DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

JUN 23 2014

Ms. Andrea Larson-Peters
Section Head, U.S. Regulatory
The Procter & Gamble Company
Mason Business Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

RE: Petition for a Qualified Health Claim for psyllium husk to reduce the risk of Type 2 diabetes mellitus (Docket No. FDA-2013-Q-0167)

Dear Ms. Larson-Peters:

This letter responds to the health claim petition dated August 30, 2012, submitted to the Food and Drug Administration (FDA or the agency), on behalf of The Procter & Gamble Company pursuant to § 403(r)(4) and presumably to § 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4) and § 343(r)(5)(D)). The petition, originally received by FDA on September 5, 2012, requested that the agency authorize a health claim regarding the relationship between the consumption of viscous soluble fiber from psyllium husk and a reduced risk of type 2 diabetes mellitus (type 2 diabetes). The petition proposed the following language for an authorized health claim for conventional foods and dietary supplements: "Diets that include 7 grams of soluble fiber per day, from psyllium husk, may reduce the risk of type 2 diabetes by lowering elevated blood sugar levels."

FDA evaluated the scientific evidence provided with the petition and other evidence related to your claim. Based on this review, FDA determined that the scientific evidence supporting the proposed health claim did not meet the "significant scientific agreement" standard necessary to bear a health claim. FDA notified you of this decision on January 25, 2013, and you submitted an email dated January 28, 2013 requesting that the petition be reviewed as a qualified health claim. FDA also sought clarification from you that the "substance" in the substance/disease relationship was psyllium husk (and not soluble fiber), and in an email message dated January 29, 2013, you confirmed that the substance was psyllium husk. Thus, FDA filed the petition on February 15, 2013 as a qualified health claim petition and posted it on the Regulations.gov website for a 60-day comment period, consistent with the agency's guidance for procedures on qualified health claims.[1] The agency did not receive any comments on this petition.

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[1] See FDA "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003).
[http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/labelingnutrition/ucm053832.htm (accessed Oct. 23, 2013)]

This letter sets forth the basis of FDA's determination that the current scientific evidence regarding the relationship between psyllium husk and type 2 diabetes is appropriate for consideration of a qualified health claim on conventional foods and dietary supplements. In addition, this letter sets forth (in the "Conclusions" section) qualified health claim language for which FDA intends to exercise enforcement discretion. This letter also sets forth the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim with respect to the consumption of psyllium husk and a reduced risk of type 2 diabetes.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general United States population, or an identified United States population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.[2] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[3]

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[4] The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[5]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses[6], review articles[7], and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in

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[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

[3] See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009. [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm (accessed July 23, 1013)]

[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

[5] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See *supra,* note 3.

[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[7] Review articles summarize the findings of individual studies.

understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.[9] If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (IOM, 2005a). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker, 1991; NRC, 2011). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a

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[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[9] Certain meta-analyses may be used as part of the health claim review process. See *supra*, note 3.

placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the United States population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review. Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[10] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the United States population or target subgroup, whether study results supporting the proposed claim have been replicated,[11] and the overall consistency[12] of the total body of evidence.[13] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)).

The petition identified psyllium husk as the substance that is the subject of the proposed claim. Psyllium husk is derived from psyllium, a harvestable grain from plants of the Plantago genus. Different types of psyllium are available, depending on the growing region. Psyllium is primarily cultivated in France, Spain, and India, with small quantities grown in the American Southwest (62 FR 28234 at 28235; May 22, 1997).

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[10] See *supra*, note 3 [Section III.F].

[11] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

[12] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B., The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

[13] See *supra*, note 3 [Section III.F].

FDA considers psyllium husk to be synonymous with psyllium seed husk, in accordance with the US Pharmacopeia (USP) National Formulary (USP, 1995). Psyllium husk is the seed coat that has been removed from the psyllium seed. The psyllium seed includes nutrients and allergenic proteins that are not components of psyllium husk (63 FR 8103 at 8105; February 18, 1998).

Psyllium husk is a concentrated source of soluble fiber and is used as a food or food component in a number of foods in the United States (62 FR 28234 at 28235). For example, psyllium husk is an ingredient in some commercially available breakfast cereals (e.g., Nature's Path Organic Smart Bran and Kellogg's All Bran Buds) and is a component of certain dietary supplements (such as Metamucil MultiHealth Fiber), which are regulated as foods by the FDA. Therefore, the agency concludes that psyllium husk, the substance identified in the petition, meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified type 2 diabetes as the disease or health-related condition that is the subject of the proposed claim.

Diabetes is a disorder of metabolism resulting from the body's impaired ability to use blood glucose (sugar) for energy.[14] In type 1diabetes, the pancreas no longer makes insulin and therefore blood glucose cannot enter the cells to be used for energy. In type 2 diabetes, either the pancreas does not make enough insulin or the body is unable to use insulin effectively (i.e., insulin resistance). A diagnosis of type 2 diabetes can be made after positive results on any one of three tests, with confirmation from a second positive test on a different day. The three tests are: (1) random (taken any time of day) plasma glucose value of 200 mg/dL or more, along with the presence of diabetes symptoms; (2) a plasma glucose value of 126 mg/dL or more after a person has fasted for 8 hours; and (3) an oral glucose tolerance test (OGTT) plasma glucose value of 200 mg/dL or more in a blood sample taken 2 hours after a person has consumed a drink containing 75 g of glucose dissolved in water. Elevated or abnormally high blood glucose (sugar) levels (fasting blood glucose of >100 mg/dL and <126 mg/dL) and insulin resistance[15] are considered risk factors for type 2 diabetes.[16,17]

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[14] National Institutes of Health (NIH), "Diabetes Overview." [http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm#what (accessed July 23, 2013)]

[15] Insulin resistance is a condition in which the cells of the body become resistant to the effects of insulin. As a result, higher levels of insulin are needed for glucose to enter the cells and to achieve normal blood glucose concentration. See NIH, National Diabetes Information Clearinghouse, "Insulin Resistance and Prediabetes." [http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/index.aspx (accessed July 23, 2013)]

[16] "Diabetes Risk Factors" [http://ndep.nih.gov/am-i-at-risk/DiabetesRiskFactors.aspx (accessed July 23, 2013)]

[17] NIH, National Diabetes Information Clearinghouse, "Insulin Resistance and Prediabetes." [http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/index.aspx (accessed July 23, 2013)]

The agency concludes that type 2 diabetes meets the definition of a disease under 21 CFR 101.14(a)(5) because, in this state, the glucose metabolism systems of the body have been damaged such that the body is not functioning properly.

