DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

OCT 29 2004

Bob Bauer
The North American Olive Oil Association
3301 Route 66
Suite 205, Building C
Neptune, New Jersey 07753

RE: Health Claim Petition - Monounsaturated fatty acids from olive oil and coronary heart disease (Docket No 2003Q-0559)

Dear Mr. Bauer:

This letter responds to the health claim petition dated August 28, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of the North American Olive Oil Association pursuant to § 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)). The petition requested that the agency authorize a health claim characterizing the relationship between consumption of monounsaturated fats from olive oil and reduced risk of coronary heart disease (CHD) for use on labels and in labeling of olive oil and certain foods containing olive oil. This petition proposed as a model health claim: "Monounsaturated fats from 13.5 g per day of olive oil (one tablespoon) may reduce your risk of heart disease when included in a moderate-fat diet low in saturated fat and cholesterol."

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 does not meet the "significant scientific agreement" standard under § 403(r)(3)(B)(i) of the Act. FDA notified you of this decision and you submitted a letter dated December 5, 2003 agreeing to the petition being reviewed as a qualified health claim. Thus, FDA filed the petition on December 19, 2003 as a qualified health claim petition and posted it on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedures on qualified health claims.[1]

The agency received a total of nineteen comments on this petition. Seventeen of the comments were from industry and two were from individuals. Fourteen of the comments supported the claim unconditionally, while the remainder supported the claim with conditions concerning the substance of the proposed qualified health claim petition. FDA considered the relevant comments in its evaluation of this petition.

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[1] Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements, July 10, 2003. (http://www.cfsan.fda.gov/~dms/nutftoc.html).

This letter sets forth the basis of FDA's determination that the current evidence for the proposed health claim is appropriate for consideration of a qualified health claim on conventional foods. This letter also sets out the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim with respect to consumption of monounsaturated fatty acids (MUFAs) from olive oil and a reduced risk of coronary heart disease.

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

In a review of a qualified health claim, FDA considers the data and information provided in the petition, in addition to other data and information available to the agency that may assist in its review of the relationship between the substance and the disease or health-related condition. Consistent with its guidance entitled "Interim Evidence-based Ranking System for Scientific Data,"[2] the agency evaluates the scientific studies to determine what studies are useful to its review in evaluating the relationship. The agency may conclude that certain design flaws in a study are so significant that the study may not be helpful to the agency's evaluation of the relationship. Such design flaws may include the lack of a control group or the lack of any statistical analysis of the data (Spilker et al., 1991; Federal Judicial Center, 2000).

In addition to human studies, FDA also considers other data and information in its review, such as meta-analyses[3], review articles[4], and animal[5] and *in vitro*[6] studies. These other types of data and information are useful in assisting the agency with an understanding of the scientific issues about a disease or health-related condition, but generally do not themselves establish a health claim relationship in the absence of supporting human intervention or observational data. After the agency decides what scientific studies are useful to its review about whether there is evidence to support a relationship between a substance and a disease or health-related condition, the agency categorizes these studies into: (1) most persuasive studies, which are studies the agency finds reliable in evaluating whether there is a relationship between the substance and disease outcome; and (2) less persuasive studies, which are studies that were designed in a way to make them less reliable in evaluating a substance/disease relationship or less applicable to the U.S. population. The most persuasive studies are given the greatest consideration. FDA rates the most and less persuasive studies independently for

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[2] This guidance published on July 10, 2003. (http://www.cfsan.fda.gov/~dms/hclmgui4.html).

[3] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (i.e., primary reports) (Spilker, p 793., 1991). FDA uses meta-analyses to identify relevant primary reports, which the Agency then evaluates individually.

[4] Review articles summarize the findings of primary reports. FDA uses review articles to identify primary reports that are relevant for review. FDA also uses review articles to identify information that is useful to understand the scientific issues about the substance-disease relationship (i.e., used as background information).

[5] The physiology of animals is different than that of humans, thus animals often respond differently to dietary interventions compared to humans.

[6] *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 that affect how humans respond to the consumption of foods and dietary substances. Therefore, *in vitro* studies generally are not able to provide scientific evidence about the relationship between a substance and disease risk.

methodological quality. Factors that determine whether a study is most or less persuasive are not used to determine study quality. This independent methodological quality rating is based on several criteria including study population characteristics, intervention design (e.g., presence of a placebo control versus a control without a placebo), data collection (e.g., dietary assessment method), the quality of the statistical analysis, and the validity of outcome measures. For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Lower methodological quality ratings (e.g., moderate and low) would be given based on the extent of the deficiencies or uncertainties in the methodological quality criteria.

Collectively, FDA then rates the strength of the total body of evidence that it determines is useful to its review, using criteria such as level of persuasiveness (most or less), the study type (e.g., intervention), methodological quality, quantity (number of the various types of studies and sample sizes), and consistency of the results. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, and then determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

The petition submitted 88 publications as evidence to substantiate the relationship for this claim. These publications consisted of 72 intervention studies, four meta-analysis articles, three observational studies, one *in vitro* study, and eight review articles (see petition in Docket # 2003Q-0559).

The agency did not consider all the publications cited in the petition to be useful in its review of this substance/disease relationship. While useful for background information, the review articles and meta-analyses did not contain sufficient information on the individual studies reviewed and therefore FDA could not determine their pertinence regarding factors such as the study population characteristics or the composition of the products used. Similarly, the lack of detailed information on the studies summarized in the review articles and meta-analysis studies did not allow FDA to determine if the studies are flawed in critical elements such as its design, execution, and data analysis. FDA must be able to review the critical elements of a study to determine whether credible conclusions can be drawn from it. FDA did not consider the *in vitro* study that was submitted in the petition as providing any supportive information about the substance/disease relationship because the study was conducted in an artificial environment that could not mimic normal physiology that may be involved in the risk reduction of CHD, nor could the study mimic the human body's response to consumption of MUFAs from olive oil.

