



MAR 9 2004

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Covington & Burling  
1201 Pennsylvania Avenue N.W.  
Washington, DC 20004-2401

RE: Health Claim Petition: Walnuts and Coronary Heart Disease (Docket No. 02P-0292)

Dear Ms. Taylor:

This letter responds to the health claim petition dated March 15, 2002, submitted to the Food and Drug Administration (FDA or the agency), on behalf of the California Walnut Commission, pursuant to Section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 343(r)(4)). The petition requested that the agency authorize a health claim characterizing the relationship between consumption of English walnuts and reduced risk of coronary heart disease (CHD) for use on labels and labeling of whole or chopped walnuts. The petition proposed as a model health claim: "Diets including walnuts can reduce the risk of heart disease."

FDA filed the petition for comprehensive review on June 21, 2002, in accordance with section 403(r)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21 of the Code of Federal Regulations (CFR) section 101.70(j). Following mutual agreement by you and FDA, the deadline for the agency's action was initially extended to December 18, 2002, and subsequently to February 28, 2003, June 16, 2003, and finally to July 14, 2003. During this period, FDA met with representatives of the petitioner on four occasions (March 24, 2003; May 13, 2003; June 3, 2003; and June 26, 2003) to discuss issues related to the petition. FDA notified you by letter dated July 14, 2003, of our decision to consider the exercise of enforcement discretion concerning the use of a qualified health claim under appropriate conditions. In the July 14, 2003, letter, we also stated that we planned to issue another letter to explain our decision on the health claim petition in more detail.

After reviewing the scientific evidence provided with the petition and other evidence relevant to your proposed claim, FDA evaluated the relationship of walnut consumption and CHD risk under the "significant scientific agreement" standard. FDA's current regulations, which mirror the statutory language in 21 U.S.C. 343(r)(3)(B)(i), provide that the agency may issue a regulation authorizing a health claim only "when it determines, based on the totality of publicly

02P-0292

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available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence” (21 CFR 101.14(c)). For the reasons set forth below, FDA has concluded that the scientific evidence supporting the proposed health claim does not meet the “significant scientific agreement standard.”

FDA next considered whether it would be appropriate to consider the exercise of enforcement discretion for a qualified claim about this substance-disease relationship, consistent with the agency’s approach to evaluating proposed health claims when the significant scientific agreement standard is not met. This letter outlines FDA’s rationale for its determination that the current evidence supporting the proposed health claim does not meet the significant scientific agreement standard, why the evidence is appropriate for consideration of a qualified claim, and the conditions under which the agency intends to consider the exercise of its enforcement discretion for a qualified claim with respect to consumption of walnuts and CHD risk reduction. In addition, we identify in this letter revised wording for a qualified health claim that reflects the agency’s review of the totality of publicly available scientific evidence.

## **I. Scientific Evaluation**

FDA focused its review of the evidence for the relationship between walnut consumption and reduced risk of CHD to primary reports from human intervention and observation studies that measured CHD directly or measured changes in serum LDL-cholesterol, a validated surrogate marker of CHD risk. Among the references cited in the science review appended to the petition are reports of 11 human studies (6 intervention and 5 observation) relating consumption of nuts, or, in some instances, specifically walnuts, and CHD-related outcome measures.<sup>1</sup> The remaining references, which consisted of pre-clinical studies that did not directly relate diet to CHD outcomes in humans, were considered as additional evidence but were not relied upon in the agency’s review due to the availability of human studies. FDA also included in its scientific evaluation a report in the petition of an expert panel convened by the Life Sciences Research Organization (LSRO) under contract to the petitioner to evaluate the scientific evidence (petition Attachment 1) and the reviews of three independent experts under contract to FDA.

### **A. Substance That is the Subject of the Claim**

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). In the preamble to the final rule on general principles for health claims, FDA stated that a phrase such as “eat apples to...” would constitute a reference to a substance and would satisfy the first element of a health claim. A reference to a particular food, such as apples

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<sup>1</sup> There are more articles included in the petition than the number of studies because some studies have several articles that report on the same study.

or, in this case, walnuts, is an implied claim about a substance in the food (58 FR 2478 at 2480; January 6, 1993).