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify the claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the substance, which is either a food or an ingredient that is the source of the substance, is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (21 CFR 101.70(f)). Dietary ingredients in dietary supplements are not subject to the food additive provisions of the Act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. § 342) and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. § 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994. The applicable adulteration provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. § 342(f)(1)(A)). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. § 342(f)(1)(D)).

The petition states that psyllium husk has a long history of safe human consumption in food, as a component of food, and in over-the-counter drug products. As previously mentioned, psyllium husk is derived from the psyllium seed, which is a part of the psyllium plant. The psyllium plant is a grain of natural biological origin that is harvested in several areas of the world.

As pointed out in the petition, a 1993 Life Sciences Research Office report that evaluated the health effects and safety aspects of psyllium seed husk concluded that "[t]here is no evidence … that demonstrates, or suggests reasonable grounds to suspect a hazard to the public when it is used in a number of food categories and at levels of addition that would result in total consumption of as much as 25 g/day of psyllium seed husk. However, it is not possible to determine without additional data whether a significant increase in consumption above 20 to 25 g/day would constitute a dietary hazard."

The petition also referred to a 2005 report by the Institute of Medicine indicating that there is no tolerable upper intake level (UL) for adverse events associated with the consumption of total fiber. According to the IOM report, "...due to the bulky nature of fibers, excess consumption is likely to be self-limiting. Therefore, a UL was not set for these individual fibers."

In a 1998 final rule entitled "Food Labeling: Health Claims; Soluble Fiber from Certain Foods and Coronary Heart Disease – Final rule," FDA agreed that there is a history of human oral consumption of psyllium husk, both in food and over-the-counter drug products (63 FR 8103 at 8111). FDA also concluded that the petitioner of the soluble fiber health claim had provided evidence that satisfied the requirements in 21 CFR 101.14(b)(3)(ii), that the use of psyllium seed husk at the levels necessary to justify the claim regarding soluble fiber and coronary heart disease was safe and lawful (63 FR 8103 at 8112). FDA reached that conclusion with respect to the use of psyllium seed husk in both conventional food products and dietary supplement products.

FDA discussed several issues relative to the safety of psyllium seed husk in the final rule on the soluble fiber health claim (63 FR 8103 at 8111). Among the issues discussed were whether long term exposure to high levels of psyllium seed husk could contribute to the proliferation of colonic epithelial cells and thereby serve as a possible risk factor for colon cancer; the potential of psyllium husk to cause allergic reactions; and the potential for esophageal and gastrointestinal obstructions to occur following consumption of psyllium husk in the absence of sufficient liquid to ensure thorough hydration (63 FR 8103 at 8111-8114).

In the final rule on the soluble fiber health claim, FDA concluded that colonic epithelial proliferation was not sufficiently validated as a reliable endpoint for prediction of colon tumorigenesis and therefore the issue of epithelial cell proliferation was not a basis on which to deny that health claim (63 FR 8103 at 8112).

With respect to the allergic potential of psyllium husk, FDA indicated that the purity of the psyllium husk appeared to be inversely related to its allergenicity (63 FR 8103 at 8113). Therefore, FDA adopted a purity criterion (at least 95% pure) for psyllium husk in order to be eligible for the soluble fiber health claim. Further, FDA stated that declaring psyllium husk on the ingredient list would be adequate to alert consumers about a possible allergenic ingredient and that no further labeling would be required. However, FDA stated that it would not object if companies wanted to place additional truthful, nonmisleading information regarding allergenicity on the label (63 FR 8103 at 8113).

The petitioner did not mention or propose the use of this or any purity criterion in its petition. FDA is considering, as a factor in the exercise of its enforcement discretion, that psyllium husk shall have a purity of no less than 95%, as specified in 21 CFR 101.81(c)(2)(ii)(B)(*1*), in foods bearing a psyllium husk qualified health claim that is the subject of this letter.

With respect to the potential for esophageal and gastrointestinal obstructions to occur following consumption of psyllium husk, in the final rule on the soluble fiber health claim FDA 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 in the context of Section 201(n) of the Act (21 U.S.C. § 321(n)) (63 FR 8103 at 8114). Therefore, 21 CFR 101.17(f)(1) requires that foods containing dry or incompletely hydrated psyllium husk and bearing a health claim on the association between soluble fiber from psyllium husk and reduced risk of coronary heart disease, bear a label statement: informing consumers that the appropriate use of such foods requires consumption with adequate amounts of fluids; alerting consumers to potential consequences of failing to follow usage recommendations; and informing persons with swallowing difficulties to avoid consumption of the product. 21 CFR 101.17(f)(1) also provides that 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.

21 CFR 101.17(f)(2) requires that the label statement required under 21 CFR 101.17(f)(1) 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 label statement must be preceded by the word "NOTICE" in capital letters (21 CFR 101.17(f)(2)). For example, the label statement might state the following: "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" (21 CFR 101.17(f)(1)).

The petitioner did not mention or propose the use of this or any warning statement in its petition. FDA is considering, as a factor in the exercise of its enforcement discretion, that, subject to the exception discussed below, foods containing dry or incompletely hydrated psyllium husk bearing a psyllium husk qualified health claim that is the subject of this letter contain the label statement required by 21 CFR 101.17(f). Without this information, the agency would consider the qualified health claim to be misleading under sections 403(a)(1) (21 U.S.C. § 343(a)(1)) and 201(n) of the Act because it would fail to reveal facts material in light of the representations being made and facts material with respect to consequences which may result from the use of these foods. However, in keeping with 21 CFR 101.17(f)(1), 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.

Thus, the agency concludes under the preliminary requirements of 21 CFR 101.14(b)(3)(ii) that the petitioner has demonstrated to FDA's satisfaction that the use of psyllium husk in conventional foods and dietary supplements is safe and lawful[18] when the psyllium husk is at least 95% pure and when an appropriate warning statement, as described above, is provided.

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[18] This conclusion does not apply to the use of granular forms of psyllium husk. FDA does not read the petition as applying to granular forms, which to the agency's knowledge are not used in conventional foods or dietary supplements. Note that in 2007, FDA issued a final rule entitled "Laxative Drug Products for Over-the-Counter

II. The Agency's Consideration of a Qualified Health Claim

FDA identified the following four endpoints, including three surrogate endpoints of type 2 diabetes, to use in identifying type 2 diabetes risk reduction for purposes of a health claim evaluation: (1) incidence of type 2 diabetes; (2) fasting blood glucose level; (3) oral glucose tolerance test (OGTT); and (4) insulin resistance. Insulin resistance is assessed by various measurements of insulin sensitivity,[19] including the euglycemic hyperinsulinemic clamp method, homeostasis model assessment (HOMA), and quantitative insulin sensitivity check index (QUICKI). Therefore, to evaluate the potential effects of psyllium husk consumption on type 2 diabetes risk, FDA considered these endpoints as indicators or predictors of type 2 diabetes.

