhesive mass (i.e., viscous gel) that can block the throat or esophagus. Because of this risk, the agency requires warning and direction statements for OTC drug products containing water soluble gums, including psyllium husk, as active ingredients when these products are marketed in a dry or partially hydrated form (§ 201.319). Fully hydrated water soluble gums were acknowledged to not pose any significant risk of causing esophageal obstruction (58 FR 45194 at 45196).

In the final rule on "Warning Statements Required for OTC Products Containing Water-Soluble Gums as Active Ingredients," the agency stated that it will continue to evaluate the use of water-soluble gums in any product marketed for human consumption, food or drug, and appropriate warnings will be proposed if a need to do so is found (58 FR 45194 at 45196).

The agency anticipates that authorization of a health claim for soluble fiber from psyllium husk may result in an increase of both the type and number of foods containing psyllium husk, and that foods eligible to bear the psyllium husk health claim will contain amounts of psyllium husk comparable to that commonly found in OTC laxative drugs. However, the agency recognizes that there are inherent differences between foods in conventional food form, which contain other food ingredients such as salt, sugar, and flour in addition to psyllium husk, and OTC drug products that would influence the likelihood of esophageal obstruction occurring from the ingestion of psyllium husk-containing foods. For example, drug products are formulated in tablets, capsules, and powders that are usually intended to be ingested and swallowed as a single bolus, whereas a serving of food is not swallowed as a single bolus, but eaten in several bites, chewed, and swallowed over a period of time. Psyllium husk-containing conventional foods also differ from drug products in that the psyllium husk in a food in conventional food form is dispersed within a larger volume of other food components (e.g., sugars, salt, wheat flour, egg). Dispersion in other ingredients prevents the soluble fiber of psyllium husk from physically associating to form a gel network (i.e., a viscous adhesive mass) (Refs. 41 and 42). Because a strong gel network is not formed due to the presence of these other ingredients, the food product will swell and thicken in a similar fashion to other high fiber foods (e.g., ready-to-eat cereals), without forming a viscous mass capable of causing obstruction (Ref. 42). The agency believes that, because the composition and manner of consumption of psyllium husk-containing conventional foods, unlike OTC products, inhibit the formation of a viscous gel in the esophagus, the label requirements for OTC drug products may not be applicable to certain foods containing psyllium husk that bear a health claim.

Section 201(n) of the act (21 U.S.C. 321(n)) states that, in determining whether labeling is misleading, the agency shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations made or suggested in the labeling or material with respect to consequences which may result from use of the article to which the labeling relates under the conditions of use as are customary or usual (see 21 CFR 1.21). Thus, the omission of certain material facts from the label or labeling on a food causes the product to be misbranded within the meaning of sections 403(a)(1) and 201(m) of the act (21 U.S.C. 343(a)(1)).

As discussed out in the final rule on warning statements for OTC products (58 FR 45194), esophageal obstruction and asphyxiation are potential health risks associated with the oral consumption of dry or incompletely hydrated psyllium husk when these products are ingested without adequate fluid or when they are used by individuals with esophageal narrowing or dysfunction, or with difficulty swallowing. There is the possibility that esophageal obstruction and choking from ingestion of psyllium husk-containing food would be a consequence of extending the food use of psyllium husk to certain types of food products, such as those that are predominately composed of psyllium husk. Therefore, FDA has determined that the potential for esophageal blockage from not consuming adequate amounts of fluids when consuming certain types of dry or incompletely hydrated psyllium husk-containing food is a material fact.

The agency concludes that it would be misleading under section 201(n) of the act for certain foods to contain dry or incompletely hydrated psyllium husk without a label statement relative to potential risks and concerns for adequate fluid intake. Therefore, in this final rule FDA is amending its regulations to require a statement [hereinafter "label statement"] to inform consumers of the potential consequence if the psyllium husk-containing food is not consumed appropriately, to inform consumers of the action necessary to avoid the consequence, and to advise persons with swallowing difficulties to avoid consumption of the product.

Because the concern for esophageal obstruction exists whether or not the food bears a health claim, FDA is codifying the need for the required label statement in § 101.17 *Food labeling warning and notice statements* (21 CFR 101.17) rather than in the health claim regulation. The required label statement is also reflected in § 101.81(c)(1). Accordingly, FDA is adding paragraph (f)(1) to § 101.17 to specify that when dry or incompletely hydrated psyllium husk is present in a food and the food bears a health claim, the label must include a statement such as:

The food should be eaten with at least a full glass of liquid. Eating this product without enough liquid may cause choking. Do not eat this product if you have difficulty swallowing.

In the psyllium proposed rule, the agency had specifically requested comments on whether psyllium husk-containing foods should carry a statement advising that the product be consumed with liquids. However, the agency had not suggested that it was considering requiring labeling for all psyllium husk-containing foods regardless of whether the food label bears a health claim statement. Therefore, FDA is not attempting, in this final rule, to extend the required statement to psyllium husk-containing foods not subject to this rulemaking, i.e., foods not bearing a health claim. Instead, the agency plans to propose, in a separate rulemaking, that the required label statement be extended to other psyllium husk-containing foods that do not bear a health claim.

