July 21, 2017

Mark Stavro, Ph.D.
Global Marketing Director
Bunge Limited
50 Main Street
White Plains, New York, 10606

RE: Qualified Health Claim Petition – Soybean Oil and Reduced Risk of Coronary Heart Disease (Docket No. FDA-2016-Q-0995)

Dear Dr. Stavro:

This letter responds to the qualified health claim petition received from Bunge Limited by the Food and Drug Administration (FDA or the agency) on February 8, 2016. The petition was submitted in accordance with FDA's guidance on the procedures for the submission of qualified health claim petitions ("interim procedures for QHC").[1] The petitioner requested a qualified health claim for the relationship between the consumption of unmodified soybean oil and a reduction in risk of coronary heart disease.

The petition proposed the following language for the health claim: "Supportive but inconclusive scientific evidence suggests that eating about 1 ½ tablespoons (19.5 grams) of soybean oil daily may reduce the risk of coronary heart disease. To achieve this possible benefit, soybean oil is to replace a similar amount of saturated fat and not increase the total number of calories you eat in a day. One serving of this product contains [x] grams of soybean oil."

As requested by FDA, on February 23, 2016, the petitioner clarified the use of a certain reference in substantiating the claim, and provided information with respect to nonclinical laboratory trials as required in 21 CFR 101.70(c) and with respect to clinical or other human investigations as required in 21 CFR 101.70(d). FDA filed the petition for comprehensive review on March 24, 2016 and posted the petition on the regulations.gov website for a 60-day comment period, consistent with the qualified health claims procedures guidance. The agency received no comments in response to the petition.

[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 May 10, 2017)]. Although not the case for this petition, many qualified health claim petitions are also submitted pursuant to § 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)).

This letter sets forth the results of FDA's scientific review of the evidence for the qualified health claim requested in the petition, as well as the basis of FDA's determination that the current evidence supports a qualified health claim on foods concerning the relationship between unmodified soybean oil and a reduced risk of coronary heart disease (CHD). Accordingly, this letter discusses the factors that FDA intends to consider in the exercise of enforcement discretion for a qualified health claim with respect to the consumption of soybean oil and a reduced risk of CHD.

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 U.S. population, or an identified U.S. 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 are 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 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

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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 May 10, 2017)].

[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.

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 supplements.[10] 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). 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 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.,

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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.
[10] Institute of Medicine (2005). Dietary Supplements: A Framework for Evaluating Safety. Chapter 7, Categories of Scientific Evidence – In Vitro Data.

disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. 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 from which FDA cannot draw scientific conclusions cannot be used to support the health claim relationship, and therefore 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.[11] 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 U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[12] and the overall consistency[13] of the total body of evidence.[14] 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 a food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified soybean oil, rather than any specific component in the soybean oil, as the substance that is the subject of the proposed claim. However, the petition stated that the unsaturated fatty acid (UFA) content of this oil is likely the most important component responsible for its cardioprotective properties. The UFA composition of soybean oil is primarily polyunsaturated fatty acids (PUFA) that are characterized by a unique mixture of omega-6 PUFA and omega-3 PUFA.

Therefore, the agency concludes that UFA from soybean oil is a component of food and thus meets the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

[11] See *supra*, note 3 [Section III.F].
[12] 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).
[13] 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 (accessed May 10, 2017)], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."
[14] See *supra*, note 3 [Section III.F].

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 coronary heart disease as the disease or health-related condition that is the subject of the proposed claim.

The agency concludes that coronary heart disease is a disease and therefore the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3), if the substance is to be consumed at other than decreased dietary levels, the substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR 170.3(o) to the food and must retain that attribute when consumed at levels that are necessary to justify a claim (21 CFR 101.14(b)(3)(i)). 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 must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (the Act). For conventional foods, this evaluation involves considering whether the 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 (see 101.70(f)).

The petition noted that under 21 CFR 101.14(b)(3)(i), unmodified soybean oil provides nutritive value. The definition of "nutritive value" is "a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy." (See 21 CFR 101.14(a)(3)). Unmodified soybean oil provides nutritive value to the diet by serving as a source of energy and essential nutrients. Like all dietary fats, soybean oil provides 9 kcal/g. Data from the United States Department of Agriculture, National Nutrient Database for Standard Reference show that soybean oil provides 120 kcal per one tablespoon Reference Amount Customarily Consumed (RACC). These data also show that unmodified soybean oil contains approximately 6 percent of the Daily Value (DV) of Vitamin E (1.1 mg α-tocopherol per RACC). In addition, two of the PUFAs found in soybean oil (linoleic acid (LA) (18:2, n-6)) and α-linolenic acid (ALA) (18:3, n-3)) are essential nutrients, as noted in the Institute of Medicine, 2002 report. The Adequate Intake (AI) of LA for adults ranges from 11g/d for women >70 years of age to 17 g/d for men aged 19-50 years. The AI for ALA is 1.1 g/d for women and 1.6 g/d for men 19 years of age and older. FDA agrees that soybean oil contributes nutritive value.

In order to receive a possible benefit from consumption of soybean oil and a reduced risk of CHD, the scientific evidence suggests that the daily minimum amount of UFA from soybean oil that should be consumed in place of foods high in saturated fatty acids (SFAs), while not increasing caloric intake, is approximately 16.5g of UFA, which corresponds to about 20.5 g of soybean oil. An intake of 20.5 g of soybean oil provides approximately 181 calories. But because the qualified health claims (see Section V), in accordance with the petition and the scientific evidence, specify that soybean oil is to replace saturated fat in the diet while not increasing

caloric intake, an individual's saturated fat intake should not increase based on the recommendations in the claim.

UFAs can be separated into two categories: monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). Based on a lack of information on adverse effects, a Tolerable Upper Intake Level for MUFA has not been set by the Institute of Medicine (IOM), and because of insufficient evidence relating low and high intakes of MUFA and chronic disease, an Acceptable Macronutrient Distribution Range (AMDR) has not been set by the IOM. Median MUFA intake, however, ranges from approximately 25 to 39 g/day for men and 18 to 24 g/day for women (IOM, 2002). According to data from USDA (U.S. Department of Agriculture, 2016), 20.5 g of soybean oil would provide about 4.7 g of MUFA.

The IOM has classified PUFA into two categories: n-3 PUFA and n-6 PUFA. According to data from the (USDA, 2016), the PUFA in soybean oil consist primarily of n-6 PUFA. Based on a lack of information on adverse effects, a UL for n-6 PUFA has not been set by the IOM. Lacking safety data upon which to base a UL, the IOM has set an AMDR for n-6 PUFA (linoleic acid) of five to ten percent of energy. The ten percent of energy "upper boundary" for the AMDR is based on the approximate highest intake levels for individuals in North America (IOM, 2002). The Continuing Survey of Food Intakes by Individuals, 1994-1996, 1998, which represents a wide range in the amount of foods consumed in the U.S., showed that the 99th percentile of n-6 PUFA intake for all individuals (31.3 g/day) would exceed the sum of the median intake of PUFA (12 g/day). In addition, the PUFA from 20.5 of soybean oil are about (11.8 g/day). Because the 99th percentile of intake was used to set the upper boundary of the AMDR for n-6 PUFA, consuming 20.5 g of soybean oil per day falls well within the boundaries of the AMDR for n-6 PUFA intake. Finally, linoleic acid (the major fatty acid in soybean oil) has been authorized as a direct food additive in 21 CFR 184.1065.