A. Substance

A health claim characterizes the relationship of any 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 MUFAs from olive oil as the substance for the proposed claim. MUFAs are fat components that occur naturally in

many foods. Therefore, the agency concludes that MUFAs from olive oil, identified in the petition, are a component of food and therefore meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

As stated previously, five of the nineteen comments concerned the substance that is the subject of the proposed qualified health claim petition. Three of these five comments suggested that all vegetable oils high in MUFAs be allowed to use the qualified health claim. While there are several vegetable oils high in MUFAs such as sunflower oil and high oleic safflower oil the subject of the current qualified heath claim petition is MUFAs from olive oil. Therefore, the agency reviewed the studies that evaluated the relationship between MUFAs from olive oil and CHD risk. The agency has not reviewed the scientific evidence concerning the relationship between MUFAs from all other vegetable oils and CHD risk because this information does not apply to the substance that is the subject of the proposed claim, nor did the petition contain all of the scientific evidence concerning the relationship between MUFAs from all vegetable oils and CHD. The remaining two comments requested FDA to allow the qualified health claim to be used in the labeling of all vegetable oils that are high in MUFAs as well as polyunsaturated fatty acids (PUFAs), provided the vegetable oils had high unsaturated fat to saturated fat ratios. One of these comments concluded that FDA should not allow for the qualified health claim petitioned by the North American Olive Oil Association unless the claim was broadened to include other vegetable oils high in MUFAs and/or PUFAs. FDA does not agree that the present qualified health claim should be delayed for the comment's reasons. The substance of the present qualified health claim petition is MUFAs from olive oil. Accordingly, the agency has evaluated the scientific evidence in the petition and determined that a qualified health claim characterizing the relationship between MUFAs from olive oil and CHD risk is appropriate. The agency has not, however, reviewed the scientific evidence concerning PUFAs from all vegetable oils and CHD risk. This comment also requested that FDA consider their comment as a separate request (i.e., petition) for vegetable oils with high levels of MUFAs and PUFAs relative to saturated fatty acids (SFAs) and CHD risk. FDA does not consider a comment as a health claim petition unless it includes the information required under 21 CFR 101.70 and this comment did not contain all of the information required under 21 CFR 101.70.

FDA has not been petitioned to authorize a health claim or allow a qualified health claim for any vegetable oil high in MUFAs and/or PUFAs, except for olive oil, which is high in MUFAs. However, vegetable oil manufactures and others may petition the agency to allow for the use of claims for vegetable oils high in MUFAs and/or PUFAs relative to saturated fatty acids (SFAs). Health claim petitions must include all of the information required in 21 CFR 101.70, including scientific evidence that supports the relationship between a substance and a disease or health-related condition.

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 CHD as the

disease that is the subject of the proposed qualified health claim. The agency concludes that CHD 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)(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 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 Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is GRAS, approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)).

The petition asserts that MUFAs are ubiquitous, natural components of the food supply and provide nutritive value to the diet under 21 CFR 101.14(b)(3)(i), by serving as a key source of energy. FDA agrees that MUFAs are ubiquitous, natural components of the food supply that provide nutritive value to the diet. Furthermore, the agency notes that MUFAs from olive oil have historically been consumed as part of the diet over a wide range of consumption levels.

The Institute of Medicine (IOM) has not set an Adequate Intake, an Estimated Average Requirement, or a Recommended Dietary Allowance for MUFAs because there is no evidence to indicate that MUFAs are essential in the diet, and MUFAs have no known independent role in preventing chronic diseases (IOM, chapter 8, p. 8-30, 2002). Based on the lack of data on adverse effects of MUFAs, a Tolerable Upper Intake Level has not been set (IOM, chapter 8, p 8-51, 2002). The IOM has, however, set an Acceptable Macronutrient Distribution Range (AMDR) for total fat, which is 20 to 35% of total energy (IOM, chapter 8, 2002). Based on data in the Continuing Survey of Food Intakes by Individuals, 1994-1996, 1998, the median MUFA intake ranged from approximately 25 to 39 g per day for men and 18 to 24 g per day for women and the mean daily intake of MUFAs in the U.S. in all individuals is 28.7 g, which corresponds to 258 calories (IOM, chapter 8, p 8-41, 2002). Data from the 1987 – 1988 Nationwide Food Consumption Survey indicated that mean intakes of MUFAs were 13.6 to 14.3% of energy (IOM, chapter 8, p 8-41, 2002).

FDA has determined that in order to receive a possible benefit from consumption of MUFAs from olive oil and a reduced risk of CHD, the scientific evidence suggests that the daily minimum amount of MUFAs from olive oil that should be consumed in place of foods high in SFAs, while not increasing caloric intake is approximately 17.5 g of MUFAs, which corresponds to about 23 g of olive oil (see Section F). An intake of 17.5 g of MUFAs provides 157 calories. If 17.5 g of MUFAs from olive oil were added to the average U.S. diet MUFAs would comprise roughly 21% of the average daily caloric intake, which is below the AMDR for total fat. Further, the qualified health claim specifies that MUFAs from olive oil are to replace SFAs in the diet while not increasing

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

Approximately 92% of total dietary MUFAs are oleic acid, which is an n-9 cis monounsaturated fatty acid (IOM, chapter 8, 2002). Oleic acid has been specifically authorized for direct addition to food under 21 CFR 172.860. According to 21 CFR 172.860, oleic acid may be safely used in foods as a lubricant, binder, and as a defoaming agent in accordance with good manufacturing practice or as a component in the manufacture of other food-grade additives.

MUFAs are ubiquitous, natural components of the food supply that provide nutritive value to the diet, the level of MUFAs from olive oil necessary to justify the claim is well below the AMDR for total fat, and the major MUFA component from olive oil has been approved as a direct food additive. Therefore, FDA concludes that under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), that the use of MUFAs from olive oil at 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 endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation: coronary events (MI, ischemia), cardiovascular death, atherosclerosis, high blood pressure, serum total cholesterol, and serum LDL-cholesterol. High blood pressure, serum total cholesterol, and serum LDL-cholesterol levels are considered surrogate endpoints for CHD.[7] Low HDL-cholesterol levels are considered a risk factor for CHD (NIH Consensus Conference, 1993). Atherosclerosis is the underlying cause of CHD, which can lead to the signs of CHD including coronary events (MI, ischemia) and cardiovascular death, high blood pressure, serum total cholesterol, and serum LDL- cholesterol.[8] To evaluate the potential effects of MUFAs from olive oil on CHD risk, these types of disease measures were considered.

