CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements
September 8, 2004

Letter Responding to Health Claim Petition dated June 23, 2003 (Wellness petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease

(Docket No. 2003Q-0401)

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RE: Health Claim Petition: Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease (Docket No. 2003Q-0401)

Dear Mr. Emord:

This letter responds to the health claim petition dated June 23, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Wellness Lifestyles, Inc. and Life Extension Foundation Buyers Club (collectively, Wellness petition) pursuant to Sections 403(r)(4) and 403 (r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343 (r)(4) and 343(r)(5)(D)). The petition requested that the agency authorize a health claim characterizing the relationship between the consumption of omega-3 fatty acids (specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) and a reduced risk of coronary heart disease (CHD). The petition requested that the disclaimer on the existing omega-3 fatty acids and CHD dietary supplement health claim, as stated in a letter dated October 31, 2000[1] (subsequently modified by a letter dated February 16, 2001[2] and by a letter dated February 8, 2002[3]) be removed and that the claim be extended to omega-3 fatty acid containing foods. This petition proposed the model health claim: "Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease."

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 21 U.S.C. § 343 (r)(3)(B)(i) of the Act. FDA notified you of this decision and you submitted a letter on August 12, 2003 agreeing to the petition being reviewed as a qualified health claim. Thus, FDA filed the petition on September 3, 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.[4]

FDA received a qualified health claim petition (the Martek petition) from Mr. Martin J. Hahn on November 4, 2003, as both a petition and a comment on your petition. Mr. Hahn submitted the petition on behalf of Martek Biosciences Corporation. The Martek petition requested an extension of the existing omega-3 fatty acid and CHD dietary supplement qualified health claim to conventional foods, including foods fortified with omega-3 fatty acids (specifically EPA and DHA). Because the substance and disease and the request for an extension of the existing omega-3 fatty acids and CHD qualified health claim were the same in each petition, FDA consolidated the petitions in the same docket (Docket No. 2003Q-0401).

The agency received several comments on the petitions. You submitted two comments. Other comments were from industry, a professional organization, and an individual. The comments addressed various issues including the substance of the claim, mercury content in fish, minimum effective levels of EPA and DHA, disqualifying nutrient levels, minimum nutrient content requirements, and claim statements. All support extending the omega-3 fatty acid qualified health claim to conventional foods. FDA considered the relevant comments in its evaluation of this petition.

This letter sets forth the basis of FDA's determination that the current evidence for the proposed health claim is appropriate for consideration for a qualified health claim on conventional foods and dietary supplements. This letter also sets out the factors that FDA intends to consider for the exercise of its enforcement discretion for a qualified health claim, for both conventional foods and dietary supplements, with respect to consumption of EPA and DHA omega-3 fatty acids and a reduced risk of coronary heart disease. This letter is an update to the previous letters on the use of a qualified health claim on EPA and DHA omega-3 fatty acid dietary supplements and coronary heart disease risk (the October 31, 2000 letter,[5] the February 16, 2001 letter,[6] and the February 8, 2002 letter[7]) and provides FDA's current thinking with respect to the use of this qualified health claim on both dietary supplements and conventional foods. Throughout the text of this letter, the phrase "omega-3 fatty acid qualified health claim" will be used to refer to the qualified health claim about the consumption of EPA and DHA omega-3 fatty acids 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,"[8] the agency evaluates the scientific studies to determine what studies are pertinent 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 decision about whether the particular study supports a relationship. Such design flaws may include the lack of a control group or the lack of any 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[9], review articles[10], and animal[11] and *in vitro*[12] 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 relevant to its review about whether there is evidence to support a relationship between a substance and a disease or health-related condition, (i.e., what studies to rate based on study quality), the agency categorizes these studies into: (1) the most persuasive studies, which are studies designed to evaluate whether there is a relationship between the substance and disease outcome (e.g., intervention studies that manipulate the intake level of the substance while controlling for other factors that can affect disease risk reduction and/or; (2) less persuasive studies (e.g., studies that my have design flaws that make them less reliable in evaluating a substance/disease relationship or less applicable to the U.S. population (conducted in countries where usual intakes of the substance is much lower or higher than in the U.S.). The most persuasive studies are given the greatest consideration. FDA rates the most and less persuasive studies for quality. Scientific quality is based on several criteria including study population, intervention design (e.g., presence of a placebo control), data collection (e.g., dietary assessment method), statistical analysis, and outcome measures. For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high quality rating. Lower quality ratings (e.g., moderate and low) would be given based on the extent of the deficiencies or uncertainties in the quality criteria.