However, as discussed previously, the agency recognizes that there are factors that suggest that the formation of a viscous adhesive mass, which is associated with a risk of choking, does not result from consumption of certain psyllium husk-containing foods that are in a conventional food form. Therefore, the agency believes that certain dry or incompletely hydrated conventional food products, i.e., those that do not form a viscous adhesive mass under usual conditions of use, would not require the label statement. The agency believes that an exemption from the label statement should be available to firms when a viscous adhesive mass is not formed when the product is exposed to fluids so that the product poses no greater risk to the consumer than a comparable product without psyllium husk. The agency does not currently

have data or information on which it could base such an exemption for specific conventional food products. Moreover, because FDA, under § 101.70(j)(4)(i), is obligated to publish this final rule within the time limitation established for issuing final rules for health claim proceedings, the agency is unable, in this final rule, to specify the conditions under which exemptions to the label statement for certain conventional food products are warranted. Consequently, the agency will provide firms that seek such an exemption with guidance as to what would be necessary to demonstrate that such an exemption to the label statement is warranted. The agency will further evaluate the need for the label statement on specific types of psyllium husk-containing foods that bear a health claim in the separate rulemaking that will address the extension of the label statement to psyllium husk-containing foods that do not bear a health claim. If the agency challenges a firm's determination that its conventional food product is entitled to the exemption in § 101.17(f)(1), and as a result is not misbranded within the meaning of section 201(n) of the act without such label statement, the agency will evaluate the basis for the firm's exemption on a case-by-case basis.

Section 403(f) of the act requires that mandatory label information be prominently placed on the label with such conspicuousness (compared with other words, statements, designs, or devices in the labeling) as to render it likely to be read and understood by the ordinary individual under customary conditions of use. FDA has generally considered the label information panel to be the appropriate location for notice and warning statements. As discussed in the agency's rulemaking requiring warning statements on iron-containing dietary supplements (62 FR 2218, January 15, 1997), consumer focus group studies establish that a warning statement need not be placed on the principal display panel (PDP) to be effective in informing consumers of the hazard. Participants in the focus groups reasoned that the front of the product package was used for marketing purposes and stated that they were accustomed to looking at the "back of products" for nutrition and factual information, including warning statements (Ref. 43). Consequently, in the case of iron-containing dietary supplements, the agency required that the warning statement appear on the information panel.

The agency believes that for the required label statements on psyllium husk-containing products, the requirement for prominence and conspicuousness would similarly be met if the statements appeared on the information panel. However, the agency would not object to firms placing the required statement on the PDP, because the PDP would provide even greater prominence. Accordingly, FDA is requiring in § 101.17(f)(2) that the required statement for psyllium husk-containing foods appear either on the product information panel or on the PDP.

The requirement in the act for prominent display means that the required label statement must appear in a manner that makes it readily observable and likely to be read. The agency notes that 21 CFR 101.2(c) requires that mandatory information appearing on the PDP and information panel, including information required by § 101.17, appear prominently and conspicuously in a type size no less than one-sixteenth inch.

In addition, current agency regulations that require a "warning" statement on the product label or in labeling (e.g., the statement required by § 101.17(e) on iron-containing dietary supplements in solid oral dosage form) or a label "notice" statement (e.g., the statement required by § 101.17(d)(3) on protein products that are not covered by the requirements of § 101.17(d)(1) and (d)(2)) require that the identifying term "WARNING" or "NOTICE" be capitalized and immediately precede the language of the applicable labeling statement. Based on FDA's experience in rulemaking pertaining to warning statements on protein products (47 FR 25379, June 11, 1982), as the severity of the consequences lessens, the severity of the warning may also lessen. Therefore, the agency considers the term "NOTICE" to be appropriate to alert consumers to the label statement. Accordingly, the agency is requiring in § 101.17(f)(2) that the capitalized word "NOTICE" immediately precede the required elements of the label statement.

4. Laxative effects

(Comment 17)

One comment noted that psyllium husk is primarily consumed for its laxative effect. This comment asserted that the label and labeling of psyllium husk-containing foods should inform consumers about the adverse effects of consuming excess amounts of psyllium by including a disclosure statement such as "Consumption of psyllium in excess of —— mg may cause diarrhea." Other comments noted that intake of psyllium-containing foods is self-limiting due to satiety and laxative effects.