A. Assessment of the Intervention Studies

FDA identified a total of 73 intervention studies for its review of this qualified health claim (see petition in Docket # 2003Q-0559). In addition to the intervention studies in your petition, FDA considered one additional intervention study by Jansen et al., (1999) from a PubMed literature search. FDA did not consider 61 of these studies useful in its evaluation of a substance-disease relationship for the following reasons (see appendix #1): 1) The source of MUFAs was not from olive oil or the MUFA source was from several types of MUFA-containing oils, and thus FDA could not determine if the effects

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[7] 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, Page 3 (U.S. Department of Health and Human Services, 2001, http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm)

[8] 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, Page 3 (U.S. Department of Health and Human Services, 2001, http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm)[8] See footnote # 7

were from olive oil; 2) the macronutrient or dietary cholesterol intakes differed greatly between the intervention and control groups. Such large differences in nutrient intakes makes it difficult to clearly delineate what may be causing a change in serum cholesterol levels; thus, the results of the study could not be interpreted; 3) the duration of the study intervention was too short (less than three weeks) to adequately determine if changes in serum cholesterol levels were reflective of the intervention treatment (Bonanome et al., 1988); 4) the studies were designed to determine if fish oils were beneficial to heart disease with olive oil used as a control source (not an intervention) and therefore lacked an adequate control for olive oil; and 5) other reasons including inappropriate experimental design (diets were comparing similar amounts of MUFAs), statistics (no statistical comparisons between the two intervention diets, thus we are unable to determine the differences between the control and intervention diet), or not measuring valid surrogate endpoints for CHD (e.g., total- and LDL- cholesterol levels).

Thus, FDA considered 12 intervention studies (Kris-Etherton et al., 1993; Mata et al., 1992; Jansen et al., 1999; Fuentes et al., 2001; Kris-Etherton et al., 1999; Choudhurry et al., 1995; Kratz et al., 2002; Lichenstein et al., 1993; Ng et al. 1992; Mensink et al., 1987; Pederson et al., 2000; Nydahl et al., 1994) as useful in the agency's evaluation of the substance/disease relationship. There were four most persuasive studies that addressed the substance/disease relationship, measuring the risk reduction of the disease itself for an accepted surrogate endpoint for the disease in a general healthy population that is relevant to the U.S. population (Kris-Etherton et al., 1993; Mata et al., 1992; Jansen et al., 1999; Fuentes et al., 2001). The four most persuasive studies had adequate intervention time to allow blood lipid levels to reflect dietary interventions, sufficient control groups, and dietary cholesterol levels were the same between the control and intervention groups. All of these studies received high or moderate ratings for methodological quality factors.

A randomized double-blind crossover trial performed in 33 healthy young males (mean age of 26) from the United States (Kris-Etherton et al., 1993) compared diets high in SFAs from butter or cocoa butter, high in MUFAs from olive oil, or high in PUFAs from soybean oil. The four diets (butter, cocoa butter, olive oil, or soybean oil) contained similar amounts of energy, protein, carbohydrates, dietary cholesterol, and total fat. Each subject was on each dietary intervention for 26 days. The MUFA/olive oil diet replaced approximately 14% of total daily calories from SFAs with MUFAs from olive oil. The PUFA/soybean oil diet replaced approximately 14% of total daily calories from SFAs with PUFAs from soybean oil. Replacing SFAs with MUFAs from olive oil or with PUFAs from soybean oil significantly ($p<0.05$) lowered total and LDL-cholesterol levels in these subjects compared to the butter and cocoa butter containing diets. None of the diets altered HDL-cholesterol levels in the subjects.

A non-randomized and non-blinded crossover intervention trial reported by Mata et al. (1992) used 21 normolipidemic women (mean age 43) from Spain to compare high SFA, MUFA (from olive oil), or PUFA (from sunflower oil) containing diets on serum lipid levels. The SFA-, MUFA-, and PUFA-containing diets had similar amounts of energy, total fat, protein, carbohydrates, and dietary cholesterol. The subjects were on each diet (SFA, MUFA, and PUFA) for four weeks. The MUFA/olive oil diet replaced

approximately 8% of total daily calories from SFAs with MUFAs from olive oil and the PUFA/sunflower diet replaced approximately 8% of total daily calories from SFAs with PUFAs from sunflower oil. Replacing SFAs with MUFAs from olive oil and with PUFAs from sunflower oil significantly ($p<0.05$) lowered the total and LDL-cholesterol levels in these subjects. The MUFA diet significantly increased ($p<0.05$) HDL-cholesterol levels while the PUFA diet significantly lowered ($p<0.05$) HDL-cholesterol levels compared to the SFA containing diet.

A non-randomized and non-blinded crossover intervention study by Jansen et al. (1999) compared a MUFA containing diet (olive oil rich diet), a National Cholesterol Education Program (NCEP) Step I diet (low fat diet, but the SFA is replaced with carbohydrates) and a high SFA containing diet in 41 healthy males (mean age 20) from Spain. The MUFA, NCEP, and high SFA diets had similar amounts of energy, protein, and dietary cholesterol. The subjects followed each diet (MUFA, NCEP and SFA) for four weeks. The MUFA/olive oil diet replaced approximately 13% of total daily calories from SFAs with MUFAs from olive oil, both diets contained similar amounts of total fat and carbohydrates. The NCEP diet decreased the calories from total fat/SFA by 10% and increased the total carbohydrate intake by 10% compared to the SFA diet. All of the dietary interventions were isocaloric. The MUFA and NCEP dietary interventions significantly ($p<0.05$) lowered the total and LDL-cholesterol levels in these subjects compared to the SFA diet. The NCEP diet significantly ($p<0.05$) decreased HDL-cholesterol levels compared to the SFA diet. The MUFA diet did not alter HDL-cholesterol compared to the SFA diet.