The walnut petition does not identify a specific substance(s) in walnuts that is responsible for the purported benefit, but rather requests that walnuts be the subject of the proposed claim. In the absence of an identified substance in walnuts that is responsible for the purported effect, FDA considered whether: a) the purported benefits of walnuts are due to a substance that is unique to walnuts and can only be obtained if walnuts are included in diets on a daily basis at a minimally effective level; b) the purported benefits of walnuts are due to a substance that is also found in other foods and, therefore, the benefits can be obtained by choosing among a variety of foods that contain the substance; or c) the purported benefits are not due to a biologically active substance in the walnuts but rather to a replacement of other foods that increase CHD risk.

The petition did not contain sufficient scientific evidence to enable the agency to identify a biologically active substance unique to walnuts or to a larger group of foods that decreases CHD risk. Further, the petition did not contain sufficient evidence for the agency to determine that the beneficial effect is simply due to a replacement effect from walnuts of other foods that increase CHD risk. The petition discusses the fact that walnuts, unlike other nuts, contain a relatively large proportion of alpha-linolenic acid, an omega-3 polyunsaturated fatty acid (omega-3 PUFA). The petition suggests that the omega-3 PUFA content of walnuts adds to their purported benefits and also makes walnuts likely to be more effective than other nuts in reducing CHD risk. However, the petition did not include a comprehensive review of the relationship of omega-3 PUFA intakes and reduced CHD risk (i.e., did not include a review of the "totality of the evidence" on this relationship). Additionally, the petition did not include any studies that provided a basis for evaluating whether the omega-3 PUFA content of walnuts made it more effective than other nuts that lack similar amounts of this fatty acid. Therefore, FDA was not able to evaluate whether omega-3 PUFA contribute, in part or in total, to any benefit of walnuts in reducing CHD risk.

Although it is recognized that the beneficial effects of walnuts could be due to, in part, 1) the presence of unsaturated fats and/or fiber, 2) low levels of saturated fat and/or 3) the lack of cholesterol, there is insufficient evidence to identify the substance(s), if any, in walnuts that may be responsible for the beneficial effects. Therefore, FDA considers walnuts to be the subject of the claim for purposes of this review. The claim about walnuts and reduced risk of CHD satisfies the first element of a health claim, i.e., that a claim about walnuts constitutes an implied reference to a substance in the food. FDA believes that walnuts, as a food, meets the requirements for a health claim in that it characterizes the relationship between a substance, though implied, and a disease (CHD) under 21 CFR 101.14(a)(1).

#### **B. Disease or Health-Related Condition That is the Subject of the Claim**

The petition has identified CHD risk reduction as the subject of the claim. FDA has consistently identified two endpoints with which to identify CHD risk reduction for purposes of health claims

evaluations: a) reduction in incidence of, or decreased mortality from, CHD disease, and b) decreased levels of serum LDL-cholesterol (for example 21 CFR 101.81, 101.82, and 101.83). To evaluate the potential effect of walnut consumption on CHD risk, these types of disease measures were considered.

### **C. Safety Review**

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

The petition asserts that the history of consumption of walnuts as human food at a wide range of intake levels establishes the safety of walnut consumption. FDA agrees that walnuts are a food that has historically been consumed as part of the diet, over a range of consumption levels. As noted in section D below, however, the amounts of walnuts fed in the intervention studies result in dietary PUFA intake levels that exceed the upper boundaries of the Acceptable Macronutrient Distribution Range (AMDR). In the 2002 Macronutrient Dietary Reference Intake Report, the Institute of Medicine reviewed safety data for dietary PUFAs and found insufficient evidence of adverse effects on which to set a Tolerable Upper Intake Level for either the omega-3 PUFAs or the omega-6 PUFAs. Lacking safety data upon which to base a Tolerable Upper Intake Level, the Institute of Medicine established an "upper boundary" for an AMDR based on the approximate highest intake levels for individuals in North America.