Collectively, FDA then rates the strength of the total body of evidence that it determines is relevant to its review, using criteria such as the study type (e.g., intervention), 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, then determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

The Wellness petition cited 24 publications as evidence to substantiate the relationship for this claim. These publications consisted of 6 reports of intervention studies,[13] 8 observational studies,[14] 3 review articles,[15] 1 position paper from the American Heart Association,[16] 1 editorial,[17] 1 meta-analysis of intervention studies on omega-3 and CHD,[18] 1 food composition survey,[19] and 3 *in vitro* studies.[20]

The agency did not consider all the publications cited in the Wellness petition to be pertinent to its review of this substance/disease relationship. While useful for background information, the review articles, position paper and meta-analysis 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 (e.g., food, dietary supplement); similarly, the lack of detailed information on the studies summarized in the review articles, position paper and meta-analysis did not allow FDA to determine if the studies are flawed in critical elements such as its design, execution, and data analysis. FDA must review the scientific quality of a study to determine whether credible conclusions can be drawn from it. The food composition survey measured how much omega-3 fatty acid was in a given food. FDA did not consider the food composition survey as pertinent

because it did not measure whether omega-3 fatty acids reduced the incidence of disease or affected a surrogate endpoint for CHD. FDA did not consider the *in vitro* studies that were submitted in the petition as providing any supportive information about the substance/disease relationship because *in vitro* models of disease are conducted in artificial environments that cannot mimic normal physiology that may be involved in the risk reduction of CHD, nor can *in vitro* models mimic the human body's response to consumption of omega-3 fatty acids.

In addition to the studies in your petition that the agency considered, FDA considered 7 intervention studies (5 from the Martek petition[21]; 1 from a comment[22]; 1 identified by FDA through a literature search[23]), 3 observational studies from the Martek petition[24]and 2 chapters from a report compiled by the Institute of Medicine from the Martek petition.[25]

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). The petitions identified the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as the substance for the proposed claim. EPA and DHA are components of some fatty fish (primarily cold water fish),[26] fish oils, other foods (e.g., seaweed), dietary supplements, and food ingredients (e.g., algal oils). Therefore, the agency concludes that the substances, EPA and DHA omega-3 fatty acids, identified in the petition are components of food and therefore meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified coronary heart disease (CHD) as the disease for the proposed claim. The agency concludes that CHD is a disease and therefore that 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 levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act.

The Wellness petition stated that omega-3 fatty acids, as EPA and DHA, have been a naturally occurring ingredient in foods consumed safely in the United States prior to January 1, 1958, and that there is no evidence that when consumed either in foods or as dietary supplements there is a cumulative effect in the diet that is unsafe. The Martek petition stated that omega-3 fatty acids occur in conventional foods with a long history of safe use, such as fish, and are generally recognized as safe (GRAS) when used as direct food ingredients intended to increase omega-3 fatty acids. Some comments to the petition expressed an interest in using the omega-3 fatty acid qualified health claim for foods that contain EPA and DHA as a food ingredient from

sources including fish oil and algal oil.

In order to meet the safe and lawful requirement for health claims (21 CFR 101.14(b)(3)(ii)), the use of EPA and DHA omega-3 fatty acids, when used in conventional food or as a dietary supplement at levels necessary to justify the claim, must be demonstrated, to FDA's satisfaction, to be safe and lawful. FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the 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)). Dietary ingredients in dietary supplements, however, are not subject to the food additive provisions of the act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342) and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994. The term "dietary ingredient" is defined in section 201(ff)(1) of the act and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