A study by Fuentes et al. (2001) placed 22 healthy males (mean age 40.5 years old) with moderately elevated cholesterol levels from Spain on a high SFA-containing diet for four weeks. The subjects were then randomized and placed either on diets high in MUFAs (olive oil) or a NCEP Step I diet for four weeks. After four weeks, the subjects were then placed on the other dietary intervention (NCEP or olive oil diet, respectively). All of the diets had similar levels of protein and dietary cholesterol. Approximately 10% of the total daily calories from SFAs from the SFA diet were replaced by MUFAs or carbohydrates for the MUFA/olive oil or NCEP Step I diets, respectively. Both MUFA/olive oil and NCEP Step I diets significantly ($p<0.05$) lowered total and LDL-cholesterol compared to a diet high in SFAs. There were no differences in HDL cholesterol between the SFA, MUFA, or NCEP Step I diet groups.

Eight less persuasive intervention studies were considered for this claim (Kris-Etherton et al., 1999; Choudhurry et al., 1995; Kratz et al., 2002; Lichenstein et al., 1993; Ng et al. 1992; Mensink et al., 1987; Pederson et al., 2000; Nydahl et al., 1994). These studies were considered less persuasive because of the following factors: 1) moderate differences in the intake of dietary cholesterol between control and intervention groups that could affect the outcome marker, 2) insufficient controls (e.g., compared MUFA and PUFA containing diets), and/or 3) an intervention time of less than 4 weeks but greater than 3 weeks (a shorter intervention time may not allow blood lipid levels to fully reflect dietary interventions). All of these studies received high or moderate ratings for methodological quality factors. A brief synopsis of the results from each study is outlined below.

A crossover intervention study comparing a high SFA diet, a NCEP low fat Step II diet (diet low in SFAs but high in carbohydrates) and three different MUFA (olive oil, peanut oil, or peanut butter) containing diets was performed in healthy adults from the United States (Kris-Etherton et al., 1999). All of the dietary interventions significantly ($p<0.05$) reduced the total and LDL- cholesterol levels compared to the high SFA diet. However, HDL-cholesterol was significantly lower ($p<0.05$) in the NCEP diet group compared to the SFA diet. The MUFA-olive oil diet did not alter HDL-cholesterol compared to the SFA diet. Another study by Kratz et al. (2002) demonstrated that a high MUFA containing diet (olive oil) and high PUFA containing diet (sunflower oil) significantly ($p<0.05$) reduced total, HDL-, and LDL- cholesterol levels compared to a high SFA diet given at the beginning of the study period. Lichtenstein et al. (1993) compared two high MUFA diets (olive oil and canola oil), a high PUFA diet (corn oil) and a high SFA diet in middle aged adults from the United States. The olive, canola, and corn oil intervention diets significantly ($p<0.05$) lowered total and LDL- cholesterol levels compared to the SFA diet. Both the canola and corn oil diets significantly ($p\leq0.05$) reduced HDL-cholesterol levels compared to the SFA diet; the olive oil diet did not effect HDL-cholesterol levels compared to the SFA diet group.

A study by Ng et al. (1992) compared three different diets, two high in SFA (coconut or palm oil) and a high MUFA containing diet (olive oil). The results from this study were inconclusive; total and LDL-cholesterol levels were significantly lower in the olive oil group compared to coconut oil, however there were no differences in cholesterol levels between the palm and olive oil diets. The coconut and palm oil diets are high in SFAs; however, the palm oil did contain a higher percentage of MUFAs and PUFAs compared to the coconut oil.

Mensink et al. (1987) compared a diet high in MUFAs (olive oil), high in SFAs, and low-fat high carbohydrate diet on total cholesterol levels in 48 healthy adults in the Netherlands. There were no changes in total cholesterol levels between the groups; LDL-cholesterol was not measured. HDL-cholesterol was significantly increased ($p<0.05$) in the MUFA diet compared the SFA diet. The high carbohydrate diet significantly decreased ($p<0.05$) HDL-cholesterol compared to the SFA diet group. An intervention study conducted by Choundry et al. (1995) in 21 healthy young adults from Australia found no changes in total, HDL-, or LDL- cholesterol levels when a high SFA diet (palm oil) was compared to a high MUFA diet (olive oil). A crossover study performed in 21 hyperlipidemic adults (Nydahl et al., 1994) compared two diets, a high MUFA diet (olive oil), and a high PUFA diet (corn oil). There were no differences in total, HDL- or LDL-cholesterol levels between the olive oil and corn oil containing diets. Pedersen et al. (2000) evaluated if diets high in MUFAs (olive oil), moderate in MUFAs and PUFAs (rapeseed oil), or high in PUFAs (sunflower oil) could alter the cholesterol levels in 18 healthy men from Sweden. A high SFA diet was not used as a control in this study. There were no differences in the total or HDL-cholesterol levels among the olive, rapeseed, and sunflower oil containing diets. The rapeseed and sunflower oil containing diets had a significantly ($p<0.05$) lower LDL-cholesterol levels compared to the olive oil containing diet.

B. Assessment of Observational Studies

Of the three observational studies submitted, none of the studies specifically evaluated MUFAs from olive oil and CHD or validated surrogate endpoints. Therefore, these studies were not considered as capable of evaluating the substance/disease relationship.

III. Strength of the Scientific Evidence

FDA rated the strength of the body of scientific evidence based on the following factors: the level of persuasiveness (most or less persuasive), study type (intervention), study methodological quality, quantity (number of studies and subjects per study), consistency of the findings, and applicability to the general U.S. population. FDA relies principally on human studies that are primary reports of data collection when attempting to establish a substance-disease relationship and has consistently identified two endpoints with which to identify disease risk reduction for purposes of health claims evaluations: a) reduction in incidence of a disease, and; b) beneficial changes in surrogate endpoints for the disease[9].