Although the evidence concerning a reduction in LDL-cholesterol as a result of walnut consumption is limited, the lowest intake level that showed a significant reduction in LDL cholesterol level was 43g/2,000 kcal/day, or 1.5 ounces/day (Iowamoto et al., 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., including walnuts, showed that the 99<sup>th</sup> percentile of PUFA intake for all individuals ( $\approx 34$  g/day) would exceed the sum of the median intake of PUFAs (13 g/day) (IOM, 2002) plus the PUFAs from 1.5 ounces of walnuts (20 g/day). Because the 99<sup>th</sup> percentile of intake was used to set the upper boundary of the AMDR for PUFAs, the agency concludes that consuming 1.5 ounces of walnuts per day falls within the margin of safe PUFA intake.

Consequently, FDA concludes that, under the preliminary requirement of 21 CFR 101.14(b)(3)(ii), the use of walnuts at levels of 1.5 ounces per day is safe and lawful. Further, FDA concludes that the use of this level in the qualified claim as a condition of the agency's consideration of its enforcement discretion is appropriate.

#### **D. Assessment of Intervention Studies**

Reports from six intervention studies concerning the relationship between walnuts and CHD were cited in the health claim petition.<sup>2,3</sup> The treatment periods in all intervention studies were of short duration (3 - 6 weeks) and the sample sizes were small (16 to 49 subjects). All intervention studies used changes in serum lipids as their measure of CHD risk; they did not have direct measures of CHD incidence. Therefore, none of these studies was useful in evaluating whether the omega-3 PUFA component of walnuts, or some other component in walnuts, contributed to CHD risk reduction independent of an LDL-cholesterol effect in reducing CHD risk. Four of these studies used randomized crossover dietary periods (Sabaté et al., 1993; Chisholm et al., 1998; Zambón et al., 2000; and Iwamoto et al., 2002); two others were conducted as non-randomized sequential dietary periods (Abbey et al., 1994; and Almario et al., 2001).

In our evaluation of the walnut intervention studies, we rated each individual study to be of poor to moderate scientific quality, and therefore generalizations of the results from these studies require caution. In rating the scientific quality of the intervention studies, we considered factors such as randomization, concurrent walnut and reference diet intakes, sample size, and study duration. Using these quality factors, we considered two studies to be of poor scientific quality (Abbey et al., 1994; Almario et al., 2001). We found the study reported in Abbey et al., 1994 particularly questionable because it was a non-randomized study without a concurrent reference diet group. A sequential treatment design in which there is a baseline control period followed by the treatment period is an inadequately controlled study design because it does not control for confounding variables (Kris-Etherton and Dietschy, 1997). Thus, it is not possible to tell whether changes in the endpoint of interest (i.e., LDL-cholesterol) are due to the treatment diet or to unrelated and uncontrolled extraneous factors. In addition, subjects in this study consumed the three test diets sequentially for only 3-week periods, each without any break between the three dietary periods. Study durations should be long enough that the endpoint measure of interest (i.e., LDL-C) has stabilized, thus ensuring that its level reflects the effect of the treatment (i.e., walnut) diet rather than being influenced by the diet consumed prior to the treatment diet. In study designs for intervention trials to examine effects of dietary fat on cardiovascular disease risk factors, it is recommended that the duration of the feeding periods be at least 3 – 4 weeks and include a break between periods to ensure a stable endpoint measurement (Kris-Etherton and Dietschy, 1997). Lack of randomization in the order of diet interventions, lack of concurrent diet

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<sup>2</sup> Two articles included in the petition (Zambón et al., 2000; and Muñoz et al., 2001) report data from the same walnut intervention study.

<sup>3</sup> One report, retracted in 2000 from *The Journal of Nutrition* (Iwamoto et al., 2000. *J. Nutr.* 130:171-176; Iwamoto et al., 2000. *J. Nutr.* 130:2407), was included in the petition as an unpublished manuscript and subsequently published in *The European Journal of Clinical Nutrition* (Iwamoto et al., 2002).

reference groups, inadequate study duration, and very small sample size make the comparisons of serum lipids during the reference diet and walnut diet periods unreliable. For these reasons, FDA considered the results of the Abbey et al., 1994 study not credible and did not rely on them in evaluating the strength of the evidence supporting the petitioned health claim.