The petition provided a total of 62 publications (4 abstracts, 47 publications of human intervention studies, and 11 clinical study reports) as evidence to substantiate the relationship for the proposed claims (see Docket FDA-2013-Q-0167).[20] For the reasons discussed in Section IIA below, the four abstracts[21] were not evaluated by FDA. Included among the 47 publications of human intervention studies was a publication by Cicero et al. (2010) that was a republication of the study by Cicero et al. (2007). FDA used data and information from both of these publications in our evaluation but the agency considers the two publications by Cicero et al. to represent one study. Thus, the petitioner submitted a total of 46 published studies.

The 11 clinical study reports submitted by the petitioner were based on intervention studies that were sponsored by the petitioner. Four of these intervention studies had previously been published in peer reviewed journals so the petitioner submitted a total of seven unpublished clinical study reports. However, the four published intervention studies evaluated the relationship between psyllium husk and coronary heart disease. Consequently, these publications did not include all of the relevant data (such as data on blood glucose levels) needed to evaluate the relationship between psyllium husk and diabetes. The additional information for these four published studies was provided in four of the clinical study reports that were submitted by the petitioner.[22] Thus, excluding the four abstracts, the 58 publications provided by the petitioner represent a total of 53 individual human intervention studies (46 published studies and seven unpublished clinical study reports) that were evaluated by FDA.

Human Use; Psyllium Ingredients in Granular Dosage Forms" (72 FR 14669; March 29, 2007), in which the agency concluded that over-the-counter laxative drug products in granular dosage form containing the bulk-forming psyllium ingredients (psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), psyllium seed husks, plantago ovata husks, and plantago seed) are not generally recognized as safe and effective. This 2007 final rule did not apply to psyllium laxatives in non-granular dosage forms, such as powders, tablets, or wafers (72 FR 14669).

[19] Insulin sensitivity is the degree to which cells respond to a particular dose of insulin by lowering blood glucose levels. Reduced insulin sensitivity means increased resistance to insulin.

[20] Two copies of one publication (Frati-Munari et al., 1998) were included in the petition. Thus, the total number of publications included was 63.

[21] Gibb et al., 2011; Florholmn et al., 1982a; Fagerberg et al., 1982a; Ziai et al., 2004

[22] Pastors et al., 1991(P &G LX 104); Bell et al., 1989 (P&G LX 102); Anderson et al., 2000 (P&G LX 122); Sprecher et al., 1993 (P&G LX 123).

A. Assessment of Abstracts

FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Although useful for background information, the abstracts submitted by the petitioner do not provide sufficient information on the individual studies they contain, and therefore FDA cannot draw any scientific conclusions from this information. For example, FDA could not determine such factors as the study population characteristics or the composition of the products (i.e., conventional foods or dietary supplements) used from this information. Similarly, the lack of detailed information on the studies summarized in the abstracts prevented FDA from determining whether these studies are flawed in critical elements such as design, conduct, and data analysis. Consequently, the abstracts submitted by the petitioner did not provide adequate information from which scientific conclusions could be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of Intervention Studies

FDA evaluated 53 individual intervention studies that were designed to investigate the relationship between intake of psyllium husk and reduction in risk of type 2 diabetes. Of the 53 intervention studies reviewed and evaluated, scientific conclusions could not be drawn from 47 of these studies for the reasons discussed below.[23] Seventeen studies[24] examined the acute or short term impact of psyllium husk intake on glycemic index,[25] glycemic load,[26] or surrogate endpoints of type 2 diabetes. The duration of these acute studies was too short (approximately 90 minutes to four hours) to adequately evaluate the long-term effect of psyllium husk consumption on the risk of type 2 diabetes. Such short-term studies cannot evaluate the long-term effect of psyllium husk consumption on the body's ability to metabolize glucose such that lower blood glucose levels may result in increased insulin sensitivity. Therefore, the agency could not draw scientific conclusions from these studies.

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[23] In this section, significant flaws in the reports of intervention studies from which scientific conclusions could not be drawn are generally discussed. Such studies may have other flaws in addition to those specifically mentioned.

[24] Cherbut et al., 1994; Frati-Munari et al., 1989; Frost et al., 2003; Jarjis et al., 1984; Karhunen et al., 2010; Rai et al., 2005; Riguad et al., 1998; Sierra et al., 2001; Wolever et al., 1991; Sierra Vega et al., 1999; Abraham and Mehta 1988; Sud et al., 1988a; Sud et al., 1988b; Frati-Munari 1985; P&G 2009001; Frape and Jones 1995; Welsh et al., 1982.

[25] The glycemic index (GI) is a marker used to compare glycemic response (the relative blood glucose response) to consumption of foods. The GI is determined after ingestion of a set amount of carbohydrate in a food compared to the same amount of carbohydrate from a reference food (white bread or glucose solution). The area under the curve for the increase in blood glucose during the 2-hour post prandial period is measured (in the same individual and under the same conditions). The initial blood glucose concentration is used as baseline [Dietary Guidelines Advisory Committee (DGAC), 2010].

[26] The glycemic load is an indicator of the blood glucose response or insulin demand that is induced by total carbohydrate intake. The glycemic load is determined by multiplying the weighted mean of the dietary GI of an individual by the percentage of total energy from carbohydrate (DGAC, 2010).

Five studies did not include statistical analyses in comparing the results of the control group and the intervention group.[27] Conducting a statistical analysis of a relationship is critical because it provides a basis for comparing subjects who consumed psyllium husk and those who did not consume psyllium husk to determine whether there was an actual reduction in the risk of type 2 diabetes.[28] When appropriate statistical tests are not performed on the specific substance/disease relationship, it cannot be determined whether there is a significant difference between the experimental groups. Consequently, no scientific conclusions could be drawn from these five studies because they provided no information about whether psyllium husk consumption significantly reduced the risk of type 2 diabetes.

Six studies included other substances (such as glucomannan, oats, white wheat bran, sugar beet fiber, pectin gums and mucilages) in the test diets in addition to psyllium.[29] Because the test diets contained such additional substances as well as psyllium husk, it is not possible to determine whether any observed effects on an endpoint for assessing type 2 diabetes risk reduction in these studies were due to psyllium husk.[30] Therefore, these six studies cannot be used to evaluate the independent effect of psyllium husk on the risk of type 2 diabetes.