FDA disagrees that the possible effects on bowel function of consuming 10 g/d of psyllium seed husk in foods would be considered as causing diarrhea or an adverse health consequence. Diarrhea is characterized by loose, watery bowel movements. The water-holding capacity and bulking effect of undigested soluble fiber from psyllium husk softens colonic contents and stimulates peristalsis, both of which facilitate movement of the colonic contents. Ingestion of psyllium husk does not lead to diarrhea. The expected effect of the use of bulk-forming fiber laxatives is an increase in stool volume and frequency of bowel movements. There is no reason to consider that a daily intake of 10 g of psyllium seed husk as a component of food would have any effect on the bowel other than to promote normal functioning by softening fecal contents and increasing fecal volume. Because the daily intake of psyllium seed husk that is approved for this health claim is the same customary daily intake when used as a laxative, amounts in excess of that required for laxation are not needed to obtain potential benefits, in reduced risk of CHD, from consumption of psyllium seed husk. Moreover, consumption in excess of 10.2 g/d of psyllium seed husk would not be expected to result in diarrhea because intake of psyllium husk increases stool volume and frequency of bowel movements. Softening of fecal contents is not diarrhea and does not represent an adverse health effect as suggested by the comment. Therefore, the agency finds that there is no basis on which to require, as suggested by the comment, a warning statement to alert consumers about possible adverse effects from consuming psyllium husk-containing foods.

H. General Health Claim Issues

1. Health claims for substances with OTC drug uses.

(Comment 18)

One comment stated that approving a claim on a product that incorporates an OTC drug into a food would set a precedent for allowing claims on "functional foods," foods consumed primarily for their purported ability to prevent or treat disease. The comment stated that this was not the intent of Congress when it passed the 1990 amendments.

FDA notes that bran, as well as psyllium husk, are listed as effective bulk-forming laxative active ingredients in the tentative final monograph on laxative drug products for OTC human use (50 FR 2124, January 15, 1985) and that oat bran is also an eligible source of soluble fiber from whole oats for this

health claim. The fact that a substance also has uses as an OTC drug does not bear on its recognized status as a food. FDA notes that psyllium seed husk is a recognized source of dietary fiber and an established food ingredient. Therefore, the comment is not relevant to this rulemaking.

2. Food-Specific Health Claims

(Comment 19)

Some comments stated that the proposed claim for a specific soluble fiber should not be authorized because claims for specific foods create the false impression that consumption of those foods is a more important factor than is the overall diet in reduction of risk of CHD. Other comments asserted that allowing health claims for individual substances portrays specific foods as panaceas or functional foods and undermines the purpose of the 1990 amendments. One comment expressed concern that claims about individual sources of dietary fiber are inconsistent with the important dietary guidance of choosing diets high in fruits, vegetables, whole grain foods, and other good sources of fiber. One comment stated that the proposed claim does not inform the consumer that frequent, long-term consumption of soluble fiber from psyllium husk is necessary to lower cholesterol levels.

FDA addressed the issue of the appropriate subject of health claims in rulemaking leading to, and including, the January 6, 1993, final rule on general requirements for health claims (see 56 FR 60537 at 60542, November 27, 1991; 58 FR 2478 at 2479, January 6, 1993). While some comments to proposed rulemaking maintained that health claims should only be permitted for nutrients listed in nutrition labeling, others argued that Congress intended claims to be authorized for foods as well as nutrients. Comments quoted private and public health organizations' testimony before Congress that health claims should reflect dietary recommendations about foods and "should assist the public to integrate specific food products into a well balanced diet" (58 FR 2478 at 2479). After extensive discussion, final rules implementing the 1990 amendments defined health claims as claims characterizing the relationship of any substance to a disease or health-related condition, and defined "substance" as a specific food or component of food (§ 101.14(a)(1) and (a)(2)). This permitted health claims to be established for both nutrients and foods.

In the soluble fiber from whole oats final rule, the agency addressed comments that expressed concern that a claim on whole oat foods would portray the specific food as a "magic bullet" in reducing heart disease risk. This concern was ameliorated when the scientific evidence supported changing the subject of the claim to soluble fiber from whole oats. In addition, the importance of a total diet low in saturated fat and cholesterol to the nutrient/disease relationship was emphasized (62 FR 3584 at 3585 and 3590). FDA noted that diets low in saturated fat and cholesterol are considered by expert groups to be the most effective dietary means of reducing heart disease risk. The agency stated that while soluble fiber from whole oats contributes to this effect, its role is generally recognized as being of smaller magnitude (62 FR 3584 at 3590 and 3594).

Likewise, the agency concludes that the concerns described previously that were raised in comments to the psyllium husk proposed rule are adequately addressed by the fact that a health claim on psyllium-containing foods will be required to state the subject of the claim as "soluble fiber from psyllium husk" and to describe the nutrient/disease relationship in the context of a diet low in saturated fat and cholesterol. The comment provided no evidence to suggest that health claims about specific foods or food ingredients will not encourage consumers to follow dietary recommendations to eat a varied diet containing other foods that are also good sources of fiber.

FDA notes that the subject health claim, as is the case for all authorized health claims, requires that the claim be stated in the context of a daily diet. This is accomplished through specific requirements describing the nature of the claim, i.e., the relationship of the substance to the disease or health-related condition in paragraph (c)(2)(i) of each health claim regulation. These requirements are intended to show the nature of the relationship between the subject of the claim and the disease or health condition and to prevent any misunderstanding that health benefits will accrue from single or infrequent consumption of the subject nutrient or adherence to the suggested dietary regimen. Examples of such wording include "throughout life" in the calcium/osteoporosis claim (21 CFR 101.72), "daily" in the folate/neural tube defect claim (21 CFR 101.79), "diets low in fat * * *" in health claims pertaining to cancer (21 CFR 101.73, 101.76, and 101.78) and "diets low in saturated fat and cholesterol * * *" in health claims pertaining to heart disease (§§ 101.75, 101.77, and 101.81). Therefore, the agency is making no changes in response to this comment.