In 1997, FDA affirmed, as GRAS, menhaden oil as a direct human food ingredient with specific limitations of use to ensure that the total daily intake of EPA and DHA would not exceed 3.0 grams per person per day (g/p/d) (62 FR 30751; June 5, 1997; 21 CFR184.1472). EPA and DHA are the major omega-3 fatty acids in fish oil and together comprise about 20 percent by weight of menhaden oil. FDA established maximum use levels of menhaden oil in certain foods because of concerns over possible adverse effects of fish oil consumption on bleeding time, glycemic control, and LDL cholesterol (62 FR 30751 at 30757; June 5, 1997). In 2002, FDA published a proposed rule to reallocate the uses of menhaden oil in conventional food, while maintaining the total daily intake of EPA and DHA from menhaden oil at a level not exceeding 3.0 g/p/d (67 FR 8744; February 26, 2002). FDA placed specific limitations, including the category of foods, the functional use of the ingredient, and the level of use, to ensure that the consumption of EPA and DHA from conventional food sources would not exceed 3.0 g/p/d. FDA then published a tentative final rule (69 FR 2313; January 15, 2004) to additionally require that menhaden oil not be used as an ingredient in foods in combination with other added oil that is a significant source of EPA and DHA to ensure that total intake from conventional food sources do not exceed 3.0 g/p/d.

In addition, FDA has not objected to certain GRAS notifications for additional sources of EPA and DHA as food ingredients (fish oils other than menhaden oil) (GRAS Notice Nos: GRN000097, GRN000102, GRN000105, GRN000109, GRN 000137, GRN000138).[27] These GRAS notices proposed maximum use levels consistent with those specified in the tentative final rule affirming, as GRAS, menhaden oil as a direct human food ingredient with specific limitations of use.

FDA has also responded without objection to a GRAS notification on algal oil DHA from Martek Biosciences Corporation. Martek estimated that the use of algal oil in a number of food categories at the maximum proposed use levels would result in a mean exposure of no more than 1.5 grams of DHA per day (GRAS Notice No. GRN000137).

The mean exposure to EPA and DHA from menhaden oil in all conventional food categories is

estimated to be 2.7 g/p/d (67 FR 8744 at 8746; February 26, 2002). This is a conservative estimate with substantial margin for safety, and the agency believes, consistent with its prior decision on the use of a qualified health claim for DHA and EPA omega-3 fatty acids (October 31, 2000 letter), that the addition of menhaden oil to food products has not come close to this conservative mean estimate exposure. FDA further believes that the GRAS uses for which it received a GRAS notification for other sources of EPA and DHA omega-3 fatty acids also provide conservative estimates of exposure and that the addition of these EPA and DHA sources to food products do not come close to the conservative mean estimates. Not all foods in the marketplace within those permitted food categories would contain menhaden oil or other sources of EPA and DHA omega-3 fatty acids that substitute for other edible fat or oil. Also, because not all foods that a consumer eats every day would contain menhaden or other EPA and DHA oil used as a substitute oil, the actual total daily intakes of EPA and DHA from menhaden or other EPA and DHA oil for an average person should be significantly below 3.0 g/p/d (67 FR 8744 at 8746; February 26, 2002).

It is difficult to estimate the actual total consumption of EPA and DHA. The Continuing Survey of Food Intakes by Individuals (1994-1996, 1998)[28] estimated EPA and DHA intakes from conventional foods.[29] The 50th percentile intake of EPA and DHA from the survey was between 0.06 g and 0.07 g for adult women and 0.07 g and 0.1 g for adult men. The 90th percentile intake was between 0.18 g and 0.22 g for women and between 0.20 g and 0.43 g for men. Thus, EPA and DHA consumption from conventional foods in the United States is low. FDA is not aware of any nationally representative consumption data on EPA and DHA from dietary supplements. In the October 31, 2000 letter, FDA expressed concern about the exposure to EPA and DHA omega-3 fatty acids potentially exceeding 3.0 g/p/d if a qualified health claim were to appear on dietary supplements. This concern was due to conventional foods containing omega-3 fatty acids that were on the market; the use of structure/function claims on products containing EPA and DHA omega-3 fatty acids, which may promote product purchase; and dietary supplements that FDA found in the marketplace that contained significant amounts of EPA and DHA.

With this letter, the requested use of this qualified health claim is now extended to conventional foods. The agency believes that there is likely to be some increased consumption of EPA and DHA omega-3 fatty acids based on conventional foods that bear the qualified health claim; however, the amounts of EPA and DHA that can be used and the foods in which such food ingredients can be safely used are limited. The agency has established specific limitations of use under its menhaden oil GRAS rule (62 FR 30751; June 5, 1997), proposed and tentatively finalized reallocation of the use of menhaden oil without changing total exposure levels (67 FR 8744; February 26, 2002, 69 FR 2313; January 15, 2004). Also, manufacturers that have submitted GRAS notifications for other sources, to which the agency has not objected, have established conditions of use similar to those in the menhaden oil GRAS rule.