The evidence for a relationship between MUFAs from olive oil and reduced risk of CHD were from 12 intervention studies that directly evaluated the effect of replacing MUFAs from olive oil with SFAs on serum total-, LDL, and or HDL-cholesterol levels. The studies were conducted in the U.S. as well as a variety of developed countries. The intervention diets contained similar macronutrient profiles, (i.e., total fat, protein and carbohydrate were similar in the SFA and MUFA diets across studies) and all of the subjects were generally healthy. The four most persuasive studies (Kris-Etherton et al., 1993; Mata et al., 1992; Jansen et al., 1999; Fuentes et al., 2001) had small sample sizes (range from 21-41 subjects), which represented a total of 117 subjects and the majority of subjects (82%) in these studies were young healthy men. The study populations in these studies were relevant to the general healthy U.S. population. The duration of these studies (approximately 28 days) was long enough to show the effect of the intervention despite possible differences in background diets, and there were no other intervening factors (e.g., genetic, environmental) that the agency identified that might confound the results, as applied to the U.S. population. However, the fact that the studies were primarily done on young men limits to some degree the relevance of the studies to the entire U.S. population. Further, the fact that each study had such few subjects also limits the findings of these studies. With these limitations, there was a significant ($p<0.05$) decrease in serum total and/or LDL-cholesterol levels when MUFAs from olive oil replaced SFAs in the diet in the four most persuasive studies. In addition, MUFAs did not decrease HDL-cholesterol in the majority of these studies, and decreased HDL-cholesterol is a risk factor for CHD. The most persuasive studies provide some evidence to suggest that altering the fat composition of the diet by replacing SFAs with MUFAs from olive oil lowers serum total and LDL-cholesterol levels and has no effect on HDL-cholesterol.

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[9] Interim Evidence-based Ranking System for Scientific Data, July 10, 2003. (http://www.cfsan.fda.gov/~dms/hclmgui4.html).

All eight of the less persuasive studies included small sample sizes (range 15-58 subjects per study) (Kris-Etherton et al., 1999; 1995; Kratz et al., 2002; Lictenstein et al. 1993; Ng et al., 1992; Mensink et al., 1987; Pederson et al., 2000; Nydahl et al., 1994; Choudhurry et al., 1995). There was a significant ($p<0.05$) decrease in total and/or LDL-cholesterol levels when MUFAs from olive oil replaced SFAs in the diet in three of the eight less persuasive studies (Kris-Etherton et al., 1999; 1995; Kratz et al., 2002; Lictenstein et al., 1993). MUFAs did not alter HDL levels in the majority of these studies.

In summary, four most persuasive studies that collectively represent 117 subjects provide some evidence to suggest a relationship between replacing one fat, SFAs, with another, MUFAs from olive oil, and reduced risk of coronary heart disease. The majority of less persuasive studies did not observe a relationship between MUFAs from olive oil and reduced risk of CHD. None of the most persuasive or less persuasive studies suggested that MUFAs from olive oil, independent of SFAs displacement, would lower serum total and LDL-cholesterol levels. The petitioner recognized this in their scientific review (page nine second paragraph) "the majority of their (MUFAs) benefit is likely due to the fact that they can displace saturated and *trans* fatty acids in the diet."

Based on FDA's review of the strength of the total body of scientific evidence for the proposed claim, FDA concludes that the scientific evidence is credible and supports the substance/disease relationship. However, due to the small number of subjects in the 4 most persuasive studies, the fact that the majority of the most persuasive studies examined only a subset of the target population (young males), and the fact that the majority of the less persuasive studies did not suggest a reduced risk of CHD, FDA believes that the scientific evidence represents a low level of comfort among qualified scientists that the claimed relationship is scientifically valid. Therefore, FDA intends to consider the exercise of its enforcement discretion for a qualified health claim about MUFAs from olive oil on the label or in labeling of olive oil that includes a truthful and non-misleading description of the strength of the body of scientific evidence, e.g., "limited but not conclusive scientific evidence suggests." However, in order for the claim to be truthful and not misleading, the agency will consider, as a factor in the exercise of its enforcement discretion, that the claim specify that MUFAs from olive oil need to replace SFAs sources of fat in the diet while not increasing caloric intake. Other factors that FDA intends to consider in deciding whether to exercise its enforcement discretion with regard to the use of this qualified health claim on particular foods are discussed below.

IV. Other Enforcement Discretion Factors

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

For the purpose of this enforcement discretion letter, the following definitions will be used: (1) "olive oil" means products that are essentially pure olive oil and are labeled as

such[10]; (2) "vegetable oil spread" means margarine (21 CFR 166.110) and margarine-like products, formulated to contain olive oil; (3) "dressings for salads" means dressings for salads formulated to contain olive oil; (4) "shortenings" means vegetable oil shortenings, formulated to contain olive oil; and (5) "olive oil-containing foods" means all other foods, such as sauces or baked goods, formulated to contain olive oil, excluding olive oil, vegetable oil spreads, dressings for salads, and shortenings. The term "olive oil products" refers to items 2 – 5 in the above list. Approximately 97% of olive oil is fat in the form of glycerides the remaining components of olive oil are diglycerides, monoglycerides, and other classes of compounds (Bailey's Industrial Oil and Fat Products, p. 254 – 258, 1996).

Based on data provided by the United States Department of Agriculture, olive oil contains approximately 13% SFAs, 74% MUFAs, and 10% PUFAs (U.S. Department of Agriculture, Agricultural Research Service. 2004. USDA Nutrient Database for Standard Reference, Release 17. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp).

A. Total fat, Saturated Fat, and Cholesterol Criteria for 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 MUFAs from olive oil and CHD risk on olive oil, vegetable oil spreads, dressings for salads, shortenings and olive oil-containing foods. Later in Section B, FDA discusses total fat, saturated fat, and cholesterol 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 reference amount customarily consumed (RACC), or, for foods with a RACC of less than 30 g or less than 2 tablespoons, per 50 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, while total fat is not

[10] FDA intends to exercise its enforcement discretion for olive oil and certain products containing olive oil, as such products were included in the studies that suggested benefit. For purposes of this letter, "olive oil" means virgin olive oil, or blends of virgin olive oil and refined olive oil. "Virgin olive oil" means the oil resulting from the first pressing of olives and is suitable for human consumption without further processing. "Refined olive oil" means oil obtained from subsequent pressings and which is suitable for human consumption by refining processes which neutralize the acidity or remove particulate matter. We do not intend to exercise our enforcement discretion for other types of oils.