The petition also noted the "ubiquity" of soybean oil in the United States food supply. The petition provided evidence from the Economic Research Service, United States Department of Agriculture (USDA), that soybean oil is by far the most commonly consumed vegetable oil in the U.S., as evidenced by an annual domestic disappearance of 17,900 million pounds in 2010. (Economic Research Service, USDA, Oil Crops Yearbook, 2012/13, Table 31). The petitioner also noted that FDA has already acknowledged the appropriateness of qualified health claims for other edible vegetable oils and risk of CHD. Specifically, the agency has concluded that olive oil[15] corn oil[16], and canola oil[17] are safe and lawful in the context of a qualified health claim for

[15] Letter of Enforcement Discretion for Olive Oil and CHD Risk [http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072963.htm (accessed May 10, 2017)].
[16] Letter of Enforcement Discretion for Canola Oil and CHD Risk [http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072956.htm (accessed May 10, 2017)].
[17] Letter of Enforcement Discretion for Canola Oil and CHD Risk [http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072958.htm (accessed May 10, 2017)].

CHD risk by replacing various amounts of saturated fatty acids from the diet without increasing the total calories.

UFAs are ubiquitous, natural components of the food supply that provide nutritive value to the diet; certain individual UFA components have been approved as direct food additives or authorized for use in foods; and the level of UFA from soybean oil necessary to justify the claim should not increase an individual's saturated fat intake due to the replacement of SFA in the diet. FDA agrees that the petitioner has demonstrated to FDA's satisfaction that soybean oil at the levels necessary to justify the claim is safe and lawful under the applicable food safety provisions of the Act. Therefore, FDA concludes that under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), the use of soybean oil at the levels necessary to justify the claim is safe and lawful.

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

FDA has identified the following disease endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation: the incidence of coronary events (myocardial infarction (MI), ischemia), cardiovascular death, coronary artery disease, and atherosclerosis. In addition, the following surrogate endpoints have been identified by FDA for evaluating CHD risk reduction for the purposes of a health claim: high blood pressure, blood (serum or plasma) concentrations of total cholesterol (TC), and blood (serum or plasma) concentrations of low density lipoprotein cholesterol (LDL-C).[18] These disease and surrogate endpoints were used to evaluate the potential effects of soybean oil on CHD risk.

The petition cited 160 publications as evidence to substantiate the relationship for the proposed claim (see Docket number FDA-2016-Q-0995), including 19 publications describing 15 human intervention and observational studies evaluating the relationship between soybean oil consumption and CHD risk. In addition, the petition cited 24 review articles; 13 meta-analyses; 10 opinion papers/letters to the editor; 15 publications from Federal agencies or professional associations; two publications on the chemical composition of soybean oil; two animal studies; and 75 observational and intervention studies that did not evaluate the substance-disease relationship. We identified one additional publication that did not evaluate the substance-disease relationship. We identified one additional intervention study through a literature search that evaluated the relationship between soybean oil and risk of CHD (Ganji et al., 1996).

A. Assessment of Background Materials

"Background materials" here refers to review articles, meta-analyses, reports from federal agencies and professional associations, and opinion papers/letters. Although useful for background information and identifying additional studies, these materials do not contain

[18] National Heart, Blood and Lung Institute (NHLBI), Heart and Blood Vessel Diseases [http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html] and National Cholesterol Education Program, U.S. Department of Health and Human Services, 2001 [http://www.nhlbi.nih.gov/files/docs/resources/heart/atp-3-cholesterol-full-report.pdf]. Accessed May 10, 2017)].

sufficient information on the individual studies that they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. For example, FDA could not determine factors such as the study population characteristics or nutrient composition of experimental diets. Similarly, the lack of detailed information on studies summarized in these materials 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. As a result, the background materials supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of Animal Studies

FDA uses animal studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal studies cited with the petition as providing any supportive information about the substance-disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of CHD, nor can the studies mimic the human body's response to the consumption of soybean oil. Therefore, FDA could not draw any scientific conclusions regarding soybean oil intake and the reduction of risk of CHD from the animal studies cited in the petition.

C. Assessment of Intervention Studies

FDA evaluated 19 publications describing 15 individual intervention studies investigating the relationship between consumption of soybean oil and risk of CHD. Of the 19 publications reviewed and evaluated, scientific conclusions could not be drawn from 13 of these publications (Controlled trial of soya-bean oil in myocardial infarction, 1968; Ganji et al., 1996; Hamazaki et al., 1996; Han et al., 2002; Han et al., 2012; Harris et al., 2008; Holguin et al., 2005; Kurowska et al., 1997; Laine et al., 1982; Lichtenstein et al., 2006; Lu et al., 1997; Svegliati Baroni et al., 1999; Trifiletti et al., 2005).[19]

Han et al. (2002) was not considered for further review because the relevant lipid and lipoprotein data reported in the publication were a subset of previously published data (Lichtenstein et al., 1999).[20] The original study is described below. The study by Ganji et al. (1996) was not considered for further review because the duration of the intervention (7-day diet periods) was insufficient to achieve steady state of the surrogate endpoints (e.g., minimum of three weeks for

[19] 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.

[20] The data presented in Han et al, 2002 were part of a secondary analysis. The primary analysis of lipid/lipoprotein data for the entire study population was included in the publication by Lichtenstein et al, 1999, which was considered as part of the evidence evaluating the substance-disease relationship. Considering the subset of data presented in Han et al. 2002 would not add additional insight because the subset consists of a smaller sample size of the same people included in the larger dataset analyzed in the Lichtenstein et al. 1999 publication.

TC, LDL-C, as discussed in Kris-Etherton et al., 1997). [21] Therefore, scientific conclusions about the relationship between soybean oil and risk of CHD cannot be drawn from these studies.

Six publications did not include a control group, or used an inappropriate control group based on the proposed claim (Hamazaki et al., 1996; Han et al., 2012; Harris et al., 2008; Holguin et al., 2005; Kurowska et al., 1997; Lichtenstein et al., 2006). Without an appropriate control group, it cannot be determined whether changes in the endpoints of interest are due to the replacement of SFA with soybean oil or due to unrelated and uncontrolled extraneous factors (Spilker, 1991). In assessing the appropriateness of the control for this qualified health claim, we considered the differences in the fatty acid composition between the soybean oil and the control diet. The differences in the fatty acid composition should reflect the differences in fatty acids that result from substituting soybean oil for sources of saturated fatty acids (SFA) (e.g., similar or lower amounts of SFA, and higher amounts of unsaturated fatty acids (UFA) in the soybean oil diet compared with the control diet). Otherwise, the control diet is inappropriate for evaluating the replacement of SFA with UFA from soybean oil, and scientific conclusions cannot be drawn from such studies. Holguin et al. (2005) also did not measure an accepted surrogate endpoint for CHD risk.