The preamble of the soluble fiber from whole oats health claim final rule considered the impact of the health claim on consumer perception of food label references to oats (62 FR 3584 at 3596). A comment had suggested that as consumers become aware of the relationship between soluble fiber from whole oats and reduced risk of CHD, statements such as "made with oat bran" would be an implied nutrient content or health claim. In response to this comment, FDA stated that it did not have information from which to conclude that terms such as "oat bran," "rolled oats," or "whole oat flour" are always in a context that constitutes an implied nutrient content or health claim, and as such FDA would continue its policy to evaluate the context of label statements on a case-by-case basis (62 FR 3584 at 3597). The agency further noted that if experience with label statements about oat ingredients or other information persuades FDA that additional regulatory controls are needed, the agency can take action to establish appropriate regulations. The agency does not have reason at this time to change this policy.

III. Environmental Impact

The agency has previously considered the environmental effects of this rule as announced in the psyllium husk proposed rule (62 FR 28234). The proposed rule incorrectly cited a claim of categorical exclusion under previous 21 CFR 25.24(a)(11). The agency has determined, based on information contained in an environmental assessment prepared under previous 21 CFR 25.31a(b)(5), that this action has no significant impact on the environment and that an environmental impact statement is not required. No new information or comments have been received that would affect this determination. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

IV. Analysis of Economic Impacts

A. Benefit-Cost Analysis

FDA has examined the impacts of the final rule under Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory approach that maximizes net benefits (including potential

economic, environmental, public health and safety effects; distributive impacts; and equity). According to Executive Order 12866, a rule is significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million, adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. FDA finds that this rule is not a significant rule as defined by Executive Order 12866.

In addition, FDA has determined that this rule does not constitute a significant rule under the Unfunded Mandates Reform Act of 1995 requiring cost-benefit and other analyses. A significant rule is defined in section 1531(a) as "a Federal mandate that may result in the expenditure by State, local, and tribal governments in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation) in any 1 year * * *."

Finally, in accordance with the Small Business Regulatory Enforcement Fairness Act, the administrator of the Office of Information and Regulatory Affairs of the Office of Management and Budget has determined that this final rule is not a major rule for the purpose of Congressional review.

The authorization of health claims about the relationship between soluble fiber from psyllium seed husk and CHD results in either costs or benefits only to the extent that food manufacturers elect to take advantage of the opportunity to use the claim. The authorization of the health claim will not require that any labels be redesigned, or that any product be reformulated. However, the labels of foods containing whole oats and bearing the health claim will require revision to specify the daily dietary intake of β-glucan soluble fiber from whole oats necessary to achieve the claim effect. Because FDA is allowing firms to wait to incorporate this change with other regularly scheduled changes, this provision will not result in additional costs.

This final health claim will allow manufacturers to highlight the benefits of soluble fiber from psyllium seed husk in addition to other eligible food sources of soluble fiber for which FDA has already approved a health claim. The benefit of establishing this health claim is to provide for new information in the market regarding the relationship between soluble fiber from psyllium seed husk and risk of heart disease and to provide consumers with the assurance that this information is truthful, not misleading, and scientifically valid.

B. Small Entity Analysis

FDA has examined the impacts of the final rule under the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the economic impact of that rule on small entities.

Small entities will incur costs only if they opt to take advantage of the marketing opportunity presented by this regulation. FDA cannot predict the number of small entities that will choose to use the claim. However, no firm, including small entities, will choose to bear the cost of redesigning labels unless they believe that the claim will result in increased sales of their product. Therefore, this rule will not result in either a decrease in revenues or a significant increase in costs to any small entity. Accordingly, under the Regulatory Flexibility Act, 5 U.S.C. 605(b), the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

V. Paperwork Reduction Act

In the psyllium proposal, FDA stated its tentative conclusion that the proposed rule contained no information collection provisions necessitating clearance by the Office of Management and Budget (OMB) and asked for comments on whether the proposed rule imposed any paperwork burden. No comments addressing the question of paperwork burden were received. FDA has evaluated the final rule and concludes that it contains no information collection provisions. Although the final rule would amend § 101.17 to require a label statement on foods containing psyllium husk and bearing a health claim, FDA is supplying the information that must be disclosed in the label statement. Therefore, the label statement is a "public disclosure of information originally supplied by the Federal government to the recipient for purpose of disclosure to the public" (5 CFR 1320(c)(2)); as such, it is not a "collection of information" subject to OMB review under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Kellogg Co., *Kellogg's Bran Buds Cereal with natural wheat bran and psyllium* (product packaging) Kellogg Co., Battle Creek, MI, 1997.

2. The U.S. Pharmacopeia (USP 23), The National Formulary (NF 18), United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1341–1342, 1995.