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 calorie intakes. There have been several exceptions to this criterion in the past. Products derived from whole soybeans without added fat are exempted from the "low fat" criterion in the soy protein and CHD health claim (21 CFR 101.82(c)(2)(iii)(C)). In the plant sterol/stanol esters and CHD health claim, FDA does not require foods bearing the claim to meet the "low fat" criterion but requires that total fat level of foods not exceed the total fat disqualifying level (21 CFR 101.14(a)(4)) with an exception for spreads and dressings for salads on a per 50 g basis (21 CFR 101.83(c)(2)(iii)(C)). In not requiring the "low fat" criterion, FDA noted that the Dietary Guidelines for Americans, 2000 (USDA & DHHS, 2000) 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.

Olive oil exceeds the "low fat" criterion because it is essentially entirely fat. Furthermore, FDA intends to exercise enforcement discretion for olive oil products that contain 6 g or more olive oil per RACC (see Section F), and thus would not meet the "low fat" criterion. The most and less persuasive scientific studies that suggest a relationship between MUFAs from olive oil in replacement of SFAs and reduced risk of CHD used olive oil in cooking, as well as several types of foods containing olive oil. The MUFAs from olive oil and CHD qualified health claim will inform consumers that they may lower their risk of CHD by consuming MUFAs from olive oil and olive oil products in place of 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 since olive oil contains no cholesterol and less saturated fat than other fat sources. Olive oil is a plant food and does not contain cholesterol. Furthermore, FDA concurs with current dietary guidelines that consuming diets low in saturated fat and cholesterol 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 olive oil, vegetable oil spreads, dressings for salads, shortenings, and olive oil-containing foods that bear a MUFAs from olive 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. A RACC of olive oil contains approximately 1.8 g of saturated fat and 13.5% of calories from saturated fat.

Olive oil does not meet the definition of a "low saturated fat" food. Furthermore, FDA intends to exercise enforcement discretion for olive oil products that contain 6 g or more

olive oil per RACC (see Section F). Six grams of olive oil contains approximately 0.8 g of SFAs and olive oil products that contain this amount of SFAs from olive oil alone are likely to exceed the "low saturated fat" criterion. The most and less persuasive scientific studies that suggest a relationship between MUFAs from olive oil in replacement of SFAs and reduced risk of CHD used olive oil in cooking, as well as several types of foods containing olive oil. The MUFAs from olive oil and CHD qualified health claim will inform consumers that they may lower their risk of CHD by consuming MUFAs from olive oil in place of 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, since olive oil contains no cholesterol and less saturated fat than other fat sources. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that olive oil, vegetable oil spreads, dressings for salads, shortening, and olive-oil containing foods that bear a MUFAs from olive oil and CHD qualified health claim meet the "low saturated fat" criterion.

FDA does, however, believe that it would be appropriate to consider, as a factor in the exercise of its enforcement discretion, that olive oil when labeled with a MUFAs from olive 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. Furthermore, FDA believes that it would be appropriate to consider, as a factor in the exercise of its enforcement discretion that olive oil products that bear a MUFAs from olive oil and CHD qualified health claim and do not meet the "low saturated fat" criteria also 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.

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 SFAs.

"Low cholesterol" criterion

Like all plant-based foods, olive oil does not contain cholesterol, and therefore, a low cholesterol nutrient content requirement would not limit the use of a qualified health claim for MUFAs from olive oil and CHD risk to be used on the label or in labeling of olive oil. Several vegetable oil spreads, dressings for salads, shortenings and olive oil-containing foods may contain cholesterol from sources other than olive 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 olive oil, vegetable oil spreads, dressings for salads, shortenings and olive oil-containing foods labeled with a MUFAs from olive oil and

CHD qualified health claim meet the "low cholesterol" criteria as defined in 21 CFR 101.62(d)(2).

B. 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 § 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 MUFAs from olive oil and CHD qualified health claims on olive oil, vegetable oil spreads, dressings for salads, shortenings and olive oil-containing foods are discussed below. FDA does not intend to exercise its enforcement discretion for any type of meal product (21 CFR 101.13(l)) or main dish product (21 CFR 101.13(m)), as none of the scientific evidence that suggested a relationship between MUFAs from olive oil in replacement of SFAs and reduced risk of CHD used these types of foods.

"Total fat" disqualifying levels

In the previous section (Section IV A), FDA explained that the agency has decided not to consider, in the exercise of its enforcement discretion, that olive oil, vegetable spreads, dressings for salads, shortenings, and olive oil-containing foods that bear a MUFAs from olive oil and reduced risk of 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.

Olive oil exceeds the disqualifying total fat level because it is essentially entirely fat. However, the MUFAs from olive oil and CHD qualified health claim will inform consumers that they might lower their risk of CHD by consuming foods containing MUFAs from olive oil in place of similar foods high 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 that consuming diets low in saturated fat and cholesterol 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 olive oil meet the disqualifying total fat level to bear a MUFAs from olive oil and CHD qualified health claim.

The most and least persuasive scientific studies that suggest a relationship between MUFAs from olive oil in replacement of SFAs and reduced risk of CHD used olive oil incorporated into several types of foods that are traditionally high in fat, namely vegetable oil spreads, dressings for salads, and shortenings. Products labeled as margarine (21 CFR 166.110) must contain at least 80% vegetable oil by weight[11] and shortenings are essentially all fat. Foods that contain these levels of fat will necessarily exceed the disqualifying total fat level. 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 relationship, from bearing the claim. Olive oil-containing foods are generally not vehicles for delivering fat. However, given that FDA intends to exercise enforcement discretion for olive oil products that contain 6 g or more olive oil per RACC, and the food may be formulated with additional olive oil and still contribute to the claimed effect, FDA concludes that applying the disqualifying levels of total fat to olive oil-containing foods would unduly limit the foods that could contribute to beneficial effects from bearing the claim. Further, FDA has concluded that foods labeled with a MUFAs from olive oil and 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 SFAs and more MUFAs 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 olive-oil containing foods that bear a MUFAs from olive oil and CHD qualified health claim meet the total disqualifying 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) required by 21 CFR 101.13(h) must be placed immediately adjacent to and directly beneath the claim, with no intervening material, in the same size, typeface, and contrast as the claim itself.