Three publications did not describe the statistical methods used (Controlled trial of soya-bean oil in myocardial infarction, 1968; Svegliati Baroni et al., 1999) or used inappropriate statistical analyses for the particular study design (e.g., overall treatment effect was not tested before individual comparisons between diets were made, which may increase the chance of drawing incorrect conclusions) (Laine et al., 1982). Conducting a statistical analysis of a relationship is critical because it provides a basis for comparing individuals who consumed soybean oil and those who did not consume soybean oil to determine whether there was an actual reduction in the risk of CHD.[22] When appropriate statistical tests are not described or not performed on the specific substance-disease relationship, it cannot be determined whether there is a significant difference between the experimental groups.

Two publications were lacking important information on the composition of certain nutrients in the diets consumed by the study subjects that are known to affect the substance-disease relationship. Specifically, two publications lacked information about the absolute amounts of saturated fatty acids (SFA), monounsaturated fatty acids, and polyunsaturated fatty acids in the study subjects' diets (Lu et al., 1997; Trifiletti et al., 2005). In particular, the absolute amount of SFA of the experimental diets is critical in evaluating the substance-disease relationship due to the proposed claim language of substituting soybean oil for SFA. Scientific conclusions cannot be drawn about the relationship between a substance and a disease when the amounts of other substances that are known to affect the risk of the disease that is subject of the claim are different, or not reported, between the control and experimental diets.[23]

[21] See *supra*, note 3 [Section III. D].
[22] See *supra*, note 3 [Section III. D].
[23] See *supra*, note 3 [Section III. D].

Consequently, scientific conclusions could not be drawn from a total of 13 studies about the relationship between soybean oil consumption and risk of CHD. Scientific conclusions could be drawn from six of the 19 publications describing four intervention studies that evaluated the relationship between soybean oil consumption and risk of CHD (Kris-Etherton et al., 1993; Lichtenstein et al., 1999; Lichtenstein et al., 2003; Utarwuthipong et al., 2009; Vega-Lopez et al., 2006; Zhang et al., 1997). Three of the four studies utilized highly controlled diets (controlled-feeding) (Kris-Etherton et al., 1993; Lichtenstein et al., 1999; Lichtenstein et al., 2003; Vega-Lopez et al., 2006; Zhang et al., 1997), while one study was a free-living study in which diets were not strictly controlled but rather dietary intake was assessed by food records (Utarwuthipong et al., 2009). Both types of studies are considered to be an intervention design. However, the three studies that controlled the subject's dietary intakes provide stronger evidence for the substance/ disease relationship since compliance was more strictly monitored.

Kris-Etherton et al. (1993) conducted a moderate quality randomized, crossover, controlled-feeding study in normocholesterolemic young males in the U.S. (n = 19; age = 26 years). Baseline TC ranged from 120 to 205 mg/dL (10^{th} – 75^{th} percentile). Participants were fed each of the following three relevant fats and oils as part of isocaloric controlled diets for 26 days: soybean oil (~97 g/day; SFA: 6.3% of energy intake), cocoa butter (SFA: 21% of energy intake), and butter (SFA: 21% of energy intake). There was a one month wash-out between each diet. The authors report that diets were formulated to allow for specific comparisons between specific fatty acids; however, they do not provide any other details about the diets, such as whether there were any other differences between the diets besides the test oils—thus making it difficult to assess the role that the oil substitution played in achieving the study results. The soybean oil diet lowered TC and LDL-C by 16-27% when compared with diets that were higher in SFA (diets containing butter and cocoa butter) ($P < 0.01$).[24].

Zhang et al. (1997) conducted a moderate quality randomized, parallel, controlled feeding study in China (n = 30/group). Normocholesterolemic young males (age = 18 – 25 years; TC = 108-193 mg/dL) consumed a 3-week run-in diet and were then assigned to one of four controlled isocaloric diets for six weeks: soybean oil (~53 g/day; SFA: ~6% of energy intake), palm oil (SFA: ~13% of energy intake), peanut oil (SFA: ~9% of energy intake), and lard (SFA: ~10% of energy intake). Diets included cereals, lean pork and chicken, bean curd and green vegetables. The authors reported that menus were developed based on subjects' preferences, but details were lacking regarding any differences in the diets besides the oils—thus making it difficult to assess the role that the oil substitution played in achieving the study results. The soybean oil diet decreased TC and LDL-C by 16% and 22%, respectively, compared to the lard diet ($P < 0.05$). There were no statistical differences between the soybean oil diet and the palm oil or peanut oil diets for TC or LDL-C ($P > 0.05$ for all). The diets used in this study may have limited applicability to the healthy U.S. population because the foods consumed were those of a typical Chinese diet, but may not be representative of a typical U.S. diet.

[24] 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].

Utarwuthipong et al. (2009) conducted a moderate quality randomized, crossover, free-living study in hypercholesterolemic women in Thailand (n = 16; age = 44 – 67 years). Individuals were recruited with TC between 240 and 280 mg/dL and LDL-C between 130 and 159 mg/dL. All participants started with an 8-week free-choice diet and were then randomized to a treatment sequence of four 10-week isocaloric diets, which included the same background diet with four different test oils: soybean oil, palm oil (PO), rice bran oil (RBO), and mixture of RBO/PO. The soybean oil (~ 36 g/day of soybean oil; SFA: 9% of energy intake) and palm oil (SFA: 13% of energy intake) diets were considered relevant and evaluated for the proposed health claim. Strictly controlled diets were not administered during the study, but rather participants were instructed to follow a diet that met National Cholesterol Expert Panel guidelines and dietary intake was assessed by food records. Compared with the diet containing palm oil (SFA: 13% of energy), the soybean oil diet (SFA: 9% of energy intake) decreased TC and LDL-C by 13% and 15%, respectively ($P < 0.05$). The diets used in this study may have limited applicability to the healthy U.S. population due to differences in the composition of the typical U.S. diet versus diets typically consumed in Thailand.

The study by Lichtenstein et al. (1999) was a high quality randomized, crossover, controlled-feeding study in U.S. adults (n = 36; 18 males, 18 females). Participants were required to be greater than 50 years old with baseline LDL-C greater than 130 mg/dL (mean age = 63 years; mean baseline LDL-C = 167 mg/dL). Six isocaloric controlled diets (35 days each) were provided to participants, two of which were relevant and evaluated for the relationship of soybean oil and risk of CHD. All of the foods in the diets were identical with the only difference being the test fats used to make up two thirds of the fat in the diets. Compared with the butter diet (SFA: 17% of energy intake), the soybean oil diet (~55g/day of soybean oil; SFA: 7% of energy intake) lowered TC and LDL-C by 10% and 13%, respectively ($P < 0.05$). At the end of the initial intervention (6 controlled diets), the same participants were given the option to participate in two additional phases (35 days each), which consisted of controlled diets with palm oil and canola oil, in random order. Vega-Lopez et al. (2006) presented the data (n = 15; 5 males, 10 females) from four of the diets (two of the initial diets and two of the additional diets), of which two were considered relevant to the evaluation of the present claim: soybean oil (~53 g/day; SFA: 7% of energy intake) and palm oil (SFA: 15% of energy intake). Compared with the palm oil diet, the soybean oil diet decreased TC and LDL-C by 9% and 14%, respectively ($P < 0.05$).