We also considered the results of the Almario et al., 2001 study to be of poor scientific quality. This study was conducted in four non-random sequential dietary periods of 6 weeks. As noted above, lack of randomization and lack of concurrent controls introduce a source of error that precludes being able to determine whether changes in LDL-cholesterol are due to walnuts or to extraneous and uncontrolled factors. A further limitation on the reliability of the Almario data is that the researchers relied upon measurements from single blood samples taken at the end of each dietary period. Serum cholesterol concentrations in the same individual vary greatly from one blood sampling to the next, and at least two and preferably three samples from separate days are recommended (Kris-Etherton and Dietschy, 1997). The study reported in Almario et al., 2001 included two comparisons, one for walnuts added to a "habitual diet" (approximately 2,000 kcal/day and 31 percent energy from fat) and the second for walnuts added to a very low fat diet (approximately 1,600 kcal/day and 19 percent energy from fat). We consider the latter diet too atypical of diets in the U.S. and not capable of being sustained for long periods of time without significant weight loss for the results to be generalized. Almario et al. 2001 was among the smallest of the walnut intervention studies, having data from only 18 subjects, which further served to limit our rating of its quality. For these reasons, FDA considered the results of the Almario et al., 2001 study as not credible and did not rely on them in evaluating the strength of the evidence supporting the petitioned health claim.

FDA considered the remaining four walnut intervention studies to be only of moderate scientific quality (Zambón et al., 2000, Chisholm et al., 1998, Iwamoto et al., 2002, and Sabaté et al., 1993) because they had one or more study components (e.g., short study durations, small sample size) that suggested caution in interpreting their results. Of these four trials of moderate scientific quality, two showed walnuts effective at reducing serum LDL-cholesterol when walnuts isocalorically replaced other fat containing foods (Iwamoto et al., 2002; and Sabaté et al., 1993); one showed a similar effect on serum LDL-cholesterol when walnuts replaced olive oil and other fatty foods in a Mediterranean-style diet assumed to be "heart healthy" (Zambón et al., 2000), and one showed no effect of walnuts when they were eaten in addition to the reference diets instead of being substituted for other sources of dietary fat (Chisholm et al., 1998). Limited, reproducible credible evidence indicates a relationship between walnuts and LDL-cholesterol concentration, a valid biomarker for CHD risk. Although it is not possible to determine whether walnuts have an independent benefit in reducing LDL-cholesterol, or whether the benefit is the result of the replacement of other foods that tend to raise LDL-cholesterol, the available evidence suggests that any beneficial effect from walnuts occurs when walnuts are used as a calorie replacement. Therefore, based on the available scientific evidence, a qualified health claim is appropriate to suggest that there may be a relationship between a substance ( i.e., an implied substance in walnuts), and a disease or health-related condition (i.e., CHD) when walnuts are used as a replacement for calories in the diet.

In summary, the results from two intervention studies (Abbey et al., 1994; and Almario et al., 2001) were considered by FDA as not credible because of their study designs, and thus, were not relied upon in our evaluation of evidence supporting the petitioned health claim. Four intervention studies were of moderate scientific quality because they had one or more study components (e.g., short study durations, small sample sizes) that suggested caution in interpreting their results (Chisholm et al., 1998; Iwamoto et al., 2002; Sabaté et al., 1993 and Zambón et al., 2000). Of these four trials of moderate scientific quality, two showed walnuts effective at reducing serum LDL-cholesterol when walnuts replace an equal amount of calories in a reference diet and when the diet is low in saturated fat and cholesterol (Iwamoto et al., 2002; Sabaté et al., 1993). One showed no difference from a Mediterranean-style diet assumed to be "heart healthy" (Zambón et al., 2000), and one showed no effect of walnuts when they were added to the diets instead of being substituted for other sources of dietary fat (Chisholm et al., 1998). The walnut intervention study of Iwamoto et al., 2002 reported a beneficial effect of walnuts on serum LDL-cholesterol but found the effect to be limited to females. As such, it is unclear that a benefit would extend to all people.