In the October 31, 2000 letter,[30] FDA stated that a consumer could consume nearly 1 gram of EPA and DHA per day in the diet from conventional foods. The agency is uncertain about how much consumers will increase their intake of EPA and DHA omega-3 fatty acids from EPA and DHA containing conventional foods and dietary supplements due to the extended use of the qualified health claim. In order to help consumers gauge their total intake of EPA and DHA and to provide them a way to keep their intake of EPA and DHA within 3 grams per day, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that conventional foods and dietary supplements that bear an omega-3 fatty acid qualified health claim declare the

amount of EPA and DHA per serving in the claim. FDA recommends that the information on EPA and DHA content for use in a qualified health claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD be presented in a manner that is consistent with FDA's guidance entitled, "FDA Nutrition Labeling Manual--A Guide for Developing and Using Data Bases." You may contact CFSAN's Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS) for further information. The dietary supplement may declare the amount of EPA and DHA per serving in "Supplement Facts," instead of making the declaration in the claim. Also, to ensure further that consumers do not exceed a 3.0 g/p/d intake, FDA will educate consumers not to exceed 3.0 g/p/d from all food and dietary supplement sources through print and web outreach information. Further, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements not recommend or suggest in labeling that consumers ingest more than 2 grams of EPA and DHA per day. FDA encourages manufacturers to limit their dietary supplement products bearing the qualified health claim to products recommending or suggesting daily intake of 1 gram or less of EPA and DHA omega-3 fatty acids.

Based on the data and information that FDA considered, which includes data and information that FDA relied upon in reaching its conclusions about the safety of EPA and DHA omega-3 fatty acids in its GRAS affirmation of menhaden oil, the data and information in the 1991 proposed (56 FR 60663; November 27, 1991) and 1993 final rules (58 FR 2683; January 6, 1993), and its current scientific literature review for other possible safety concerns, FDA concludes that the use of EPA and DHA omega-3 fatty acids used as a GRAS ingredient, consistent with FDA's GRAS rule for menhaden oil and GRAS notifications to which FDA did not object, and the use as a dietary supplement is safe and lawful under 21 CFR 101.14 provided that daily intakes of EPA and DHA omega-3 fatty acids from conventional food and dietary supplement sources do not exceed 3.0 g/p/d. In section IV, FDA sets forth factors under which it plans to exercise enforcement discretion for EPA and DHA containing conventional foods and dietary supplements bearing the qualified claim, to ensure, among other things, that such use will be safe.

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 for EPA and DHA omega-3 fatty acids: Coronary events (MI, ischemia), cardiovascular death, atherosclerosis, and high blood pressure. Artherosclerosis is the underlying cause of CHD, which can lead to the signs of CHD including coronary events (MI, ischemia) and cardiovascular death.[31] High blood pressure, serum total cholesterol, serum LDL-cholesterol, and serum HDL-cholesterol are considered as surrogate endpoints for CHD.[31] However, FDA concluded in its October 31, 2000 letter[32] that omega-3 fatty acids do not affect serum cholesterol levels (total, LDL, HDL). To evaluate the potential effects of EPA and DHA omega-3 fatty acid consumption on CHD risk, FDA considered coronary events (myocardial infarction (MI), ischemia), cardiovascular death, atherosclerosis, and high blood pressure as indicators or predictors of disease.

In considering the qualified health claim for EPA and DHA omega-3 fatty acid dietary supplements in October 2000, FDA focused on human data that had become available since FDA's 1991-93 review and on human studies that quantitatively measured or estimated the omega-3 fatty acid intakes in relation to a direct measure of CHD risk or a surrogate endpoint

for CHD risk. Several, but not all, of the studies[33] that FDA had considered in its October 31, 2000 letter were submitted in these current petitions. Studies that have been published since that letter were also included in the petitions. For purposes of this review, FDA, in determining the scientific support for a relationship between EPA and DHA omega-3 fatty acid dietary supplements and CHD, focused on the more recent studies to determine whether these studies added any support to the scientific evidence that was used for the current qualified health claim for EPA and DHA omega-3 fatty acid dietary supplements. For purposes of determining whether there is a relationship between EPA and DHA omega-3 fatty acids from conventional foods and reduced risk of CHD, FDA determined whether the relevant studies cited in the petition, in addition to other relevant studies that the agency had already reviewed in its previous reviews, support a qualified health claim.