The publication by Lichtenstein et al. (2003) reported blood pressure data on a subset of the participants (n = 23) from the same intervention conducted and described in Lichtenstein et al., 1999. There were no significant differences in blood pressure between the soybean oil and butter diets ($P > 0.05$).

D. Assessment of Observational Studies

There was one retrospective observational study that evaluated the relationship between soybean oil consumption and risk of CHD (Kabagambe et al., 2005). The moderate quality case-control study was conducted in adults in Costa Rica (n = 2,111 case-control pairs; mean age = 58 years).

The cases were survivors of a first acute myocardial infarction, and were matched to randomly selected controls. Dietary intake was assessed with a validated semiquantitative food frequency questionnaire and confirmed with adipose tissue fatty acid profiles. After multivariate adjustment, palm oil users were more likely to have a myocardial infarction than users of soybean oil (adjusted odds ratio = 1.33; 95% confidence interval: 1.08-1.63).[25] SFA intake was similar between cases and controls (12% of energy intake). The soybean oil used in Costa Rica at the time of the study consisted of 5% *trans* fatty acid content, which is higher than soybean oil currently used in the U.S.

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 U.S. population or a target subgroup, whether study results supporting the proposed claim have been replicated,[26] and the overall consistency[27] of the total body of evidence.[28] 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 soybean oil and CHD risk includes seven publications describing four intervention studies and one observational study. All four intervention studies were small (15-36 subjects per study or treatment group) randomized controlled trials of high or moderate methodological quality. Two of the four intervention studies used diets that have limited applicability to the healthy U.S. population, due to differences in the composition of the typical U.S. diet versus diets typically consumed in China and Thailand (Utarwuthipong et al., 2009; Zhang et al., 1997), as recognized by the petitioner (pages 51 and 61). The studies were conducted in individuals with baseline TC and LDL-C that ranged from normal to high. Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.[29] Three of the four intervention studies demonstrated that diets containing soybean oil decrease TC and

[25] An odds ratio is the odds of developing the disease in exposed compared to unexposed individuals. It is calculated in case control studies by measuring disease development in subjects based on exposure to the substance. An adjusted odds ratio controls for potential confounders. Confidence intervals are ranges that provide a statistical analysis of comparative measures of risk (e.g., relative risk, odds ratio and hazard ratio). Confidence intervals are significant when the entire range is less than or greater than "1" (e.g., 0.7-0.9 or 1.1-1.5). If the confidence interval includes "1" within its range, then it cannot be concluded that a relationship exists between the substance and the disease.
[26] See *supra*, note 12.
[27] See *supra*, note 13.
[28] See *supra*, note 3 [Section III. F].
[29] See *supra*, note 3 [Section III. F].

LDL-C when compared with diets that are higher in saturated fat (specifically, diets containing butter, cocoa butter, lard and palm oil) (Kris-Etherton et al., 1993; Lichtenstein et al., 1999; Utarwuthipong et al., 2009). One of the four studies reported mixed results when comparing a diet containing soybean oil with diets higher in SFA, with no significant differences in TC and LDL-C between the soybean oil diet and the palm oil or peanut oil diets, but decreases in TC and LDL-C when compared to the lard diet (Zhang et al., 1997).

In summary, there were four high or moderate quality intervention studies that reported on eight comparisons of diets containing soybean oil versus diets with higher amounts of SFA. Three of the four studies, reporting on five of eight comparisons, demonstrated a lowering of TC and LDL-C with the soybean oil diet; one study reported mixed results, with only one of three comparisons (to a diet with higher amounts of SFA) lowering TC and LDL-C. None of the intervention studies suggested that soybean oil, independent of SFA displacement, would lower TC and LDL-C. The observational study was a large (n = 2,111) case-control study of moderate methodological quality. In showing an association of soybean oil consumption and a reduced risk of CHD, the results from the observational study are consistent with the overall data from the intervention studies.

Based on FDA's review of the strength of the total body of scientific evidence for the proposed qualified claim, FDA concludes that the scientific evidence is credible and supports the substance/disease relationship. However, due to the small number of intervention studies, the small number of subjects per study, inconsistency of findings, and the fact that two of the four studies used diets that may not be representative of the healthy U.S. population, FDA has concluded that the evidence provides only qualified support for the scientific validity of the claimed relationship. Therefore, FDA has determined that qualifying language should be included to convey the limits on the strength of the scientific evidence supporting the relationship. FDA thus intends to consider the exercise of its enforcement discretion for a qualified health claim about soybean oil on the label or in labeling of soybean oil that includes a truthful and non-misleading description of the strength of the body of scientific evidence, i.e. “supportive but not conclusive.” Such a description is truthful and not misleading because, while the evidence provides support for the claimed relationship, the evidence is not conclusive. Further, in order for the claim to be truthful and not misleading, the agency will consider, as factors in the exercise of its enforcement discretion, certain other factors discussed below. Based on the above, FDA concludes that there is supportive but not conclusive scientific evidence for a relationship between UFA from soybean oil and reduced risk of CHD, when substituted for greater amounts of saturated fat.

IV. Other Enforcement Discretion Factors

Factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims for UFA from soybean oil and reduced risk of CHD are discussed below.

A. Qualifying Level of Soybean Oil

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)).

The agency determined the minimum amount of UFA from soybean oil necessary to substitute in place of saturated fats in order to achieve the relevant benefits by first calculating the difference in the amount of UFA between the soybean oil and high-SFA diets in the studies that used highly controlled diets that demonstrated a reduction in total cholesterol and LDL cholesterol (Kris-Etherton et al., 1993; Lichtenstein et al., 1999; Vega-Lopez et al., 2006; Zhang et al., 1997). The lowest difference that was reported in these studies was used to determine the minimum amount of UFA necessary to achieve the relevant benefits, when replaced for saturated fat. The minimum amount of soybean oil was then determined based on the UFA composition of soybean oil. This is similar to the approach that was used for previous qualified health claims with vegetable oils (e.g., UFA from corn oil, UFA from canola oil). Based on these studies, the lowest amount of UFA needed to replace SFA that may result in significant reductions in total and LDL cholesterol is 16.5 g. Soybean oil contains approximately 81% UFA (USDA Nutrient Database for Standard Reference, Release 28). Consuming 20.5 g (~ 1 ½ tablespoons) of soybean oil per day provides 16.5 g of UFA and 3.3 g of SFA.

Therefore, FDA intends to consider exercising enforcement discretion for the use of the qualified claim when the claim specifies 1 ½ tablespoons (20.5 grams) as the daily dietary intake necessary to achieve the claimed effect.