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[11] FDA recognizes that margarine-like products do not have to meet the fat criteria as defined in the standards of identity for margarine (21 CFR 166.110).

"Saturated fat" disqualifying level

In the previous section (Section IV A), FDA explained that the agency has decided not to consider, in the exercise of its enforcement discretion, that olive oil, vegetable oil spreads, dressings for salads, shortenings, and olive oil-containing foods that bear a MUFAs from olive 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 and 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.

Olive oil has 1.8 g of saturated fat per RACC, and because it has a small RACC (i.e., 30 g or less) olive oil will exceed the disqualifying saturated fat level based on the 50 gram-criterion (olive oil contains 6.7 g of saturated fat per 50 g (USDA Nutrient Database for Standard Reference, Release 17)). Margarine (21 CFR 166.110) is at least 80% vegetable oil by weight and shortening is essentially all fat and both products have a RACC of 30 g or less. If formulated with olive oil as the only vegetable oil source, 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 MUFAs from olive oil and a reduced risk of CHD would assist consumers in maintaining healthy dietary practices, since the information in the claim informs consumers that replacing SFAs in the diet with MUFAs from olive 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 olive oil products, which were included in the scientific studies that suggested a relationship, from bearing the claim. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that olive oil, vegetable oil spreads, and shortenings that bear a MUFAs from olive oil and CHD qualified health claim meet the 50 gram-criterion for the disqualifying saturated fat level. FDA does intend to consider, as a factor in the exercise of its enforcement discretion that olive oil, vegetable oil spreads or shortenings labeled with the MUFAs from olive oil and CHD qualified health claim, meet the 4g 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 olive oil and no other source of fat will contain about 2.3 g saturated fat per 50 grams. Unless there were other sources of saturated fat in the dressing for salad, a dressing formulated with up to 50% olive 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 intends to consider, as a factor in the exercise of its enforcement discretion that dressings for salads, when labeled with the MUFAs from olive oil and CHD qualified health claim, meet the 50 gram-criterion for the disqualifying saturated fat level.

Olive oil-containing foods are generally not vehicles for delivering fat, unlike olive 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 6g olive oil per serving, an olive 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 olive oil-containing foods have a RACC greater than 30 grams). Unless there were other sources of saturated fat in the olive oil-containing food, the food should be able to meet the 50 gram-criterion for the disqualifying saturated fat level. FDA believes that excusing olive oil-containing foods from the 50 gram-criterion for the disqualifying saturated fat level would not assist consumers in maintaining healthy dietary practices. Thus, FDA intends to consider, as a factor in the exercise of its enforcement discretion for the use of a MUFAs from olive oil and CHD qualified health claim on the label and in the labeling of olive-oil containing foods that meet the disqualifying saturated fat level.

C. 10 Percent 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 A, vitamin C, 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, the agency exempted spreads and dressings for salads from this requirement in the plant sterol/stanol esters and CHD health claim interim final rule (65 FR 54868 at 54711). More recently, FDA considered a qualified health claim for walnuts and a reduced risk of CHD, even though walnuts did not meet the minimum 10% nutrient requirement. (Walnuts and Heart Disease Enforcement Discretion Letter http://www.cfsan.fda.gov/~dms/qhcnuts3.html).

Olive 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, olive oil, certain vegetable oil spreads, dressings for salads and shortenings provide MUFAs 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 olive oil products, which were included in the scientific studies that suggested a relationship, from bearing the claim. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that olive oil, dressings for salads, and shortenings that bear a

MUFAs from olive oil and CHD qualified health claim meet the 10% minimum nutrient content requirement.

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 a MUFAs from olive oil and CHD qualified health claim meet the 10% minimum nutrient content requirement.

FDA also considers it appropriate that olive oil-containing foods meet the 10% minimum nutrient content requirement. Olive oil-containing foods are generally not vehicles for delivering fat, unlike olive oil, vegetable oil spreads, and shortenings, 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. FDA believes that several olive oil-containing foods can be formulated to contain enough olive oil to be eligible for the claim and meet the 10% minimum nutrient content requirement. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion that olive oil-containing foods labeled with a MUFAs from olive oil and CHD claim meet the 10% minimum nutrient content requirement.

"Cholesterol" disqualifying level

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

D. Trans Fat Levels in Foods Eligible for the Claim

The petitioner requested that olive 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 report, chapters 8, 9, and 11, 2002). FDA has issued an advanced notice of proposed rulemaking (ANPRM) to solicit comments on establishing *trans* fat nutrient content claims; to establish qualifying criteria for *trans* fat in current nutrient content claims for saturated fatty acids and cholesterol, lean and extra lean claims and health claims that contain a message about cholesterol-raising lipids; and, in addition, to establish disclosure and disqualifying criteria to help consumers make healthy food choices. The agency also solicited

comment on whether it should consider statements about *trans* fat, either alone or in combination with saturated fat and cholesterol, as a footnote in the Nutrition Facts panel or as a disclosure statement in conjunction with claims (68 FR 41507; July 11, 2003). FDA intends to consider the petitioner's request, that olive oil products contain no more than 1 gram *trans* fatty acids per RACC, in the context of the agency's activities related to the ANPRM. FDA believes that it would be premature to consider, as a factor in the exercise of its enforcement discretion, a specific nutrient disqualifying level for a MUFAs from olive oil and CHD risk reduction qualified health claim, until it has evaluated the merits of a level based on the data and information it is currently evaluating in the context of the ANPRM. Therefore, FDA declines the petitioner's request to consider a *trans* fat qualifying level as a factor in the exercise of its enforcement discretion for this qualified health claim.