3. DHHS, Public Health Service (PHS), "The Surgeon General's Report on Nutrition and Health," U.S. Government Printing Office, Washington, DC, pp. 83–137, 1988.

4. Food and Nutrition Board, National Academy of Sciences, "Diet and Health: Implications for Reducing Chronic Disease Risk," National Academy Press, Washington, DC, pp. 291–309 and 529–547, 1989.

5. LSRO, FASEB, "Physiological Effects and Health Consequences of Dietary Fiber," Bethesda, MD, 1987.

6. LSRO, FASEB, "Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships: 6. Dietary Fiber and Cardiovascular Disease," Bethesda, MD, 1991.

7. Saltsman, J., Memo to file with Table 1: "Summary of Clinical Trials: Psyllium and CHD," and Table 2: "Psyllium and CHD," Docket No. 96P–0338, Dockets Management Branch, January 28, 1997.

8. Abraham, Z. D. and T. Mehta, "Three-Week Psyllium-Husk Supplementation: Effect on Plasma Cholesterol Concentrations, Fecal Steroid Excretion, and Carbohydrate Absorption in Men," *American Journal of Clinical Nutrition*, 47:67–74, 1988.

9. Anderson, J. W., N. Zettwoch, T. Feldman, J. Tietyen-Clark, P. Oeltgen, and C. W. Bishop, "Cholesterol-Lowering Effects of Psyllium Hydrophilic Mucilloid for Hypercholesterolemic Men," *Archives of Internal Medicine*, 148:292–296, 1988.

10. Anderson, J. W, T. L. Floore, P. B. Geil, D. S. O'Neal, and T.K. Balm, "Hypocholesterolemic Effects of Different Bulk-Forming Hydrophilic Fibers as Adjuncts to Dietary Therapy in Mild to Moderate Hypercholesterolemia," *Archives of Internal Medicine*, 151:1597–1602, 1991.

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List of Subjects in 21 CFR Part 101

Food labeling, Incorporation by reference, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371.

2. Section 101.17 is amended by adding paragraph (f) to read as follows:

§ 101.17 Food labeling warning and notice statements.

* * * * *

(f) *Foods containing psyllium husk.* (1) Foods containing dry or incompletely hydrated psyllium husk, also known as psyllium seed husk, and bearing a health claim on the association between soluble fiber from psyllium husk and reduced risk of coronary heart disease, shall bear a label statement informing consumers that the appropriate use of such foods requires consumption with adequate amounts of fluids, alerting them of potential consequences of failing to follow usage recommendations, and informing persons with swallowing difficulties to avoid consumption of the product (e.g., "NOTICE: This food should be eaten with at least a full glass of liquid. Eating this product without enough liquid may cause choking. Do not eat this product if you have difficulty in swallowing."). However, a product in conventional food form may be exempt from this requirement if a viscous adhesive mass

is not formed when the food is exposed to fluids.

(2) The statement shall appear prominently and conspicuously on the information panel or principal display panel of the package label and any other labeling to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use. The statement shall be preceded by the word "NOTICE" in capital letters.

3. Section 101.81 is amended by revising the section heading, the heading for paragraphs (a) and (b), and paragraphs (a)(3), (b)(2), (c)(1), (c)(2)(i) introductory text, (c)(2)(i)(A), (c)(2)(i)(E), (c)(2)(i)(F), (c)(2)(iii)(A), (d)(2), (d)(3), and (e); by adding paragraphs (c)(2)(i)(G) and (c)(2)(ii)(B); and by removing paragraph (d)(6) and redsignating paragraph (d)(7) as (d)(6) and paragraph (d)(8) as (d)(7) to read as follows:

§ 101.81 Health claims: Soluble fiber from certain foods and risk of coronary heart disease (CHD).

(a) *Relationship between diets that are low in saturated fat and cholesterol and that include soluble fiber from certain foods and the risk of CHD.* * * *

* * * * *

(3) Scientific evidence demonstrates that diets low in saturated fat and cholesterol may reduce the risk of CHD. Other evidence demonstrates that the addition of soluble fiber from certain foods to a diet that is low in saturated fat and cholesterol may also help to reduce the risk of CHD.

(b) *Significance of the relationship between diets that are low in saturated fat and cholesterol and that include soluble fiber from certain foods and the risk of CHD.* * * *

* * * * *

(2) Intakes of saturated fat exceed recommended levels in the diets of many people in the United States. One of the major public health recommendations relative to CHD risk is to consume less than 10 percent of calories from saturated fat and an average of 30 percent or less of total calories from all fat. Recommended daily cholesterol intakes are 300 milligrams (mg) or less per day. Scientific evidence demonstrates that diets low in saturated fat and cholesterol are associated with lower blood total- and LDL-cholesterol levels. Soluble fiber from certain foods, when included in a low saturated fat and cholesterol diet, also helps to lower blood total- and LDL-cholesterol levels.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met. The label and labeling of foods containing psyllium husk shall be consistent with the provisions of § 101.17(f).