A. Assessment of the Intervention Studies

FDA identified a total of 10 intervention studies, not previously reviewed in 2000, for its current review of this qualified health claim (3 from the current petition[34]; 5 from the Martek petition [35]; 1 from a comment[36]; 1 identified by FDA through a literature search[37]). FDA did not consider some of these studies in its current review for the following reasons: 1) Marchioli, et al. (2002) was a reanalysis of GISSI et al. (1999), which FDA reviewed in 2000, and provided no additional evidence relevant for establishing a substance-disease relationship; 2) Thies et al. (2003) and Maresta et al. (2002) measured outcomes (plaque stability and percutaneous transluminal coronary angioplasty (PTCA), respectively) that are not recognized as valid surrogate endpoints for CHD; 3) the studies by Ghafoorunissa et al. (2002), Laidlaw and Holub, et al. (2003) did not include control groups for EPA and DHA (Spilker, 1991); 4) Leng et al. (1998) did not include a control for gamma-linolenic acid (GLA), which constituted the majority of the treatment (approximately six times higher than EPA), thus there is no way to determine whether the effects were due to EPA; and 5) two intervention studies that reported no benefit on CHD incidence (Angerer et al., 2002; Nilsen et al., 2001) were conducted in CHD patients and the results could not be extrapolated to the general healthy population; therefore, these data were not considered relevant to FDA's review for establishing a substance-disease relationship in the general population. Thus, FDA considered only 2 intervention studies identified since the 2000 review as capable of supporting the substance/disease relationship (Finnegan et al., 2003; Woodman et al., 2002).

The studies by Finnegan et al. (2003) and Woodman et al. (2002) were randomized, placebo-controlled, double-blind[38] intervention studies that reported the effects of fish oil on blood pressure. Finnegan et al. (2003) reported the results from a study involving 150 moderately hyperlipidemic subjects[39] assigned to 1 of 5 interventions: fish oil (0.8 or 1.7 g/day EPA+DHA); rapeseed and linseed oil (4.5 or 9.5 g/day ALA), or an n-6 PUFA control (sunflower and safflower oil) for 6 months. The fish oil intervention provided no benefit in CHD risk factors, including blood pressure, compared to the placebo control group. Woodman et al. (2002) was a 6-week intervention comparing EPA ethyl ester[40] (4 g/day) or DHA ethyl ester[40] (4 g/day) with olive oil (4 g/day) in type 2 diabetics[41] with hypertension (n=52). Neither EPA ethyl ester nor DHA ethyl ester provided any benefit to blood pressure or any other CHD risk factor compared with the olive oil treated patients.

B. Assessment of the Observational Studies

FDA identified 10 observational studies not previously reviewed in 2000. These consisted of 6 prospective cohort studies (4 from the current petition[42]; 2 from the Wellness petition[43]), 3 nested case-control studies from the current petition,[44] and 1 ecological study from the Martek petition.[45]

Two of the 10 studies on fish consumption and CHD[46] were not considered in this review because these studies only reported total fish consumption without providing details of the fish type[47] or portion sizes, thus there is no way of knowing how much, if any, EPA and DHA omega-3 fatty acid was consumed. The remaining 8 observational studies[48] were of high to moderate quality. These observational studies provide only an estimated intake of EPA and DHA omega-3 fatty acids from fish consumption and provided only an association with disease risk, and not direct causality of disease risk.

Hu et al. (2002) reported results from the Nurses' Health Study, a prospective cohort study on female registered nurses (n=84,688) with a 16 year follow-up. Fish and omega-3 fatty acid intake were calculated as an average intake from all available dietary questionnaires up to the start of each 2-year follow-up interval in which events were reported. There was an inverse correlation observed between fish/omega-3 fatty acid consumption and incidence of CHD, including CHD deaths and nonfatal MI. A subgroup analysis of diabetic nurses from this cohort (n=5,103; Hu et al., 2003) observed a reduced risk of CHD from fish consumption but the association did not extend to estimated EPA and DHA omega-3 fatty acid consumption.

Albert et al. (2002) was a case-control study nested in the U.S. Physicians Health Study (Albert et al., 1998), which was considered in the 2000 review. The nested case-control study had a 17-year follow-up and reported a significant inverse relationship between whole blood omega-3 fatty acid concentrations and CHD death.