To determine the minimum amount of soybean oil necessary to be in a food, FDA considered a provision of the general requirements for health claims requiring that a health claim enable the public to comprehend the information provided and to understand the relative significance of such information in the context of the total daily diet (see Section 403(r)(3)(B)(iii) of the Act). For health claims FDA has considered that a typical daily food consumption pattern is composed of 3 meals and a snack or four eating occasions (58 FR 2302-2379; January 6, 1993). Indeed, four eating occasions per day were used to define the qualifying level for three CHD-related health claims: soy protein (64 FR 57700, 57713, October 26, 1999); ß-glucan soluble fiber from whole oats (62 FR 3584, 3592, January 23, 1997); and soluble fiber from psyllium seed husks (63 FR 8103, 8109, February 18, 1998). FDA also used this approach to identify 6 g olive oil, 4.75 g canola oil and 4.0 g corn oil per RACC as the qualifying level for products to bear the qualified health claim for these vegetable oils. Consistent with this approach, FDA considered the number of eating occasions at which consumers might consume soybean oil products and the number of potential foods that could be labeled with the requested qualified health claim, and we based the determination of the qualifying level of soybean oil to bear the claim on four eating occasions per day. The Reference Amount Customarily Consumed (RACC) for soybean oil is one tablespoon, which contains approximately 10.9 g of UFA and 2.1 g of SFA. The minimum dose (20.5 grams per day) based on

four eating occasions per day of soybean oil is 5 g per Reference Amount Customarily Consumed (RACC) that is (20.5 g ÷ 4 = 5.13 g).

In addition, the agency included phrases in the qualified claims identified below that soybean oil, consumed at this level, (1) not result in increased caloric intake, (2) replace saturated fat, and (3) that soybean oil contains unsaturated fat. The credible evidence that is available, and on which the agency is relying for the qualified claim, suggests that soybean oil may only provide a benefit when used to replace calories and saturated fat.[30] As described above in the "Strength of the Evidence" section, the credible evidence on which the agency is relying reported on comparisons of diets in which the control diets contained amounts of saturated fat greater than the amounts contained in the soybean oil diets. Although the petitioner requested that the claim language state that the soybean oil replace a "similar amount" of saturated fat, there was no credible scientific evidence that compared a soybean oil diet to another diet with a similar amount of saturated fat. The smallest difference in the amount of saturated fat between the soybean oil diet and the control diet that was reported in the four intervention studies was 4% of energy ($P < 0.05$; Utarwuthipong et al., 2009), and statistically significant differences in the amount of saturated fat such as this are not similar.[31] The credible scientific evidence only indicates that benefits may be realized when soybean oil in the diet replaces a greater amount of saturated fat. Furthermore, a claim stating that soybean oil can result in CHD benefits when replacing a "similar amount" of saturated fat would be misleading because it would suggest that consumers could replace soybean oil with *less* saturated fat and still achieve the relevant benefits. Such an inference is not supported by the scientific evidence. Therefore, instead of including a phrase that the soybean oil replace a "similar amount" of saturated fat, we are including two alternative phrases. One phrase would state that soybean oil is "to replace saturated fat." The second phrase would state that soybean oil is "not to increase the amount of saturated fat" consumed daily. These phrases reflect the state of the science so that consumers can understand the relative significance of the claims in the context of the total daily diet. Similarly, including the phrase that soybean oil is not to "increase the total number of calories you eat in a day" in the qualified health claims also reflects the state of the science, so that consumers can similarly understand the relative significance of the claims in the context of the total daily diet with respect to calories. In addition, we are including the statement that soybean oil "contains unsaturated fat" in the claim language. The language is consistent with the approach we (and the petition) use for determining the minimum amount of soybean oil necessary to achieve the relevant benefits. In particular, that method (described above) was based on the unsaturated fat content of the diets used in the

[30] The credible evidence that the agency relied on consisted of six publications describing four intervention studies, which substituted soybean oil for greater amounts of saturated fat and did not result in increased caloric intake: Kris-Etherton et al., 1993; Lichtenstein et al., 1999; Lichtenstein et al., 2003; Utarwuthipong et al., 2009; Vega-Lopez et al., 2006; Zhang et al., 1997. There was no credible scientific evidence available that suggested the reduction in CHD risk could be achieved without replacing soybean oil in the diet for a greater amount of saturated fat. In addition, there was no credible scientific evidence available that suggested the reduction in CHD risk from soybean oil consumption could be achieved with increased caloric intake.

[31] Furthermore, small differences in saturated fat can have a significant impact on CHD disease risk. For example, a recent report by the American Heart Association demonstrates that replacing 5% of energy intake from saturated fats with equivalent energy intake from polyunsaturated fats and monounsaturated fats was significantly associated with a 25% and 15% lower risk of CHD, respectively (Sacks et al., 2017).

studies. Identifying the presence of unsaturated fat content in soybean oil thus provides consumers with information relevant to the basis for the qualifying level of soybean oil. Including the phrases that, (1) soybean oil is to replace (or not increase) saturated fat, (2) soybean oil is not to increase the total number of calories, and (3) that soybean oil contains unsaturated fat will thus allow consumers to understand the basis for the benefits of soybean oil, when substituted for saturated fat, at the qualifying level identified in the claim. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, the statements that (1) soybean oil should replace (or not increase) saturated fat, (2) consumers are not to increase the total number of calories consumed in a day, and (3) that soybean oil contains unsaturated fat.

B. Definitions Used in Letter

A qualified health claim on the label or in the labeling of soybean oil and soybean oil-containing products 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. In addition to the factors discussed above in this letter, FDA also intends to consider certain additional factors in the exercise of its enforcement discretion, as discussed below.

For the purpose of this enforcement discretion letter, the following definitions will be used: (1) "soybean oil" means products that are essentially pure soybean oil and are labeled as such; (2) "vegetable oil spread" means margarine (21 CFR 166.110) and margarine-like products formulated to contain soybean oil; (3) "dressings for salads" means dressings for salads formulated to contain soybean oil; (4) "shortenings" means vegetable oil shortenings formulated to contain soybean oil; and (5) "soybean oil-containing foods" means all other foods, such as sauces or baked goods, formulated to contain soybean oil, excluding soybean oil, vegetable oil spreads, dressings for salads, and shortenings. The term "soybean-oil containing products" refers to items 2 to 5 in the above list.

C. Total fat, Saturated Fat, Cholesterol, and 10 Percent Minimum Nutrient Content Requirement for Vegetable Oil and CHD-related Health Claims

In regulations authorizing CHD-related health claims, FDA has generally required, with a few exceptions, that foods bearing the claims meet the "low fat" criterion defined by 21 CFR 101.62(b)(2), "low saturated fat" criterion defined by 21 CFR 101.62(c)(2), and the "low cholesterol" criterion defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR §§§§§ 101.75, 101.77, 101.81, 101.82, and 101.83). The agency will discuss below how it intends to consider these criteria as factors in deciding whether to exercise its enforcement discretion for a qualified health claim about UFA from soybean oil and CHD risk on soybean oil and soybean oil-containing products. Later in section D., FDA discusses total fat, saturated fat, cholesterol, and sodium content relative to the general requirements for health claims (21 CFR 101.14), specifically, disqualifying levels (21 CFR 101.14(a)(4)).