(2) *Specific requirements.* (i) Nature of the claim. A health claim associating diets that are low in saturated fat and cholesterol and that include soluble fiber from certain foods with reduced risk of heart disease may be made on the label or labeling of a food described in paragraph (c)(2)(iii) of this section, provided that:

(A) The claim states that diets that are low in saturated fat and cholesterol and that include soluble fiber from certain foods "may" or "might" reduce the risk of heart disease.

* * * * *

(E) The claim does not attribute any degree of risk reduction for CHD to diets that are low in saturated fat and cholesterol and that include soluble fiber from the eligible food sources from paragraph (c)(2)(ii) of this section; and

(F) The claim does not imply that consumption of diets that are low in saturated fat and cholesterol and that include soluble fiber from the eligible food sources from paragraph (c)(2)(ii) of this section is the only recognized means of achieving a reduced risk of CHD.

(G) The claim specifies the daily dietary intake of the soluble fiber source that is necessary to reduce the risk of coronary heart disease and the contribution one serving of the product makes to the specified daily dietary intake level. Daily dietary intake levels of soluble fiber sources listed in paragraph (c)(2)(ii) of this section that have been associated with reduced risk coronary heart disease are :

(*1*) 3 g or more per day of B-glucan soluble fiber from whole oats.

(*2*) 7 g or more per day of soluble fiber from psyllium seed husk.

(ii) * * *

(B)(*1*) Psyllium husk from the dried seed coat (epidermis) of the seed of *Plantago* (*P.*) ovata, known as blond psyllium or Indian psyllium, *P. indica*, or *P. psyllium*. To qualify for this claim, psyllium seed husk, also known as psyllium husk, shall have a purity of no less than 95 percent, such that it contains 3 percent or less protein, 4.5 percent or less of light extraneous matter, and 0.5 percent or less of heavy extraneous matter, but in no case may the combined extraneous matter exceed 4.9 percent, as determined by U.S. Pharmacopeia (USP) methods described in USP's "The National Formulary," USP 23, NF 18, p. 1341, (1995), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC;

(*2*) FDA will determine the amount of soluble fiber that is provided by psyllium husk by using a modification of the Association of Official Analytical Chemists' (AOAC's) method for soluble dietary fiber (991.43) described by Lee et al., "Determination of Soluble and Insoluble Dietary Fiber in Psyllium-containing Cereal Products," *Journal of the AOAC International*, 78 (No. 3):724–729, 1995, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from the Association of Official Analytical Chemists International, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877–2504, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW., rm. 3321, Washington, DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC;

(iii) * * *

(A) The food product shall include:

(*1*) One or more of the whole oat foods from paragraph (c)(2)(ii)(A) of this section, and the whole oat foods shall contain at least 0.75 gram (g) of soluble fiber per reference amount customarily consumed of the food product; or

(*2*) Psyllium husk that complies with paragraph (c)(2)(ii)(B) of this section, and the psyllium food shall contain at least 1.7 g of soluble fiber per reference amount customarily consumed of the food product;

* * * * *

(d) * * *

(2) The claim may state that the relationship between intake of diets that are low in saturated fat and cholesterol and that include soluble fiber from the eligible food sources from paragraph (c)(2)(ii) of this section and reduced risk of heart disease is through the intermediate link of "blood cholesterol" or "blood total- and LDL-cholesterol;"

(3) The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between diets that are low in saturated fat and cholesterol and that include soluble fiber from certain foods and coronary heart disease and the significance of the relationship;

* * * * *

(e) *Model health claim.* The following model health claims may be used in food labeling to describe the

relationship between diets that are low in saturated fat and cholesterol and that include soluble fiber from certain foods and reduced risk of heart disease:

(1) Soluble fiber from foods such as [name of soluble fiber source from paragraph (c)(2)(ii) of this section and, if desired, the name of food product], as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies _____ grams of the [grams of soluble fiber specified in paragraph (c)(2)(i)(G) of this section] soluble fiber from [name of the soluble fiber source from paragraph (c)(2)(ii) of this section] necessary per day to have this effect.

(2) Diets low in saturated fat and cholesterol that include [_____ grams of soluble fiber specified in paragraph (c)(2)(i)(G) of this section] of soluble fiber per day from [name of soluble fiber source from paragraph (c)(2)(ii) of this section and, if desired, the name of the food product] may reduce the risk of heart disease. One serving of [name of food] provides _____ grams of this soluble fiber.

Dated: February 10, 1998

William B. Schultz,

Deputy Commissioner for Policy.

Note: The following table will not appear in the Code of Federal Regulations.