The study by Rissanen et al. (2000) reported 10-year follow-up results from the Kuopio Ischemic Heart Disease Risk Factor Study, which is an ongoing, prospective, population-based cohort study investigating risk factors for cardiovascular disease (CVD) and is part of the World Health Organization's (WHOs) MONICA project. The study enrolled 1,871 men who had no clinical CHD at baseline examination. The authors reported a decrease in acute coronary events in men at the highest quintile[49] of serum DHA+DPA[50] concentration compared with men at the lowest quintile.

Results from the Cardiovascular Health Study were reported by Mozaffarian et al. (2003). In this prospective cohort study, men (~1,500) and women (~2,400) aged ≥65 years were enrolled who were free of known CVD at baseline in 1989-1990 and had data on fish consumption. During the 9.3 years of follow-up, there were 247 ischemic heart disease (IHD)[51] deaths and 363 MIs. Estimated intake of EPA + DHA at baseline (0.55 g/day and 0.92 g/day) was associated with lower risk of fatal ischemic heart disease (IHD), but there was no association between EPA + DHA and non-fatal MI. This result is consistent with the report from a case-control study nested in the Cardiovascular Health Study (Lamaitre et al., 2003). A higher plasma concentration of EPA + DHA was associated with a lower risk of fatal IHD, but there was no association between plasma concentration of EPA + DHA and a risk of non-fatal IHD.

Hallgren et al. (2001) was a case-control study nested in the Västerbotten Intervention Programme, which was part of the WHOs MONICA project. In this study, 78 people (cases)

developed an MI, and were matched against 156 controls subjects that were randomly selected from the study. Fish intake was assessed by a food frequency questionnaire (FFQ).[52] In addition, fatty acid composition of the plasma phospholipids, including EPA and DHA, was analyzed. There was no correlation between fish intake or blood EPA+DHA and acute MI.

Torres et al. (2000) compared fish consumption in Portuguese men living in a fishing village (n=50) or rural village (n=37) with IHD-related deaths based on death certificate records for the population. There was significantly more fish consumed in the fishing village compared with the rural village and this correlated with lower IHD deaths estimated from death certificate records for the two villages.

C. Other Data and Information

The Institute of Medicine (IOM) of the National Academy of Sciences has stated in its most recent Macronutrient Report that "Growing evidence suggests that dietary *n-3* polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) reduce the risk of coronary heart disease (CHD) and stroke."[53] Therefore, by concluding that there was only "growing evidence" that is "suggestive" of the relationship for this proposed claim, the IOM recognized limitations in the current data on omega-3 and its ability to reduce risk of CHD.

III. Strength of the Scientific Evidence

FDA relies primarily on human studies that are primary reports of data collection when attempting to establish a diet-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 the disease, and; b) beneficial changes in surrogate endpoints for the disease.[54] The most persuasive evidence for a relationship between EPA and DHA omega-3 fatty acids and reduced risk of CHD would be from intervention studies with EPA and DHA omega-3 fatty acids demonstrating reduced incidence of CHD in healthy populations (i.e., primary prevention). However, no such studies for EPA and DHA omega-3 fatty acids and CHD were identified. There were 2 small intervention studies in healthy populations that measured EPA and DHA effects on blood pressure, a CHD surrogate endpoint, but no benefit was observed in these studies. Thus, the scientific evidence from intervention studies available since the 2000 review with EPA and DHA omega-3 fatty acids as the test substance, did not show a relationship between omega-3 fatty acids and reduced risk of CHD in the general population.

The remaining studies considered were high to moderate quality observational studies on healthy populations. Of these, 3 studies (Albert et al., 1998, 2002; Hu et al., 2002; Mozaffarian et al., 2003 (also Lamaitre et al., 2003)) were conducted in populations relevant to the general U.S. population, across a broad age range (30 to 84 years) and consistently reported that EPA and DHA omega-3 fatty acids reduced the risk of CHD. The largest cohorts followed 84,688 women (Hu et al., 2002) and 20,551 men (Albert et al., 1998, 2002). Of the observational studies conducted in populations considered less relevant to the general U.S. population, 1 small study (n=78 cases) (Hallgren et al. 2001) reported no benefit; whereas 2 studies (Rissanan et al, 2000; Torres et al., 2000) with sample sizes of 1,871 and 50, respectively, reported an associated benefit. Observational studies provide less compelling evidence than intervention studies for a relationship between omega-3 fatty acids and reduced risk of CHD because they