#### **E. Assessment of Observation Studies**

The petition included reports from four large prospective cohort investigations that reported an inverse association between CHD incidence and frequency of nut consumption. These studies included the Adventist Health Study (Sabaté 1999; Fraser 1999; and Fraser et al., 1992), the Nurses Health Study (Hu et al., 1998; Hu et al., 1999), the Iowa Women's Health Study (Kushi et al., 1996; Prineas et al., 1993), and the Physicians Health Study (Albert et al., 1998; Albert et al., 2002). Although these four large-scale prospective observation studies are consistent in reporting protective inverse associations of nut consumption frequency and CHD risk, they do not allow a determination as to whether the differences in CHD risk between high and low consumers of nuts are due to the nuts *per se*, or to the fact that frequent consumers of nuts have dietary and lifestyle patterns that differ in beneficial ways from non- or low-consumers of nuts. Further, these data do not allow a determination of effectiveness between types of nuts consumed. Therefore, the results are not directly relevant to a walnut-specific claim. Also, these results do not provide a basis for determining whether walnuts, because of their unique composition compared to other nuts with respect to alpha-linolenic acid (an omega-3 PUFA), provide a beneficial effect on CHD risk reduction over and above the effect of other types of nuts.

The science review appended to the petition included a report from a smaller walnut-specific observation study (Lavedrine et al., 1999). This cross-sectional study, conducted in France, looked at associations between frequency of walnut or walnut oil consumption and serum lipid levels. This study found no association of walnut consumption and serum LDL-cholesterol

levels. However, this type of observational study design is of low persuasiveness<sup>4</sup> so its results are subject to considerable uncertainty.

#### **F. Life Science Research Office (LSRO) Assessment of the Evidence**

The petition included as an appendix a report titled "Report on The Scientific Evidence for a Beneficial Health Relationship Between Walnuts and Coronary Heart Disease." The stated purpose of the report was to review and analyze the scientific evidence on the effects of the intake of walnuts on risk factors for cardiovascular disease and on the prevention of heart disease.

This report accorded clinical intervention trials the greatest weight in its evaluation of how the available scientific evidence supports a health benefit claim for walnuts. Observational evidence had a supportive role in this evaluation because nut consumption generally, rather than walnut consumption specifically, was the measured variable, and the dietary data collection was semi-quantitative. The specific conclusions of the report include, in part:

... clinical walnut intervention studies suggest reduced relative risk of coronary heart disease, yet they are inconclusive because there have been only five controlled, peer-reviewed, published trials with few subjects. There are few trials of extended duration essential for critical evaluation of the sustainability of the health-beneficial outcomes and evidence of adverse effects (e.g., body weight gain and gastrointestinal intolerance). The subjects, though, were representative of the 51% of the adult population in the United States at higher risk of coronary heart disease. The existing studies, considered in their totality, suggest that walnuts, as part of a heart-healthy diet, lower blood cholesterol concentrations. This strong trend needs to be substantiated.

#### **G. FDA Outside Expert Reviews**

FDA contracted with three individuals who are experts in the field of nutrition and heart disease to independently review the available scientific evidence pertaining to a relationship of walnut consumption and CHD risk.<sup>5</sup> The reviewers were provided with copies of the petition and the scientific articles cited in the petition. The independent experts were asked to comment on the adequacy of available scientific evidence to establish a causal relationship between walnut consumption and CHD risk in the general U.S. population. They were also asked to comment on whether results of the walnut clinical trials could be extrapolated to lower amounts of walnuts or less frequent consumption to predict a reduced CHD risk benefit for consumers from any amount

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<sup>4</sup> Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements. December 22, 1999. <http://www.cfsan.fda.gov/~dms/ssaguide.html>

<sup>5</sup> The independent reviewers are (1) William R. Harland, M.D., Senior Advisor, Division of Services and Intervention Research, National Institute of Mental Health, National Institutes of Health; (2) Alice H. Lichtenstein, D.Sc., Director, Cardiovascular Nutrition Laboratory, Gerald J. & Dorothy R. Friedman School of Nutrition Science & Policy and Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University; and (3) Scott M. Grundy, M.D., Ph.D., Professor, Department of Internal Medicine, University of Texas Southwestern Medical Center. Their comments to FDA are included in Docket No. 02P-0292.

of increased walnut consumption, and whether the evidence shows any cholesterol-lowering effects to be attributable to unique characteristics of walnuts, changes in dietary fat composition (i.e., replacing saturated fats with unsaturated fats), or some other factors.