E. Context of the total daily diet

A provision of the general requirements for health claims requires 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 § 403(r)(3)(B)(iii) of the Act (21 U.S.C. § 343(r)(3)(B)(iii)) and 21 CFR 101.14(d)(2)(v)). For health claims pertaining to CHD that are authorized by regulation, FDA requires information relative to a total diet low in saturated fat and cholesterol because this is an essential part of dietary guidance for reducing the risk of CHD. However, the information in the MUFAs from olive oil and CHD qualified health claim will provide consumers a method to reduce saturated fat and cholesterol intake, i.e., by consuming MUFAs from olive oil and olive oil products in place of SFAs. Further, the most and less persuasive scientific studies did not suggest that the intervention diet must be low in cholesterol (< 300 mg per day) in order to reduce the risk of CHD. Thus, FDA will not consider, as a factor in the exercise of its enforcement discretion, the use of a phrase or sentence relating to diets low in saturated fat and cholesterol.

F. Minimum Effective Amount of Olive Oil in Foods Eligible for the Claim

The general requirements for health claims require 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 the appropriate form to justify the claim. Where no definition of high has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)).

The agency determined the minimum effective amount of MUFAs from olive oil necessary to substitute in place of SFAs by first calculating the difference in the amount of MUFAs, in grams,[12] between the high-MUFA and high-SFA diets in the four most persuasive studies and eight less persuasive studies. This limited evidence suggests that the lowest amount of MUFAs needed to replace SFAs that may result in significant reduction in serum total and LDL-cholesterol is 17.5 g of MUFAs. Olive oil contains

[12] The amount of MUFAs in grams was calculated by multiplying the percent of energy by 2000 kcal and converting to grams.

approximately 74% MUFAs (USDA Nutrient Database for Standard Reference, Release 17). Consuming 23 g of olive oil per day provides 17.5 g of MUFAs. Twenty-three grams of olive oil is equivalent to 1.7 tablespoons, or approximately 2 tablespoons. The RACC for olive oil is one tablespoon, which contains 11 g of MUFAs and 1.8 g of SFAs.

To determine the minimum amount of olive oil necessary to be in a food, the agency considered the number of eating occasions at which consumers might consume olive oil or olive oil products and the number of potential foods that could be labeled with a qualified health claim about MUFAs from olive oil and CHD. Foods in these categories can be part of every eating occasion, and the typical American eating pattern is three meals and one snack per day. Therefore, the determination of the qualifying level of MUFAs from olive oil for a food to bear the claim will be based on four eating occasions per day. The minimum effective dose (23 g olive oil per day) based on four eating occasions per day of olive oil or the four categories of olive oil-containing products is 6 g of olive oil per RACC per day. For consumers to know the amount of olive oil in a product, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that foods that bear a MUFAs from olive oil and CHD qualified health claim state the amount of olive oil per serving in the claim.

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with your petition, and other pertinent scientific evidence, FDA concludes that there is sufficient evidence for a qualified health claim, provided that the claim is appropriately worded so as to not mislead consumers. Thus, FDA intends to consider exercising enforcement discretion for the following qualified health claim:

> "Limited and not conclusive scientific evidence suggests that eating about 2 tablespoons (23 grams) of olive oil daily may reduce the risk of coronary heart disease due to the monounsaturated fat in olive oil. To achieve this possible benefit, olive 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 olive oil."

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.]" must also be 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 enforcement for the above qualified health claim when all other 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 a qualified health claim, or that raises safety concerns about that substance that is the subject of the claim.

Sincerely,

Robert E. Brackett, Ph.D.
Director
Center for Food Safety
and Applied Nutrition

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Appendix 1

Intervention Studies that were not used in further review:
Please See Docket # 2003Q-0559 for each study and full citation.

1. The source of MUFAs was not from olive oil or the MUFA source was from several types of MUFA containing oils

Ashton et al., 2001
Berry et al., 1991
Berry et al., 1992
Christiansen et al., 1997
Cleivadence et al., 1997
Dreon et al., 1990
Foster et al., 2003
Grundy et al., 1986
Gustaffson et al., 1994
Hodson et al., 2001
Howard et al., 1995
Jenkins et al., 1997
Lovejoy et al., 2002
Luscombe et al., 1999
Muller et al., 2003
O'Bynre et al., 1998
Rivellesse et al., 2003
Skoldstam et al., 2003
Sundrum et al., 1995
Truswell et al., 1992
Vessby et al., 2001
Wardlow et al., 1990
Williams et al., 1992

2. The macronutrient or dietary cholesterol intakes differed greatly between the intervention groups.

Baggio et al., 1988
Garg et al., 1998
Garg et al., 1992
Garg et al., 1994
Ginsberg et al., 1990
Grundy et al., 1988
Gumbiner et al., 1998
Lopez-Segura et al., 1996
Morgan et al., 1997
Rasmossen et al., 1993
Rodrigueaz-Villar et al., 2000

Strycher et al., 2003
Thomsen et al., 1999
de Lorgeril et al., 1999
Goldberg et al., 2000

3. The duration of the study intervention was too short (less than three weeks).

Gimeno et al., 2002
Madigan et al., 2000
Morgan et al., 1993
Wagner et al., 2001

4. The studies were designed to determine if fish oils were beneficial to heart disease with olive oil used as a control source not an intervention.

Conner et al., 1993
Donnelly et al., 1992
Flaten et al., 1990
Mori et al., 1992
Olszewski et al., 1992
Ramirez-Tortosa et al., 1999
Reis et al., 1989
Sacks et al., 1995

5. Other miscellaneous reasons including inappropriate experimental design, statistical issues, or not measuring valid surrogate endpoints of CHD

Babagallo et al., 1999
Kratz et al., 2003
Ouibina et al., 2001
Parker et al., 2002
Salachas et al., 1994
Sanders et al., 1994
Seppanen-Lasko et al., 1993
Sitori et al., 1992
Mensink et al, 1989
Nielson et al., 2002
Nicolaew et al., 1998