“Low fat” criterion

FDA has required in the past that foods bearing CHD-related health claims meet the requirement for “low fat” as defined by 21 CFR 101.62(b)(2) as foods that contain less than 3 g of fat per RACC, or, for foods with a RACC of 30 g or less than 2 tablespoons, per 50 g. Oils, margarine and margarine-like products, and shortenings have a RACC of one tablespoon, and dressings for salads have a RACC of 30 g. The requirement of the “low fat” criterion was first introduced in the dietary lipid and cardiovascular disease proposed rule (56 FR 60727 at 60739; November 27, 1991). FDA stated that, although total fat is not directly related to increased risk for CHD, it may have significant indirect effects. The agency stated that low fat diets facilitate reduction in the intake of saturated fat and cholesterol to recommended levels. Furthermore, the agency noted that obesity is a major risk factor for CHD, and dietary fats, which have more than twice as many calories per gram as proteins and carbohydrates, are major contributors to total caloric intakes.

There have been several exceptions to this criterion in the past. In not requiring the “low fat” criterion for CHD-related claims, FDA noted that the Dietary Guidelines for Americans, 2000 (USDA & DHHS, 2000), which was current during olive oil qualified health claim considerations, recommended choosing a diet that is low in saturated fat and cholesterol and moderate in total fat. Specifically, the Dietary Guidelines recommended moderate amounts of foods high in unsaturated fat with a caution to avoid excess calories. More recently, FDA has not used the “low fat” criterion as a factor in the exercise of enforcement discretion for claims for olive oil, vegetable oil spreads, dressings for salads, shortenings, and olive oil-containing foods that bear monounsaturated fatty acids (MUFAs) from olive oil and a CHD qualified health claim; canola oil, vegetable oil spreads, dressings for salads, shortenings and canola oil-containing foods that bear UFAs from canola oil and a CHD qualified health claim; and corn oil, vegetable oil spreads, dressings for salads, shortenings and corn oil-containing foods that bear UFAs from corn oil and a CHD qualified health claim.

Soybean oil exceeds the “low fat” criterion because it is essentially entirely fat. Furthermore, FDA intends to exercise enforcement discretion for soybean oil products that contain 5 g or more soybean oil per RACC (see Section IV, A), and thus would not meet the “low fat” criterion. The scientific studies that suggest a relationship between soybean oil in replacement of SFA and reduced risk of CHD used soybean oil in cooking and various food combinations. The UFA from soybean oil and CHD qualified health claim will inform consumers that they may lower their risk of CHD by consuming soybean oil and soybean oil products in place of SFA, while not increasing caloric intake. FDA believes that this type of dietary information will help consumers maintain healthy dietary practices by providing consumers with information that can facilitate reductions of saturated fat and cholesterol intake since soybean oil contains no cholesterol and less saturated fat than other fat sources. Soybean oil is a plant food and does not contain cholesterol. Furthermore, FDA concurs with current dietary guidelines (Dietary Guidelines for Americans 2015-2020) that continue to note that consuming diets low in saturated fat is more important in reducing CHD risk than consuming diets low in total fat.

Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that soybean oil, vegetable oil spreads, dressings for salads, shortenings, and soybean oil-containing foods that bear a soybean oil and CHD qualified health claim meet the "low fat" criterion.

"Low saturated fat" criterion

"Low saturated fat," as defined by 21 CFR 101.62(c)(2), means that the food must contain less than 1 g of saturated fat per RACC and not more than 15% of calories from saturated fat.

According to information from USDA's National Nutrient Database for Standard Reference 28 about the saturated fat and calorie content of soybean oil, soybean oil does not meet the definition of a "low saturated fat" food. , Furthermore, soybean oil products that contain this amount of saturated fat from soybean oil alone are likely to exceed the "low saturated fat criterion". The scientific studies that suggested a relationship between soybean oil in replacing saturated fat and reduced risk of CHD used soybean oil in cooking, as well as several types of foods containing soybean oil. The soybean oil and CHD qualified health claim will inform consumers that they may lower their risk for CHD by consuming soybean oil in place of other sources of saturated fat, while not increasing caloric intake. FDA believes that this type of dietary information will help consumers maintain healthy dietary practices by providing consumers with information that can facilitate reductions of saturated fat and cholesterol intake, since soybean oil contains no cholesterol and has less saturated fat than other fat sources.

Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that soybean oil, vegetable oil spreads, dressings for salads, shortenings, and other soybean oil-containing foods labeled with a UFA from soybean oil and CHD qualified health claim meet the "low saturated fat" criteria as defined in 21 CFR 101.62(c)(2). Thus, for the purposes of this qualified health clam, vegetable oil spreads, dressings for salads, shortenings, and other soybean oil-containing foods do not need to meet the "low saturated fat" criteria.

FDA does, however, believe that it would be appropriate to consider, as a factor in the exercise of its enforcement discretion, that soybean oil and soybean oil products when labeled with a soybean oil and CHD qualified health claim place the statement: "See nutrition information for saturated fat content" immediately adjacent to the claim with no intervening material and in the same contrast as the claim itself.[32]

Although FDA does not intend to consider the "low saturated fat" criterion as a factor in its exercise of enforcement discretion, FDA does intend to consider as a factor in its enforcement discretion that foods that are eligible to bear the claim, as stated later in this letter, meet certain elements of the saturated fat disqualifying criteria in 21 CFR 101.14(a)(4). This will ensure that foods bearing the claim will not contain excessive amounts of SFA.

[32] We note that your petition also states that it is appropriate to include such a statement for soybean oil and soybean oil-containing foods that do not meet the "low saturated fat" criteria. *See* Petition at 109-10.

"Low cholesterol" criterion

Like all plant-based foods, soybean oil does not contain cholesterol, and therefore, a low cholesterol nutrient content requirement would not limit the use of a qualified health claim for UFA from soybean oil and CHD risk to be used on the label or in labeling of soybean oil. However, several vegetable oil spreads, dressings for salads, shortenings and other soybean oil-containing foods may contain cholesterol from sources other than soybean oil. Dietary cholesterol is known to increase serum total and LDL-cholesterol levels, which is a risk factor for CHD.

Therefore, FDA intends to consider, as a factor in its exercise of enforcement discretion, that vegetable oil spreads, dressings for salads, shortenings and other soybean oil-containing foods labeled with a soybean oil and CHD qualified health claim meet the "low cholesterol" criteria as defined in 21 CFR 101.62(d)(2).

D. Disqualifying nutrient levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in 21 CFR 101.14(a)(4). Disqualifying total fat levels for individual foods are above 13.0 g per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying saturated fat levels for individual foods are above 4.0 g per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying cholesterol levels for individual foods are above 60 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying sodium levels for individual foods are above 480 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g.