The reviewers were in agreement that the evidence from the intervention trials suggests that using relatively large amounts of walnuts to replace dietary saturated fat with unsaturated fat resulted in more favorable total and LDL-cholesterol levels, hence decreased risk of developing CHD. Furthermore, one of the reviewers stated "Lack of specificity with regard to the actual foods displaced by walnuts from the diet also limit an accurate assessment of the independent effect of walnuts versus, for example, changes in the fatty acid and cholesterol content of the diet." All clinical studies involved relatively high daily walnut intake levels and there are no dose-response data from which to extrapolate beneficial effects to lower amount or frequency of intake. The reviewers agreed that the evidence suggests that walnuts affect serum lipids by the replacement of dietary saturated fat with unsaturated fat. The reviewers also commented that, in all these studies, the contribution of walnuts to total calorie intake was high. Additionally, the reviewers noted that the PUFA intakes in the trials are relatively high and exceed current upper intake recommendations of the Institute of Medicine (2002). Finally, the reviewers expressed concern that data from some of the trials suggested that subjects might add rather than substitute walnuts in the diet. They noted that apparent caloric intake from walnut consumption would be expected to increase body weight and thus CHD risk. The duration of the trials was too short to address these concerns.

The independent reviewers were asked how they thought their conclusions with respect to a causal relationship of walnut consumption and reduced risk of CHD would compare to the opinions of other qualified experts evaluating the same evidence. The consensus of FDA's three independent reviewers was that it is uncertain from the publicly available scientific evidence that increasing consumption of walnuts will reduce the risk of CHD. The reviewers considered that their assessment would be consistent with that of other qualified experts carefully evaluating the same evidence.

#### **H. Assessment of Authoritative Statements**

FDA also considered whether other scientific bodies of the U.S. Government, or the National Academy of Sciences, had reviewed the scientific evidence on walnut consumption and CHD risk. FDA did not find any relevant authoritative statements regarding consumption of walnuts and heart disease risk.

#### **II. Agency's Consideration of Significant Scientific Agreement**

There were reports from six intervention and five observation studies available for evaluating the relationship of walnut consumption to reduced risk of CHD. In general, intervention studies are more persuasive than observation studies (Guidance for Industry: Significant Scientific

Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplement. December 22, 1999).

FDA considered the study design of two of the walnut intervention studies (Abbey et al., 1994; and Almario et al., 2001) to be of poor quality (e.g., not randomized, no concurrent control group, and small sample size) and their results not to be credible. The results of the four remaining intervention studies were equivocal in that of the four studies of moderate scientific quality, two showed an effect, although the effect in one study appeared to be limited to women (Iwamoto et al., 2002), and two showed no effect (Zambon et al., 2000; Chisholm et al., 1998). The equivocal nature of results across studies, in conjunction with the moderate scientific quality of the studies, suggests considerable uncertainty in supporting evidence for the claim. Further, the LSRO review concluded that although the available evidence suggests a strong trend for benefit from consuming walnuts, the trend needs to be substantiated. Additionally, FDA's independent reviewers concluded that it is uncertain from the publicly available scientific evidence that increasing consumption of walnuts will reduce the risk of CHD. Therefore, based on its evaluation of the totality of the publicly available scientific evidence, the agency concluded that the equivocal results from the few available intervention trials, each with design limitations, the lack of support for an effect of walnuts *per se* on CHD risk from observation studies, and the study limitations and cautions in using study results identified by the LSRO and FDA outside reviewers, demonstrate that there is not significant scientific agreement among qualified experts that a relationship exists between walnut consumption and reduced risk of CHD.

### III. Agency's Consideration of Qualified Health Claims

For a claim that does not meet the significant scientific agreement standard, FDA considers whether the exercise of enforcement discretion might be appropriate for a qualified health claim. Based on the results from two intervention studies of moderate scientific quality (Iwamoto et al., 2002; Sabaté et al., 1993), there is a suggestion of an LDL-C lowering benefit resulting from relatively high daily consumption of walnuts. Moreover, although it is not possible to determine whether walnuts have an independent benefit in reducing LDL-C, or whether the benefit is the result of the replacement of other foods that tend to raise LDL-C, the available evidence suggests that any beneficial effect from walnuts occurs when walnuts are used as a calorie replacement. In addition, the observation studies do not provide an adequate basis for determining whether an inverse association of nut consumption frequency with CHD risk is related to dietary patterns for which nuts serve as a marker rather than a key responsible component, or whether an association is related specifically to intakes of walnuts or to other nuts. Therefore, the observation studies do not provide supportive evidence of a relationship between walnuts and reduced risk of CHD.