Eighteen studies used diabetic subjects.[31] FDA considers evidence from studies in individuals already diagnosed with diabetes only if it is scientifically appropriate to extrapolate to individuals who do not have the disease.[32] That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. The petitioner has not clearly demonstrated that the mechanism of action for psyllium husk is the same for diseased populations and non-diseased populations. The petitioner hypothesizes that the viscosity of soluble fibers slows carbohydrate degradation and delivery of nutrients to the distal ileum that stimulates the release of glucagon-like peptide 1 (GLP-1). While it is hypothesized that soluble fibers such as psyllium reduce the rate of carbohydrate absorption because they hydrate quickly and develop viscosity (Jenkins and Jenkins, 1985; IOM, 2005b), the IOM has noted that viscosity should not be considered the most important attribute of fiber with respect to type 2 diabetes (IOM, 2005b).

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[27] P&G 1994048; P&G LX126; P&G LX125; Anderson et al., 2000 (P&G LX122); P&G LX121.
[28] See *supra*, note 3 [Section III. D].
[29] Kris-Etherton et. al, 2002; Aller et al., 2004; Salas-Salvado et al., 2008; Bell et al., 1990; Tai et al., 1999; Wolever and Bolognesi, 1996.
[30] See *supra*, note 3 [Section III. D].
[31] Anderson et al., 1999; Capani et al., 1980; Uribe et al., 1985; Fagerberg et al., 1982b; Florholmen et al., 1982b; Frati-Munari et al., 1983; Mucino et al., 1998; Dastjerdi et al., 2007; Sierra et al., 2002; Ziai et al., 2005; Frati-Munari et al., 1998; Pastors et al., 1991(P&G LX 104); Rodriguez-Moran et al., 1998; Mitra and Bhattacharya, 2006; Clark et al., 2006; Sartor et al., 1981; Sartore et al., 2009; P&G LX 105.
[32] See *supra*, note 3 [Section III. D].

Other studies and the IOM report *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (IOM, 2005a) have also concluded that the decrease of postprandial serum glucose and insulin concentrations seen with psyllium does not appear to be due to a delay in gastric emptying (Rigaud et al., 1998; Frost et al., 2003). Further, the results of studies that have examined the effect of psyllium husk on stimulating release of GLP-1 are inconsistent (Frost et al., 2003; Karhunen et al., 2010). Because the mechanism(s) by which psyllium husk may affect glucose metabolism and/or insulin response is hypothetical (IOM, 2005b), it is not known whether results from studies on the treatment of diabetes with psyllium husk can be extrapolated to risk reduction of type 2 diabetes in individuals without diabetes. Therefore, the agency could not draw any scientific conclusions from these studies for this claim.

The study conducted by Pal et al. (2011) was a twelve-week randomized, single-blind, parallel study in which 72 subjects were given a placebo or psyllium husk in addition to their regular diet. In this study, baseline blood glucose levels were very different in the psyllium husk group and control group. Furthermore, the fasting blood glucose results reported in the text of the paper and shown in the accompanying graph were contradictory. Therefore, it was not possible to compare the results between the two experimental groups. For these reasons, scientific conclusions about a relationship between psyllium husk and the risk of type 2 diabetes could not be drawn from this study.

Based on the rationale discussed above, scientific conclusions could be drawn from six of the 54 intervention studies that evaluated the relationship between psyllium husk intake and risk of type 2 diabetes (Anderson et al., 1988; Bell et al., 1989 (P&G LX 102); Cicero et al., 2007/2010; Levin et al., 1990; Sprecher et al., 1993 (P&G LX 123); P&G LX 129).

Anderson et al. (1988) conducted a high quality ten-week randomized, double-blind, placebo controlled parallel[33] trial in which 26 U.S. men with normal glucose tolerance consumed either a placebo (cellulose) (n=13) or 10.2 g per day psyllium husk (sugar free Metamucil) (n=13) in addition to their usual diets. There was no significant difference[34] in fasting serum glucose between the placebo group and the psyllium husk group.

The study by Bell et al. (1989) (P&G LX 102) was a high quality eight-week randomized, double-blind, placebo-controlled parallel trial in which 75 U.S. subjects with normal glucose tolerance consumed a placebo (cellulose) (n=35) or 10.2 g per day psyllium husk (sugar free Metamucil) (n=40) in addition to a Step 1 diet.[35] There was no significant difference in fasting serum glucose levels between the placebo group and the psyllium husk group.

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[33] Intervention studies with a parallel design involve two groups of subjects, the test group (also called the intervention group) and the control group, which simultaneously receive the substance or serve as the control, respectively. See *supra*, note 3 [Section III. B].

[34] For the outcome of a study to demonstrate a statistically significant difference between groups, P must be <0.05. See *supra*, note 3 [Section III. F].

[35] Step 1 diets were created by the National Cholesterol Education Program and promoted by the American Heart Association (NIH publication No. 94-2920). A Step 1 diet contains 30 percent or less of daily energy from total fat,

The study by Levin et al. (1990) was a high quality sixteen-week randomized, double-blind parallel trial in which 58 U.S. subjects with normal glucose tolerance consumed either a placebo (cellulose) (n=28) or 10.2 g per day of psyllium husk (sugar free Metamucil) (n=30) in addition to a Step 1 diet.[36] There was no significant difference in levels of fasting serum glucose between the placebo and the psyllium husk groups.

Sprecher et al. (1993) (P&G LX 123) conducted a high quality eight-week randomized, double-blind parallel trial in which 118 U.S. subjects with normal glucose tolerance consumed a placebo (cellulose) (n=59) or 10.2 g per day of psyllium husk (sugar free Metamucil) (n=59) in addition to either a high fat or low fat diet. There was no significant difference in fasting serum glucose levels between the placebo and psyllium husk group.

P&G LX 129 was a moderate quality eight-week randomized, double-blind, parallel trial in which 52 subjects with normal glucose tolerance consumed a placebo (psyllium free, sugar free Metamucil excipients) (n=23) or 10.2 g per day of psyllium husk (sugar free Metamucil) (n=29) in addition to a hypocaloric diet. There was no significant difference in fasting serum glucose levels between the placebo and psyllium husk groups.