The general requirements for health claims also provide for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, if the agency finds that such a claim will assist consumers in maintaining healthy dietary practices (21 CFR 101.14(e)(3)). In such cases, the label must also bear a disclosure statement that complies with 21 CFR 101.13(h), highlighting the nutrient that exceeds the disqualifying level.

The application of these regulatory provisions to UFA from soybean oil and CHD qualified health claims on soybean oil, vegetable oil spreads, dressings for salads, shortenings and soybean oil-containing foods are discussed below.

"Total fat" disqualifying level

In the previous section (Section IV, C), FDA explained that the agency has decided not to consider, in the exercise of its enforcement discretion, that soybean oil, vegetable oil spreads,

dressings for salads, shortenings, and soybean oil-containing foods that bear a soybean oil and CHD qualified health claim meet the "low fat" criterion as defined by 21 CFR 101.62(b)(2). FDA notes that there is a large difference in the amount of total fat between the "low fat" criterion and the disqualifying total fat level. For example, the "low fat" criterion for individual foods is equal to or less than 3 g per RACC and per 50 g if the RACC is 30 g or less or 2 tablespoons or less. The disqualifying total fat level for individual foods is above 13 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoon or less. Thus, there is a difference of 10 g for individual foods between the "low fat" criterion and the disqualifying total fat level.

Soybean oil exceeds the disqualifying total fat level because it is essentially entirely fat. However, a UFA from soybean oil and CHD qualified health claim will inform consumers that they might lower their risk of CHD by consuming foods containing soybean oil in place of similar foods higher in SFAs, while not increasing caloric intake. FDA believes this type of dietary information will help consumers maintain healthy dietary practices by providing consumers with information that can facilitate reductions of saturated fat and cholesterol intake without increasing total calorie consumption. Furthermore, FDA concurs with current Dietary Guidelines for Americans, 2015–2020 that consuming diets low in saturated fat is more important in reducing CHD risk than consuming diets low in total fat.

Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that soybean oil meet the disqualifying total fat level to bear a soybean oil and CHD qualified health claim. Thus, for purposes of enforcement discretion for this qualified health claim, soybean oil does not need to meet the disqualifying total fat level.

Products labeled as margarine (21 CFR 166.110) must contain at least 80% vegetable oil by weight, and are essentially all fat. Foods that contain these levels of fat will necessarily exceed the disqualifying total fat level. Vegetable shortenings, dressing for salads and soybean oil-containing products also contain various levels of fat. If FDA imposed the disqualifying total fat level on these products, it would prevent these products, which were included in the scientific studies that suggested a risk reduction relationship, from bearing the claim. Soybean oil-containing foods are generally not vehicles for delivering fat. However, given that FDA intends to exercise enforcement discretion for soybean oil products that contain 5 g or more soybean oil per RACC, and the food may be formulated with additional soybean oil and still contribute to the claimed effect, FDA concludes that applying the disqualifying levels of total fat to soybean oil-containing foods for the purposes of considering whether to exercise enforcement discretion would unduly limit the foods that could contribute to beneficial effects from bearing the claim. Further, FDA has concluded that foods labeled with a UFA from soybean oil and a CHD qualified health claim would assist consumers in maintaining healthy dietary practices, since the claim provides consumers with information to select products that have less SFA while not increasing their total caloric intake.

Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that vegetable oil spreads, dressings for salads, shortenings, and soybean oil-containing foods that bear a UFA from soybean oil and CHD qualified health claim meet the total fat disqualifying level. Thus, for purposes of enforcement discretion for this qualified health claim, vegetable oil spreads, dressings for salads, shortenings, and soybean oil-containing foods do not need to meet the disqualifying total fat level. However, FDA believes that it is appropriate to consider as a factor in the exercise of its enforcement discretion that when the total fat level in the food exceeds the disqualifying level as defined by 21 CFR 101.14(a)(4), the disclosure statement (i.e., See nutrition information for total fat content) as described in 21 CFR 101.13(h), is placed immediately adjacent to the claim.

"Saturated fat" disqualifying level

In the previous section (Section IV, C), FDA explained that the agency has decided not to consider, in the exercise of its enforcement discretion, that soybean oil, vegetable oil spreads, dressings for salads, shortenings, and soybean oil-containing foods that bear a UFA from soybean oil and reduced risk of CHD qualified health claim meet the "low saturated fat" criterion as defined by 21 CFR 101.62(b)(2). FDA notes that there is a difference in the amount of saturated fat between the "low saturated fat" criterion and the disqualifying saturated fat level. For example, the "low saturated fat" criterion for individual foods is equal to or less than 1 g per RACC and less than 15% of the calories from saturated fat. The disqualifying saturated fat level for individual foods is above 4 g per RACC, per label serving size and per 50 g. If the food has a RACC of 30 g or less or 2 tablespoon or less, the disqualifying saturated fat level is above 4g per 50 g.

Soybean oil has 2.1 g of saturated fat per RACC, and because it has a small RACC (i.e., 30 g or less) soybean oil will exceed the disqualifying saturated fat level based on the 50 gram-criterion (soybean oil contains about 7.8 g of saturated fat per 50 g). Margarine (21 CFR 166.110), which has at least 80% vegetable oil by weight, and shortening are essentially all fat. Both products have a RACC 30 g or less. If formulated with soybean oil as the only vegetable oil, such products would exceed the 50 gram-criterion for the disqualifying saturated fat level. As mentioned above, the general requirements for health claims provide for FDA to authorize a health claim for a food, despite the fact that a nutrient in the food exceeds the disqualifying level, if the agency finds that such a claim will assist consumers in maintaining healthy dietary practices (21 CFR 101.14(e)(3)). FDA believes that a qualified health claim about UFA from soybean oil and reduced risk of CHD would assist consumers in maintaining healthy dietary practices, since the information in the claim informs consumers that replacing SFA in the diet with UFA from soybean oil may reduce the risk of CHD. If FDA did impose the 50 gram-criterion for the disqualifying saturated fat level on vegetable oil spreads and shortenings, it would prevent these major soybean oil products, which were included in the scientific studies that suggested a risk reduction relationship, from bearing the claim.

Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion that soybean oil, vegetable oil spreads, and shortenings that bear a UFA from soybean oil and CHD

qualified health claim meet the 50 gram-criterion for the disqualifying saturated fat level. However, FDA does intend to consider, as a factor in the exercise of its enforcement discretion, that soybean oil, vegetable oil spreads or shortenings labeled with the UFA from soybean oil and CHD qualified health claim meet the 4 g per RACC criterion for the disqualifying saturated fat level.

On the other hand, dressings for salads may be formulated with varying amounts of vegetable oil. French dressings (21 CFR 169.115) must contain at least 35% vegetable oil by weight; a product formulated entirely with soybean oil and no other source of fat will contain about 2.3 g saturated fat per 50 g. Unless there were other sources of saturated fat in the dressing for salad, a dressing formulated with up to 50% soybean oil should be able to meet the 50 gram-criterion for the disqualifying saturated fat level. FDA believes that not considering the 50 gram-criterion for the disqualifying saturated fat level for dressings for salads would not assist consumers in maintaining healthy dietary practices. Thus, FDA does intend to consider, as a factor in the exercise of its enforcement discretion, that dressings for salads, when labeled with the UFA from soybean oil and CHD qualified health claim, meet the 50 gram-criterion for the disqualifying saturated fat level.