TABLE 1.—SUMMARY OF CLINICAL TRIALS WITH HYPERCHOLESTEROLEMICS: PSYLLIUM AND CORONARY HEART DISEASE

Study	Duration Treatment	Number of Subjects	Supplements (Psyllium, Placebo) Soluble Fiber g/d	Diet Intake of groups: Sat fat % E; CHOL mg/d	Magnitude of PSY Effect[1]	Magnitude of Placebo Effect
Anderson et al. (Ref. 13)	Base: 8 wk Step 1; Tx: 26 wk Step 1+supplement	PSY: 131 C: 28	10.2 g/d bulk laxative, cellulose PSY: ~7 g SF	*Sat fat*: PSY- 8.3%; C- 7.7% *CHOL*: PSY- 164 mg; C- 146 mg	*CHOL*: -5 mg/dL (2.1%)[1] *LDL-C*: -5 mg/dL (2.9%)[1]	*CHOL*: +5 (2.6%) *LDL-C*: +6 (3.9%) *HDL-C*: no sig dif (grps)
Bell et al. (Ref. 14)	Base: 12-wk Step 1; Tx: 8-wk Step 1+supplement	PSY: 40 (20 men) Pla: 35 (18 men)	10.2 g/d bulk laxative, cellulose PSY: ~7 g SF	*Sat fat*: PSY- 8–10%; C- 7.7–8.6% *CHOL*: PSY- 168 mg; C- 206 mg	*CHOL*: -9 mg/dL (4.2%) *LDL-C*: -12 mg/dL (7.7%)	*CHOL*: 0 *LDL-C*: -0.2% *HDL-C*: no sig dif (grps)
Davidson et al. (Ref. 15)	Base: 8-wk Step 1; Tx: 24-wk Step 1 + PSY or control food (3 servings/d)	PSY 1 56 (31 men) PSY 2 40 (24 men) PSY 3 43 (28 men) C 59	3.4 g, 6.8 g, 10.2 g/d; incorporated into foods: C foods: no PSY PSY 1: ~2.3 g SF, PSY 2: ~4.6 g; PSY 3: ~7 g	*SAT fat*: PSY- 7–8.6%; C- 7–8.6% *CHOL*: PSY 1-151 mg; PSY 2-181; PSY 3- 169 C- 145 mg	*CHOL*: —3% (PSY 3) *LDL-C*: —5% (PSY 3)	*CHOL*: +1.7%; LDL-C: +3% *HDL-C*: No sig dif (grps)
Everson et al. (Ref. 16)	Regular diet; 5-d Base; 2 40-d periods; 11-d washout; crossover	20 men	15.3 g/d bulk laxative, cellulose PSY: ~10 g SF	*SAT fat*: PSY- 12%; C- 13.2 % *CHOL*: PSY- 296 mg; C- 274 mg	*CHOL*: -14 mg/dL (-5%) *LDL-C*: -15 mg/dL (8%)	*CHOL*: -1.9%; LDL-C: -2.7% *HDL-C*: No sig dif (grps)
Keane et al. (Ref. 18)	Base: 12 wk Step 1; Tx: 26 wk Step 1+supplement	PSY: 40 (18m, 24f) C: 39 (7m, 32f)	10.2 g/d bulk laxative, cellulose PSY: ~7 g SF	*SAT fat*: PSY- 5%; C- 5.3% *CHOL*: PSY- 145.2 mg; C- 151.1 mg	*CHOL*: -8.7 mg/dL (3%) *LDL-C*: -11.5 mg/dL (5.9%)[1]	*CHOL*: +2 (1%) *LDL-C*: 0 *HDL-C*: no sig dif (grps)
Levin et al. (Ref. 19)	Base: 8-wk Step 1; Tx: 16-wk Step 1+supplement	PSY: 30 (26 men) Pla: 28 (23 men)	10.2 g/d bulk laxative, cellulose PSY: ~7 g SF	*SAT fat*: PSY- 6.7%; C- 6.3% *CHOL*: PSY- 166 mg; C- 135 mg	*CHOL*: -13 mg/dL (5.6%) *LDL-C*: -13 mg/dL (8.6%)	*CHOL*: 0; LDL-C -2.2%; HDL-C: —+6% (sig from PSY)
Stoy et al. (Ref. 23)	4-wk Step 1; Step 1 + (8x5x5 wks): Grp 1: PSY-Pla-PSY; Grp 2: Pla-PSY-Pla	23 men	Estimated 11.6 g/d PSY from cereal: ~8 g SF; Wheat cereal: ~3 g SF	*SAT fat*: PSY: 5.1% (Grp 1) and 5.1% (Grp 2) Wheat: 4.5% (Grp 1) and 5.0% (Grp 2) *CHOL*: PSY 141–165 mg Wheat: 164 mg (Grp 1), 117–170 (Grp 2)	*CHOL*: -10 mg/dL (4%) *LDL-C*: -11 mg/dL (6%)	*HDL-C*: No sig dif (grps)
Stoy et al. (Ref. 24)	4-wk Step 1; Step 1 + (8x5x5 wks): Grp 1: PSY-Pla-PSY; Grp 2: Pla-PSY-Pla	22 men	Estimated 11.6 g/d PSY from cereal: ~8 g SF; Wheat cereal: ~3 g SF	*SAT fat*: PSY: 4.8 (Grp 1) and 5.2% (Grp 2) Wheat: 4.7% (Grp 1) and 5.6% (Grp 2) *CHOL*: PSY 155–163 mg Wheat: 133 mg (Grp 1), 169–172 (Grp 2)	*CHOL*: -10 mg/dL (4%) *LDL-C*: -11 mg/dL (6%)	*HDL-C*: No sig dif (grps)