The study by Cicero et al. (2010) (a republication of Cicero et al., 2007) was a high quality six-month randomized, single-blind, parallel trial in which 92 Italian subjects with metabolic syndrome[37] consumed a placebo (partially hydrolyzed guar gum) (n=47) or 7 g per day of psyllium husk (n=45) in addition to a Step 2 diet.[38] Subjects in both the guar gum and psyllium husk groups had elevated fasting blood glucose levels (fasting blood glucose of >100 mg/dL and < 126 mg/dL) with fasting plasma glucose levels of 108 mg/dL and 110 mg/dL, respectively, at baseline. There was a significant difference ($p<0.01$) in fasting plasma glucose levels between the placebo and psyllium husk groups.

8-10 percent from saturated fat, 55 percent or more from carbohydrate, approximately 15 percent from protein, and less than 300 mg per day of dietary cholesterol.

[36] See *supra,* note 3 [Section III. D].

[37] "Metabolic syndrome" is the name for a group of risk factors (e.g., large waistline, high triglyceride level, low HDL cholesterol level, high blood pressure and high fasting blood sugar) that increases the risk of coronary heart disease, stroke and other health problems. Individuals with metabolic syndrome are also at an increased risk of developing type 2 diabetes. To be diagnosed with metabolic syndrome one must have at least three of these metabolic risk factors. See NIH, National Heart, Lung and Blood Institute "What is Metabolic Syndrome?" [http://www.nhlbi.nih.gov/health/health-topics/topics/ms/ (accessed June 12, 2014)] and NIH, National Heart, Lung and Blood Institute "How is Metabolic Syndrome Diagnosed?" [http://www.nhlbi.nih.gov/health/health-topics/topics/ms/diagnosis.html (accessed June 12, 2014)]. In evaluating health claims and qualified health claims, FDA considers studies that include individuals who are at risk of getting the disease that is the subject of the claim. See FDA "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final" (January 2009). [http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/labelingnutrition/ucm073332.htm (accessed June 12, 2014)]

[38] Step 2 diets were created by the National Cholesterol Education Program and promoted by the American Heart Association for higher-risk individuals. A Step 2 diet consists of 30 percent or less of daily energy from total fat, less than 7 percent from saturated fat, 55 percent or more from carbohydrate, approximately 15 percent from protein, and contains less than 200 mg per day of dietary cholesterol.

There was also a significant difference ($p<0.01$) in insulin resistance as calculated by HOMA-Index[39] between the placebo and psyllium husk groups.

C. Assessment of the Relevant Observational Studies

There were no observational studies that evaluated the relationship between psyllium husk and reduced risk of type 2 diabetes that were available to the agency.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the United States population or a target subgroup, whether study results supporting the proposed claim have been replicated,[40] and the overall consistency[41] of the total body of evidence.[42] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in Section II, the totality of the scientific evidence for a relationship between psyllium husk intake and type 2 diabetes risk includes six intervention studies (Anderson et al., 1988; Bell et al., 1989 (P&G LX 102); Cicero et al. (2007/2010); Levin et al., 1990; Sprecher et al., 1993 (P&G LX 123); P&G LX 129). Of these six studies, only the high quality, six-month intervention study reported by Cicero et al. (2007/2010) found a significant improvement in fasting plasma glucose levels and insulin sensitivity when psyllium husks were consumed compared to a placebo.

The remaining five intervention studies (Anderson et al., 1988; Bell et al., 1989 (P&G LX 102); Levin et al., 1990; Sprecher et al., 1993 (P&G LX 123); P&G LX 129) were either moderate quality or high quality randomized controlled trials. The duration of these studies ranged from 8 to 16 weeks. None of these studies reported a statistically significant association between psyllium husk intake and the risk of type 2 diabetes.

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[39] The HOMA method of estimating insulin resistance relies on calculated values using fasting blood glucose and insulin rather than direct measurement such as with a euglycemic hyperinsulinemic clamp, which is a more reliable measure of insulin resistance than HOMA. However, according to endocrinology specialists in FDA's Center for Drug Evaluation and Research, HOMA is considered to be a reasonable method for estimating insulin resistance where clamp procedures are not feasible.

[40] See *supra*, note 11.

[41] See *supra*, note 12.

[42] See *supra*, note 3[Section III. F].

Based on the above, FDA concludes that there is very little credible evidence for a relationship between psyllium husk consumption and reduced risk of type 2 diabetes.

IV. Other Enforcement Discretion Factors

A qualified health claim on the label or in the labeling of a product containing psyllium husk is required to meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. Other exceptions to the general requirements for health claims that FDA intends to consider in the exercise of its enforcement discretion for qualified claims about psyllium husk and reduced risk of type 2 diabetes are discussed below, along with enforcement discretion factors specific to psyllium husk qualified health claims.

A. Qualifying Level of Psyllium Husk

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)).

However, the agency finds that this provision should not be applied to the qualified health claim for psyllium husk and reduced risk of type 2 diabetes because there is very little scientific evidence for this relationship and the available evidence does not support the establishment of a recommended daily dietary intake level or even a possible level of effect for the general United States population. Therefore, the FDA is not specifying any minimum level of psyllium husk to be considered as a factor in the exercise of its enforcement discretion for a qualified health claim about psyllium husk and reduced risk of type 2 diabetes. However, FDA would monitor and evaluate for possible enforcement action situations where foods that bear the qualified health claim for psyllium husk and type 2 diabetes contain psyllium husk in trivial amounts. Furthermore, the agency would consider any label or labeling suggesting a specific level of psyllium husk to be useful in achieving a reduction in the risk of type 2 diabetes for the general healthy population to be false and misleading under Section 403(a) of the Act.

B. Purity Criterion

As mentioned in Section I.C., the purity of psyllium husk appears to be inversely related to its allergenicity. Therefore, FDA adopted a purity criterion (at least 95% pure) for psyllium husk when used in products bearing the soluble fiber health claim (63 FR 8103 at 8113). FDA is considering, as a factor in the exercise of its enforcement discretion, that psyllium husk shall have a purity of no less than 95%, as specified in 21 CFR 101.81(c)(2)(ii)(B)(*1*), in foods bearing a psyllium husk qualified health claim that is the subject of this letter.

C. Label Statement

As discussed in Section I.C., FDA is considering, as a factor in the exercise of its enforcement discretion, that foods containing dry or incompletely hydrated psyllium husk bearing a psyllium husk qualified health claim that is the subject of this letter contain the label statement required by 21 CFR 101.17(f). However, in keeping with 21 CFR 101.17(f)(1), 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.