After reviewing the scientific evidence in your petition, FDA concludes that there is very limited and preliminary scientific evidence supporting the relationship between consumption of walnuts and reduced CHD. Therefore, FDA intends to consider the exercise of its enforcement discretion with regard to a qualified health claim on the label or in labeling of whole or chopped walnuts.

#### **IV. Other Requirements**

The use of qualified health claims on the label or in the labeling of whole or chopped walnuts are required to meet applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception for 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. Exceptions to the general requirements for health claims that FDA intends to consider in the exercise of its enforcement discretion for qualified claims about walnuts and reduced risk of CHD are discussed below, along with enforcement discretion conditions specific to walnut and CHD qualified health claims.

##### **A. Low fat, low saturated fat, and low cholesterol criteria for CHD-related health claims.**

FDA has required that foods bearing CHD-related health claims be low in saturated fat as defined by 21 CFR 101.62(c)(2) and low in cholesterol as defined by 21 CFR 101.62(d)(2) (see 21 CFR 101.75, 101.77, 101.81, 101.82, and 101.83). In addition, most currently authorized CHD-related health claims require that the food meet the definition of a low fat food (21 CFR 101.62(b)(2) (see 21 CFR 101.75, 101.77, 101.81, and 101.82). Whole or chopped walnuts do not meet the definition of a "low saturated fat" or "low fat" food. However, because walnuts have a good ratio of unsaturated fat to saturated fat and may contain other potentially beneficial substances such as dietary fiber and phytosterols, a qualified claim about walnuts and reduced risk of CHD might assist consumers in maintaining healthy dietary practices. Thus, FDA intends to consider the exercise of its enforcement discretion on the use of a qualified health claim on whole or chopped walnuts.

##### **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 disqualifying levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4). The disqualifying level for total fat is 13 g per Reference Amount Customarily Consumed (RACC), and where the RACC is 30 g or less, per 50 g. The RACC for nuts is 30 g, therefore the disqualifying total fat level for walnuts is 13 g total fat per 50 g of walnuts. The fat content of walnuts (32.6 g total fat/50 g) exceeds the health claim disqualifying level (USDA Nutrient Database for Standard Reference, Release 16). The general requirements for health claims also provides for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, based on a finding that such a claim will assist consumers in maintaining health dietary practices. In such cases, the label must also bear a disclosure statement that complies with §101.13(h), highlighting the nutrient that exceeds the disqualifying level. FDA believes that an appropriately qualified health claim about consumption of walnuts could assist consumers in maintaining healthy dietary practices, based on the suggestive evidence of a relationship between walnuts and reduced risk of CHD. Thus, FDA intends to consider the exercise of its enforcement discretion for a qualified

health claim for whole or chopped walnuts if the disclosure statement (i.e., See nutrition information for fat content) is placed immediately adjacent to and directly beneath the claim, with no intervening material, in the same size, typeface, and contrast as the claim itself.

**C. 10% minimum nutrient content requirement.**

Under the general requirements for health claims, a food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC (see 21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods of minimal nutritional value. Although walnuts do not meet the minimum 10 percent nutrient content required by §101.14 of foods bearing a health claim, walnuts contain about 9 percent of the Daily Value per RACC for protein and about 8 percent of the Daily Value per RACC for dietary fiber (USDA Nutrient Database for Standard Reference, Release 16). FDA intends to consider exercising enforcement discretion as to section 101.14(e)(6) because the content of both protein and of dietary fiber in walnuts are very close to the 10 percent Daily Value level.