TABLE 1.—SUMMARY OF CLINICAL TRIALS WITH HYPERCHOLESTEROLEMICS: PSYLLIUM AND CORONARY HEART DISEASE—Continued

Study	Duration Treatment	Number of Subjects	Supplements (Psyllium, Placebo) Soluble Fiber g/d	Diet Intake of groups: Sat fat % E; CHOL mg/d	Magnitude of PSY Effect[1]	Magnitude of Placebo Effect
Weingand et al. (Ref. 26)	Base: 12 wk Step 1; Tx: 8 wk Step 1+supplement, crossover	23 (16m, 7f)	10.2 g/d bulk laxative, cellulose PSY: ~7 g SF	*SAT fat*: PSY- 8.7%; C- 9% *CHOL*: PSY- 162 mg; C- 203–261 mg	*CHOL*: -9 mg/dL (3.8%) *LDL-C*: -11 mg/dL (6.2%)[1]	*HDL-C*: sig higher in PSY group
Jenkins et al. (Ref. 30)	Base: 2 mo controlled Step 2 diets; Tx: 2- 1 mo Step 2 diets+ cereal, crossover	Study 1: 32 (15m, 17f)	Study 1: 11.4 g/d PSY in cereal (~7.8 g SF), wheat bran	Study 1: *SAT fat*: PSY- 4.6%; C -4.6% *CHOL*: PSY- 31 mg; C- 29 mg *MUFA*: PSY- 6%; C- 6%	Study 1: *CHOL*: -27 mg/dL[1] (9.8%) *LDL-C*: -24 mg/dL[1] (12.6%) *HDL-C*: -6.6 mg/dL (11.3%)[1]	Study 1: *CHOL*: -13.6 (5%)[2] *LDL-C*: -10 (5.5%) *HDL-C*: -2 (3.3%)
		Study 2: 27 (12m, 15f)	Study 2: 12.4 g/d PSY in cereal (~8.4 g SF), wheat bran	Study 2: *SAT fat*: PSY- 6%; C- 6% *CHOL*: PSY- 22 mg; C-22 mg *MUFA*: PSY- 12%; C- 12%	Study 2: *CHOL*: -34 mg/dL[1] (12.6%) *LDL-C*: -27.9 mg/dL[1] (14.9%) *HDL-C*: -4.3 mg/dL[1] (8%)	Study 2: *CHOL*: -29.5 (10.7%)[2] *LDL-C*: -17 (9%)[2] *HDL-C*: -1.4 (2.6%)

[1] Significant differences between treatment and placebo groups unless otherwise indicated.
[2] Significant change across the diet phase.

Abbreviations Used in Table 1

C	Control
CHOL	Blood total cholesterol
d	Day
E	Energy
g	Gram
grp	Group
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
m/f	Number of males, number of females
mg/dL	Milligrams per deciliter
Pla	Placebo
PSY	Psyllium
Sat fat	Saturated fat
SF	Soluble fiber
Sig Dif	Statistically significant difference
Step 1	≤ 30% kcals fat, < 10% kcals sat fat, < 300 mg cholesterol
TDF	Total dietary fiber
Tx	Treatment
wk	Week
~	Approximately
%	Percent

[FR Doc. 98–4074 Filed 2–12–98; 4:18 pm]
BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 510 and 529

Certain Other Dosage Form New Animal Drugs; Isoflurane

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of an abbreviated new animal drug application (ANADA) filed by Rhone-Poulenc Chemicals, Ltd. The ANADA provides for use of isoflurane, USP, as an inhalant for induction and maintenance of general anesthesia in horses and dogs.

EFFECTIVE DATE: February 18, 1998.

FOR FURTHER INFORMATION CONTACT: Lonnie W. Luther, Center For Veterinary Medicine (HFV–102), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–0209.

SUPPLEMENTARY INFORMATION: Rhone-Poulenc Chemicals, Ltd., P.O. Box 46, St. Andrew's Rd., Avonmouth, Bristol BS11 9YF, England, UK, filed ANADA 200–237 that provides for inhalant use of isoflurane, USP, for induction and maintenance of general anesthesia in horses and dogs. The drug is limited to use by or on the order of a licensed veterinarian.

Approval of ANADA 200–237 for Rhone-Poulenc Chemicals, Ltd.'s isoflurane is as a generic copy of Ohmeda Pharmaceutical Products Division, Inc.'s NADA 135–773 AErrane® (isoflurane, USP). The ANADA is approved as of December 19, 1997, and the regulations are amended in 21 CFR 529.1186(b) to reflect the approval. The basis of approval is discussed in the freedom of information summary.

Also, the sponsor has not been previously included in the list of sponsors of approved applications in § 510.600 (21 CFR 510.600). The regulations are amended in § 510.600(c)(1) and (c)(2) to reflect the the new sponsor.

In accordance with the freedom of information provisions of 21 CFR part 20 and 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20855, between 9 a.m. to 4 p.m., Monday through Friday.

The agency has determined under 21 CFR 25.33(d)(1) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.