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with the petition and other pertinent scientific evidence, FDA concludes that there is very little credible scientific evidence for a qualified health claim for psyllium husk consumption and reduced risk of type 2 diabetes, provided that the qualified health claim is appropriately worded so as to not mislead consumers.

Thus, FDA intends to consider exercising its enforcement discretion for the following qualified health claims:

> "Psyllium husk may reduce the risk of type 2 diabetes, although the FDA has concluded that there is very little scientific evidence for this claim."
>
> "Psyllium husk may reduce the risk of type 2 diabetes. FDA has concluded that there is very little scientific evidence for this claim."

FDA intends to consider exercising its enforcement discretion for the above qualified health claims when all factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will support a qualified health claim for those claims that were denied, that will no longer support the use of the above qualified health claim, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

Philip C. Spiller
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Center for Food Safety
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References

Abraham ZD, Mehta T. 1988. Three-week psyllium-husk supplementation: Effect on plasma cholesterol concentrations, fecal steroid excretion, and carbohydrate absorption in men. Am J Clin Nutr. 47(1): 67-74.

Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf].

Aller R, De Luis DA, Izaola O, La Calle F, Del Olmo L, Fernandez L, Arranz T, Gonzalez Hernandez JM. 2004. Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: A randomized clinical trial. Diabetes Res Clin Pract. 65(1): 7-11.

Anderson JW, Davidson MH, Blonde L, Brown WV, Howard WJ, Ginsberg H, Allgood LD, Weingand KW. 2000. Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. Am J Clin Nutr. 71: 1433-1438.

Anderson JW, Allgood LD, Turner J, Oeltgen PR, Daggy BP. 1999. Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia. Am J Clin Nutr. 70(4): 466-473.

Anderson JW, Zettwoch N, Feldman T, Tietyen-Clark J, Oeltgen P, et al. 1988. Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. Arch Intern Med. 148(2): 292-296.

Arreola Mucino AHH, Callejas Hernandez G, Hernandez Aguirre O, Ornelas Bernal L. 1998. Hypoglycemic agents plus acarbose vs hypoglycemic agents plus Psyllium platago in the metabolic control of non-insulin dependent diabetes mellitus [Hipoglucemiante oral (HO) mas acarbosa vs. hipoglucemiante oral mas Psyllium plantago en el control metabolico del paciente diabetico no insulinodependiente]. Medicina Interna de México. 14(6): 259-262.

Barton S. 2000. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. Br Med J. 321: 255-256.

Bell LP, Hectorne K, Reynolds H, Balm TK, Hunninghake DB. 1989. Cholesterol-lowering effects of psyllium hydrophilic mucilloid. Adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. J Am Med Assoc. 261(23): 3419-3423.

Bell LP, Hectorn KJ, Reynolds H, Hunninghake DB. 1990. Cholesterol-lowering effects of soluble-fiber cereals as part of a prudent diet for patients with mild to moderate hypercholesterolemia1-3. Am J Clin Nutr. 52: 1020-1026.

Capani F, Consoli A, Del Ponte A. 1980. A new dietary fibre for use in diabetes. IRCS Med. Sci. 8 (9): 661.

Cherbut C, Bruley des Varannes S, Schnee M, Rival M, Galmiche JP, Delort-Laval J. 1994. Involvement of small intestinal motility in blood glucose response to dietary fibre in man. Br J Nutr. 71(5): 675-685.

Cicero AFG, Derosa G, Bove M, Imola F, Borghi C, Gaddi AV. 2010. Psyllium improves dyslipidaemia, hyperglycaemia and hypertension, while guar gum reduces body weight more rapidly in patients affected by metabolic syndrome following an AHA Step 2 diet. Med J Nutrition Metab. 3(1): 47-54.

Cicero AFG, Derosa G, Manca M, Bove M, Borghi C, Gaddi AV. 2007. Different effect of psyllium and guar dietary supplementation on blood pressure control in hypertensive overweight patients: A six-month, randomized clinical trial. Clin Exp Hypertens. 29(6): 383-394.

Clark CA, Gardiner J, McBurney MI, Anderson S, Weatherspoon LJ, Henry DN, Hord NG. 2006. Effects of breakfast meal composition on second meal metabolic responses in adults with type 2 diabetes mellitus. Eur J Clin Nutr. 60(9): 1122-1129.

Dastjerdi MS, Salehioun M, Najafian A, Amini M. 2007. A randomized controlled study for evaluation of psyllium effects on kinetics of carbohydrate absorption. J Res Med Sci. 12(3): 125-130.

deMunter JS, Hu FB, Spiegelman D, Franz M, Van Dam RM. 2007. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. PLoS Med. 4(8): e261.

DGAC (Dietary Guidelines Advisory Committee). 2010. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010, to the Secretary of Agriculture and the Secretary of Health and Human Services. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC. [http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/DGAC/Report/2010DGACReport-camera-ready-Jan11-11.pdf].

Fagerberg S. 1982a. The effects of a bulk laxative (Metamucil®) on fasting blood glucose, serum lipids and other variables in constipated patients with non-insulin dependent adult diabetes. Acta Med Scand. 212: 237-239.

Fagerberg S. 1982b. The effects of a bulk laxative (Metamucil®) on fasting blood glucose, serum lipids and other variables in constipated patients with non-insulin dependent adult diabetes. Curr Ther Res Clin Exp. 31: 166-172.

FDA. 2008. Draft Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071624.pdf] (page 3).

Florholmen J, Lenner RA, Jorde R, Burhol PG. 1982a. The effect of Metamucil on the postprandial blood glucose and plasma GIP in insulin-dependent diabetics. Acta Endocrinol. 100 (Suppl.247): 23.

Florholmen J, Arvidsson-Lenner R, Jorde R, Burhol PG. 1982b. The effect of metamucil on postprandial blood glucose and plasma gastric inhibitory peptide in insulin-dependent diabetics. Acta Med Scand. 212(4): 237-239.

FDA "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm053832.htm] (accessed July, 23, 2010)

Frape DL, Jones AM. 1995. Chronic and postprandial responses of plasma insulin, glucose and lipids in volunteers given dietary fibre supplements. Br J Nutr. 73: 733-751.

Frati Munari AC, Benítez Pinto W, Raúl Ariza Andraca C, Casarrubias M. 1998. Lowering glycemic index of food by acarbose and Plantago psyllium mucilage. Arch Med Res. 29(2): 137-141.

Frati Munari AC, Flores-Garduño MA, Ariza-Andraca R, Islas-Andrade S, Chávez Negrete A. 1989. The effect of different doses of Plantago psyllium mucilage on the glucose tolerance test. Arch Invest Med (Mex). 20(2): 147-152.