**D. Context of a 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 a total daily diet (see section 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 (e.g., health claims about fruit, vegetables and grain products that contain fiber, particularly soluble fiber, and risk of CHD (21 CFR 101.77)), 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 risk of CHD. We intend to consider the presence of this information, as part of a qualified health claim about walnuts and reduced risk of CHD, to be a factor in the exercise of our enforcement discretion. The two intervention studies of moderate scientific quality that demonstrated an effect of walnuts on lowering serum LDL-cholesterol both used diets that were low in saturated fat and in cholesterol (Sabaté et al., 1993, and Iwamoto et al., 2002).

**E. Daily dietary intake needed to achieve the claimed effect.**

A provision of the general requirements for health claims requires that where a claim is about a substance for which no definition for "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)). While evidence is limited, the lowest intake level of walnuts that showed a significant reduction in LDL-cholesterol level was 43g/2000 kcal/day, or 1.5 ounces/day (Iwamoto et al., 2002). In the absence of data for lower daily walnut intake levels for LDL-cholesterol dose-response data, FDA finds that there remains uncertainty as to the lowest daily walnut intake level necessary to reduce CHD risk. Therefore, FDA intends to consider exercising enforcement discretion for the use of the qualified claim when the claim specifies 1.5 ounces as the daily dietary intake necessary to achieve the claimed effect. In addition, the agency included a phrase in the

qualified claim that walnuts, consumed at this level, not result in increased caloric intake. The credible evidence that is available, and on which the agency is relying for the qualified claim, suggests that walnuts may only be effective when used to replace other calories in the diet. Therefore, the agency is including the phrase "and not resulting in increased caloric intake" in the qualified claim to reflect the state of the science supporting this claim so that consumers can understand the relative significance of this claim in the context of the total daily diet.

## V. Conclusions

Based on FDA's reassessment of the scientific evidence subsequent to our initial July 14, 2003 qualified health claim enforcement discretion decision, the agency still concludes that there is not significant scientific agreement that the claim "Diets including walnuts can reduce the risk of heart disease" is supported by the totality of publicly available scientific evidence. Thus, FDA will consider exercising enforcement discretion for a qualified claim as presented below:

Supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease. See nutrition information for fat [and calorie] content.

In the above claim, use of the bracketed phrase "and calorie" is optional in that FDA does not intend for the presence or absence of such phrase to be a factor in whether it considers enforcement discretion for the use of the qualified health claim. FDA considered that this additional information might be beneficial to consumers to heighten their awareness of the caloric contribution from walnuts and encourages companies to include it in product labeling.

In FDA's July 14, 2003 letter to you, FDA included an additional qualified health claim statement that included "most nuts, such as walnuts"<sup>6</sup> as the subject of the claim. However, in reconsidering the basis for the exercise of our enforcement discretion, FDA has concluded that since walnuts, and not nuts in general, are the subject of the qualified health claim for which we have determined there is some credible supporting evidence, we are not including, as part of this enforcement discretion decision, this additional qualified health claim statement.

FDA intends to consider exercising enforcement discretion for the above qualified claim when: (1) the disclosure statement about total fat content is placed immediately following the claim, with no intervening material, in the same size, typeface, and contrast as the claim itself; (2) the claim meets the general requirements for health claims in 21 CFR 101.14, except for the requirements that the evidence for the claim meet the significant scientific agreement standard, that the claim be made in accordance with an authorizing regulation, that the food not exceed the

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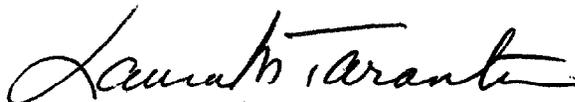
<sup>6</sup> Specifically, the qualified health claim read, "Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts, such as walnuts, as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease. See nutrition information for fat content."

Page 14 - Ms. Sarah E. Taylor, J.D., R.D., M.P.H.

disqualifying nutrient level for total fat, and that the food provide at least 10 percent of the Daily Value of calcium, iron, vitamin A, vitamin C, dietary fiber, or protein.

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 claim, or that may raise safety concerns.

Sincerely,

A handwritten signature in cursive script, appearing to read "Laura M. Tarantino".

Laura M. Tarantino, Ph.D.  
Acting Director  
Office of Nutritional Products, Labeling,  
and Dietary Supplements  
Center for Food Safety  
and Applied Nutrition

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Page 17 – Sarah E. Taylor, J.D., R.D., M.P.H.

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