Soybean oil-containing foods are generally not vehicles for delivering fat, unlike soybean oil, vegetable oil spreads, and shortenings, and contain many other ingredients that may contribute to or detract from a healthy diet. If formulated to contain 5 g soybean oil per serving, a soybean oil containing food would contain about 0.8 g of saturated fat, which is below the disqualifying saturated fat level of 4 g per RACC (most soybean oil-containing foods have a RACC greater than 30 g). Unless there were other sources of saturated fat in the soybean-containing food, the food should be able to meet the 50 gram-criterion for the disqualifying saturated fat level. FDA believes that not applying the 50 gram-criterion for the disqualifying saturated fat level to soybean oil-containing foods would not assist consumers in maintaining healthy dietary practices. Thus, FDA does intend to consider, as a factor in the exercise of its enforcement discretion, whether soybean oil-containing foods labeled with a UFA from soybean oil and CHD qualified health claim meet the disqualifying saturated fat level as specified in 21 CFR 101.14(a)(4).

“Cholesterol” disqualifying level

FDA intends to consider, as a factor in the exercise of its enforcement discretion that soybean oil and soybean oil products labeled with a UFA from soybean oil and CHD qualified health claim, meet the disqualifying cholesterol level as specified in 21 CFR 101.14(a)(4).

“Sodium” disqualifying level

FDA intends to consider, as a factor in the exercise of its enforcement discretion that soybean oil and soybean oil products labeled with a UFA from soybean oil and CHD qualified health claim, meet the disqualifying sodium level as specified in 21 CFR 101.14(a)(4).

Trans Fat Levels in Foods Eligible for the Claim

The petitioner requested that soybean oil-containing products be required to contain no more than one gram of *trans* fatty acids per RACC. Currently, there is a lack of scientific evidence to establish a Daily Value for *trans* fatty acids, but it is well known that *trans* fatty acids increase serum total and LDL-cholesterol levels (IOM, 2002). Therefore, FDA intends to consider the petitioner's request, that soybean oil-containing products bearing the qualified health claim contain no more than 1 gram *trans* fatty acids per RACC, as a factor in the exercise of enforcement discretion.

D. 10% minimum nutrient content requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10% of the Daily Value for vitamin D, potassium, iron, calcium, protein, or dietary fiber per RACC (21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods with minimal nutrition value.

FDA has previously exempted certain foods from the 10% minimum nutrient content when it has been determined that such exemptions could assist consumers in maintaining healthy dietary practices. For example, FDA exempted spreads and dressings for salads from this requirement in the plant sterol/stanol esters and CHD claim interim final rule (CFR 54868 at 54711). FDA also considered a qualified health claim for walnuts and a reduced risk of CHD, even though walnuts did not meet the minimum 10% nutrient requirement (https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072910.htm). In addition, FDA did not consider the 10 % minimum nutrient requirement as a factor in the exercise of enforcement discretion for several qualified health claims, including a qualified health claim involving olive oil and olive oil-containing dressings for salads and shortening for the MUFAs from olive oil and CHD qualified health claim (https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072963.htm), canola oil and canola oil-containing dressings for salads and shortenings from the 10% minimum nutrient requirement for the UFA from Canola Oil and CHD Qualified Health Claim (https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072958.htm), and corn oil and corn oil-containing foods from the corn oil and corn oil-containing products for the Corn Oil and Corn-Oil containing foods and CHD Qualified Health Claim (https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072956.htm).

Soybean oil, certain vegetable oil spreads, dressings for salads, and shortenings do not meet the 10% minimum nutrient content requirement of 21 CFR 101.14(e)(6). However, soybean oil, certain vegetable oil spreads, dressings for salads and shortenings provide unsaturated fatty acids that can be used in place of SFAs in the diet. FDA believes that information to help consumers reduce saturated fat and cholesterol consumption would assist consumers in maintaining healthy dietary practices. If FDA did impose the 10% minimum nutrient content requirement for these food categories, it would prevent these major soybean oil products from bearing the claim.

Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that soybean oil, dressings for salads, and shortenings products that bear a soybean oil and CHD qualified health claim meet the 10% minimum nutrient content requirement. Thus, for purposes of enforcement discretion for this qualified heath claim, FDA will not consider the 10% minimum nutrient content requirement for soybean oil, dressings for salads, and shortenings products.

Margarine (21 CFR 166.110), margarine substitutes, and margarine products labeled under 21 CFR 130.10 must contain more than 10% of the RDA for vitamin A and most commercially available margarine-like products also contain more than 10% of the RDA for vitamin D. Therefore, FDA intends to consider, in the exercise of its enforcement discretion, that vegetable oil spreads labeled with the UFA from soybean oil and CHD qualified health claim meet the 10% minimum nutrient content requirement.

FDA considers it appropriate that soybean oil-containing foods meet the 10% minimum nutrient content requirement. Soybean oil-containing foods are generally not vehicles for delivering fat, and contain many other ingredients that may contribute to or detract from a healthy diet. Thus, FDA believes that such foods should meet the 10% minimum nutrient content requirement.

Therefore, FDA does intend to consider, as a factor in the exercise of its enforcement discretion, that soybean oil-containing foods labeled with a UFA from soybean oil and CHD claim meet the 10% minimum nutrient content requirement.

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 supportive scientific evidence for a qualified health claim for UFA from soybean oil and CHD, provided that the qualified health claim is appropriately worded so as not to mislead consumers.

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

> "Supportive but not conclusive scientific evidence suggests that eating about 1 ½ tablespoons (20.5 grams) daily of soybean oil, which contains unsaturated fat, may reduce the risk of coronary heart disease. To achieve this possible benefit, soybean oil is to replace saturated fat and not increase the total number of calories you eat in a day. One serving of this product contains [x] grams of soybean oil."
>
> And:

> "Supportive but not conclusive scientific evidence suggests that eating about 1 ½ tablespoons (20.5 grams) daily of soybean oil, which contains unsaturated fat, may reduce the risk of coronary heart disease. To achieve this possible benefit, soybean oil is not to increase the amount of saturated fat in the diet or the total number of calories you eat in a day. One serving of this product contains [x] grams of soybean oil."

We intend to exercise enforcement discretion for these claims when the appropriate disclaimer statement "[See nutrition information for total fat content.]" or "[See nutrition information for saturated fat content.]" or "[See nutrition information for total fat and saturated fat content.]" is placed immediately adjacent to the claim with no intervening material and in the same contrast as the claim itself. 21 CFR 101.13(h).

FDA intends to consider exercising its enforcement discretion for the above qualified health claim 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, or that will no longer support the use of the above qualified health claims, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

Douglas A. Balentine, Ph.D.
Director
Office of Nutrition
and Food Labeling

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