Frati-Munari AC, Castillo-Insunza MR, De La Riva-Pinal H. 1985. Effect of Plantago psyllium mucilage on the glucose tolerance test. Arch Invest Med (Mex). 16(2): 191-197.

Frati-Munari, AC, Fermindez-Harp JA, Becerril M, Chavez-Negrete A, Bafiales-Ham M. 1983. Decrease in serum lipids, glycemia and body weight by Plantago psyllium in obese and diabetic patients. Arch Invest Med (Mex). 14(3): 259-268.

Frost GS, Brynes AE, Dhillo WS, Bloom SR, McBurney MI. 2003. The effects of fiber enrichment of pasta and fat content on gastric emptying, GLP-1, glucose, and insulin responses to a meal. Eur J Clin Nutr. 57(2): 293-298.

Gibb R, Ramsey D, Tse H, McCauley-Myers, McRorie J. 2011. Psyllium improves glycemic control in patients with type II diabetes. Am J Gastroenterol. 106: S85.

Hill AB. 1965. The environment and disease: Association or causation? Proc R Soc Med. 58: 295-300.

Hu GC, Hsieh SF, Chen YM, Hsu HH, Hu YN, Chien KL. 2012. Relationship of initial glucose level and all-cause death in patients with ischaemic stroke: the roles of diabetes mellitus and glycated hemoglobin level. Eur J Neurol. doi: 10.1111/j.1468-1331.2011.03647.x. [Epub ahead of print]

IOM (Institute of Medicine, National Academy of Sciences). 2005a. Dietary Supplements: A Framework for Evaluating Safety. Chapter 7, Categories of Scientific Evidence – In Vitro Data. The National Academies Press, Washington, D.C.

IOM. 2005b. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. The National Academies Press, Washington, D.C.

Jarjis HA, Blackburn NA, Redfern JS, Read NW. 1984. The effect of ispaghula (Fybogel and Metamucil) and guar gum on glucose tolerance in man. Br J Nutr. 51(3): 371-378.

Jenkins DJ, Jenkins AL. 1985. Dietary fiber and the glycemic response. Proc Soc Exp Biol Med. 1180(3): 422-431.

Karhunen LJ, Juvonen KR, Flander SM, Liukkonen KH, Lähteenmäki L, Siloaho M, et al. 2010. A psyllium fiber-enriched meal strongly attenuates postprandial gastrointestinal peptide release in healthy young adults. J Nutr. 140(4): 737-744.

Kris-Etherton PM, Taylor DS, Smiciklas-Wright H, Mitchell DC, Bekhuis TC, Olson BH, Slonim AB. 2002. High-soluble-fiber foods in conjunction with a telephone-based, personalized behavior change support service result in favorable changes in lipids and lifestyles after 7 weeks. J Am Diet Assoc. 102: 503-510.

Levin EG, Miller VT, Muesing RA, Stoy DB, Balm TK, LaRosa JC. 1990. Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. Arch Intern Med. 150(9): 1822-1827.

Mitra A, Bhattacharya D. 2006. Effects of long term study of combination of nutraceuticals in non-insulin dependent diabetes mellitus patients. J Food Sci Technol. 43: 477-483.

National Diabetes Information Clearinghouse, "Insulin Resistance and Prediabetes." [http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/index.aspx] (accessed July 23, 2013).

National Institutes of Health (NIH), "Diabetes Overview." [http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm#what] (accessed July 23, 2013).

NIH. "Diabetes Risk Factors" [http://ndep.nih.gov/am-i-at-risk/DiabetesRiskFactors.aspx]. (accessed July 23, 2013).

NIH. "What is Metabolic Syndrome?" [http://www.nhlbi.nih.gov/health/health-topics/topics/ms/] (accessed June 12, 2014).

NIH. "How is Metabolic Syndrome Diagnosed?" [http://www.nhlbi.nih.gov/health/health-topics/topics/ms/diagnosis.html] (accessed June 12, 2014).

NIH. "Step by Step. Eating to Lower Your High Blood Cholesterol." National Institutes of Health, National Heart, Lung, and Blood Institute. U.S. Department of Health and Human Services. Public Health Service. NIH Publication No. 94-2920, Revised August 1994. [http://www.nhlbi.nih.gov/health/public/heart/chol/stepb.pdf]. (accessed October 29, 2013)

National Research Council. 2011. Reference Manual on Scientific Evidence: Third Edition. The National Academies Press, Washington, DC, page 220.Pal S, Khossousi A, Binns C, Dhaliwal S, Ellis V. 2011. The effect of a fibre supplement compared to a healthy diet on body composition, lipids, glucose, insulin and other metabolic syndrome risk factors in overweight and obese individuals. Br J Nutr. 105(1): 90-100.

Pastors JG, Blaisdell PW, Balm TK, Asplin CM, Pohl SL. 1991. Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-dependent diabetes. Am J Clin Nutr. 53(6): 1431-1435.

P&G LX 102. 1997. Efficacy of Metamucil as an adjunct to prudent diet in the treatment of mild to moderate hypercholesterolemia. Clinical Study No. LX-102.

P&G LX 104.1997. A study of Metamucil's effects on postprandial blood glucose levels in type II diabetics. Clinical Study No. LX-104.

P&G LX 105. 2011. A clinical study to determine the ability of Metamucil to reduce fasting blood glucose and HbA1c levels in type II NIDDM. Clinical Study No. 105.

P&G LX 121. 1994. A double-blind, placebo-controlled multi-site parallel study to evaluate the dose-response relationship of different doses of psyllium as a cholesterol-lowering therapy when used as adjunct to an AHA Step One diet in Patients with mild to moderate hypercholesterolemia. Clinical Study No. LX-121.

P&G LX 122. 1997. A double-blind, placebo-controlled, multi-site, parallel study to evaluate the safety and efficacy of psyllium, administered as adjunctive therapy to AHA Step One diet, in reducing serum cholesterol concentrations in patients with mild to moderate hypercholesterolemia. Clinical Study No. LX-122.

P&G LX 123. 1997. A double-blind, placebo-controlled, parallel study comparing the efficacy of psyllium (Metamucil) in reducing blood cholesterol when administered adjunctively to diets high or low hypercholesterolemia. Clinical Study No. LX-123.

P&G LX 125. 1997 A double-blind, placebo-controlled, multi-site, parallel study to evaluate the concomitant use of psyllium (Metamucil) and cholestyramine (Questran) administered as adjunctive therapy to an AHA Step One diet, in reducing blood cholesterol concentrations in patients with mild to moderate hypercholesterolemia. Clinical Study No. LX-125.

P &G LX 126. 1997. A parallel, double-blind, placebo-controlled study to assess the efficacy and safety of psyllium (Metamucil) as an adjunct to a prudent diet as a primary treatment of elderly patients with mild to moderate hypercholesterolemia. Clinical Study No. LX-126.

P&G LX 129. 1997. A double-blind, excipient-controlled, pilot study to evaluate the effect of psyllium on weight control when used as an adjunct to a hypercaloric diet in moderately obese patients. Clinical Study No. LX-129.

P&G 1994048. 1995. A confirmation study evaluating excipients of Metamucil as an appropriate placebo for laxation studies with psyllium in patients with chronic idiopathic constipation. Clinical Study P&G 1994048.

P&G 2009001. 2009. An open label, randomized, 4-period cross-over study to evaluate the effects of Metamucil taken before a meal on postprandial blood glucose in healthy males. Clinical Study P&G 2009001.

Rai J, Singh S, Gill J, Sharma G. 2005. Effect of ispaghula husk, guargum, and acarbose on postprandial blood glucose concentration in healthy volunteers. JK Pract. 12(2): 98-99.

Rigaud D, Paycha F, Meulemans A, Merrouche M, Mignon M. 1998. Effect of psyllium on gastric emptying, hunger feeling and food intake in normal volunteers: a double blind study. Eur J Clin Nutr. 52(4): 239-245.

Rodríguez-Morán M, Guerrero-Romero F, Lazcano-Burciaga G. 1998. Lipid- and glucose-lowering efficacy of Plantago Psyllium in type II diabetes. J Diabetes Complications. 12(5): 273-278.

Salas-Salvadó J, Farrés X, Luque X, Narejos S, Borrell M, Basora J, Anguera A, Torres F, Bulló M, Balanza R, Casas P, Marquez F, Brotons C, Altes A, Fernandez CG, Fernandez JL, Ferrandez C, Prieto M, Basora T. 2008. Effect of two doses of a mixture of soluble fibres on body weight and metabolic variables in overweight or obese patients: a randomised trial. Br J Nutr. 99(6): 1380-1387.

Sartor G, Carlström S, Scherstén B. 1981. Dietary supplementation of fibre (Lunelax) as a mean to reduce postprandial glucose in diabetics. Acta Med Scand Suppl. 656: 51-53.

Sartore G, Reitano R, Barison A, Magnanini P, Cosma C, Burlina S, Manzato E, Fedele D, Lapolla A. 2009. The effects of psyllium on lipoproteins in type II diabetic patients. Eur J Clin Nutr. 63(10): 1269-1271.

Sierra M, Garcia JJ, Fernández N, Diez MJ, Calle AP, Sahagún AM. 2001. Effects of ispaghula husk and guar gum on postprandial glucose and insulin concentrations in healthy subjects. Eur J Clin Nutr. 55(4): 235-243.

Sierra Vega M, Calle Pardo AP, Fernández Martínez N, Díez Liébana MJ, Sahagún Prieto A, Suárez González A, García Vieitez JJ, Alonso Alvarez ML, Carriego Ule D, Castro Gonzalez MP, Gonzalez Canga A, Moran Garcia V, Suarez Fernandez BA, De La Torre Saiz M. 1999. Effect of Ispaghula husks on postprandial glycemia in healthy female volunteers [Influencia de las cuticulas de semillas de Plantago ovate (Ispaghula husk) en Ia glucemia posprandial en voluntarias sanas]. Nutr Hosp. 14(5): 197-202.

Sierra M, García JJ, Fernández N, Diez MJ, Calle AP, Alvarez JC, Carriedo D, Castro LJ, de la Torre M, Gonzalez A, Gonzalez MA, Moran V, Prieto C, Sahagun AM. 2002. Therapeutic effects of psyllium in type 2 diabetic patients. Eur J Clin Nutr. 56(9): 830-842.

Spilker B. 1991. Guide to Clinical Studies. Raven Press, New York, New York, pp. 59-64.

Sprecher DL, Harris BV, Goldberg AC, Anderson EC, Bayuk LM, Russell BS, et al. 1993. Efficacy of psyllium in reducing serum cholesterol levels in hypercholesterolemic patients on high- or low-fat diets. Ann Intern Med. 119(7 Pt 1): 545-554.

Sud S, Siddhu A, Bijlani RL. 1988a. Effect of ispaghula husk on postprandial glycemia and insulinemia following glucose and starch drinks. Nutrition. 4(3): 221-223.

Sud S, Siddhu A, Bijlani RL, Karmarkar MG. 1988b. Nutrient composition is a poor determinant of the glycaemic response. Br J Nutr. 59(1): 5-12.

Tai ES, Fok ACK, Chu R. 1999. A study to assess the effect of dietary supplementation with soluble fibre (Minolest®) on lipid levels in normal subjects with hypercholesterolaemia. Ann Acad Med Singapore. 28(2): 209-213.

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

Uribe M, Dibildox M, Malpica S. 1985. Beneficial effect of vegetable protein diet supplemented with psyllium plantago in patients with hepatic encephalopathy and diabetes mellitus. Gastroenterology. 88(4): 901-907.

Welsh JD, Manion CV, Griffiths WJ, Bird PC. 1982. Effect of psyllium hydrophilic mucilloid on oral glucose tolerance and breath hydrogen in postgastrectomy patients. Dig Dis Sci. 27(1): 7-12.

Wilson EB. 1990. An Introduction to Scientific Research. Dover Publications, New York. pp. 46-48.

Wolever TM, Vuksan V, Eshuis H, Spadafora P, Peterson RD, Chao ES, et al. 1991. Effect of method of administration of psyllium on glycemic response and carbohydrate digestibility. J Am Coll Nutr. 10(4): 364-371.

Wolever TMS, Bolognesi C. 1996. Time of day influences relative glycaemic effect of foods. Nutr Res. 16(3): 381-384.

Ziai SA, Larijani B, Fakhrzadeh H, Dastpak A, Bandarian F, Rezai A, Badi HN. 2004. Study of psyllium (Plantago ovata L.) effects on diabetes and lipidemia in the Iranian type II diabetic patients. J Med Plants. 3: 41-50.

Ziai SA, Larijani B, Akhoondzadeh S, Fakhrzadeh H, Dastpak A, Bandarian F, et al. 2005. Psyllium decreased serum glucose and glycosylated hemoglobin significantly in diabetic outpatients. J Ethnopharmacol. 102(2): 202-207.