provide only an estimated intake of EPA and DHA omega-3 fatty acids rather than a direct measure. In addition, observational studies cannot separate the effect of EPA and DHA omega-3 fatty acids from the effects of other food components, and therefore it is not clear whether any purported benefit is related to the EPA and DHA omega-3 fatty acids or to other dietary factors. Observational studies provide only supportive rather than direct evidence for a relationship. For these reasons, FDA considers observational studies as less persuasive than intervention studies conducted in a general healthy population for establishing a substance-disease relationship. Nevertheless, primary prevention of CHD in healthy populations by EPA and DHA omega-3 fatty acids was observed in the majority of observational studies reviewed, which included 2 large prospective cohorts conducted in the US, the Nurses' Health Study (n=84,688; 16 year follow-up; Hu et al., 2002) and the U.S. Physicians Health Study (n=20,551; 11 to 17 year follow-up; Albert et al., 1998, 2002). In sum, the majority of observational studies consistently observed an associated CHD risk reduction from intake of EPA and DHA estimated from the diet in men and women in populations relevant (3 studies) or less relevant (2 studies) to the general U.S. population.

Given the inability of predicting CHD risk reduction in a general healthy population based on secondary prevention studies in diseased populations, and the limitations of the observational studies in separating the effects of EPA and DHA omega-3 fatty acids from other dietary factors, the agency evaluated other available evidence, as discussed in the October 31, 2000 letter, that provide support for a qualified health claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD. As described in detail in the October 31, 2000 letter,[55] FDA considered: (1) observational studies in the general healthy population in which fish consumption was the primary contributor of EPA and DHA omega-3 fatty acids, and (2) intervention studies in both the general healthy population and patients with established CHD that evaluated the effects of EPA and DHA omega-3 fatty acids on physiological endpoints (e.g., total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, triglycerides, platelet aggregation), some of which have been proposed as possible mechanisms for the CHD risk reduction by EPA and DHA omega-3 fatty acids. Thus, FDA is not changing its position from that outlined in the October 31, 2000 letter on the EPA and DHA omega-3 fatty acid and CHD qualified claim that there is sufficient suggestive evidence that the benefit on CHD reported in CHD patients (i.e., secondary prevention) (reviewed in the October 31, 2000 letter) applies to the general population because of: (1) The primary CHD prevention in the general population associated with EPA and DHA consumption from fish in observational studies; and, (2) intervention studies demonstrating similar physiological effects of EPA and DHA in both the diseased and general populations. FDA still concludes that the weight of the scientific evidence for a health claim for EPA and DHA omega-3 fatty acids outweighs the scientific evidence against such a claim. The most significant change in the available body of evidence since 2000 is the additional observational studies, the majority of which consistently reported an associated benefit in CHD risk from EPA and DHA consumption from fish.

The observational studies estimating EPA and DHA omega-3 fatty acid intake from conventional foods support the expansion of the existing qualified health claim for EPA and DHA omega-3 fatty acids from dietary supplements and CHD to conventional foods. 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 EPA and DHA omega-3 fatty acid-containing dietary supplements and conventional foods that provides a truthful and non-misleading description of the strength of the body of scientific evidence, e.g., "supportive but not conclusive research shows." 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, including dietary supplements, 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 EPA and DHA omega-3 fatty acids and reduced risk of coronary heart disease are discussed below. You should also know that FDA is considering its enforcement discretion as applying only to such foods in which EPA and DHA is an added ingredient that FDA has approved as a food additive or affirmed as GRAS or for which the agency has received a GRAS notification to which it did not object.

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 such claims meet the "low fat" criterion defined by 21 CFR 101.62(b)(2), the "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 sections 101.75, 101.77, 101.81, 101.82, and 101.83). The agency discusses below how the agency intends to consider these criteria as factors in deciding whether to exercise its enforcement discretion for an omega-3 fatty acid qualified health claim on conventional foods and dietary supplements. Later in Section B, FDA discusses total fat, saturated fat, and cholesterol content disqualifying levels relative to the general requirement for health claims (21 CFR 101.14(a)(4)).

"Low fat" criterion

FDA has required in the past that foods bearing CHD health claims meet the requirement for "low fat" as defined by 21 CFR 101.62(b)(2). The requirement of the "low fat" criterion was first introduced in the dietary lipid and cardiovascular disease proposed rule (56 FR 60727 at 60739; November 27, 1991). FDA stated that, although total fat is not directly related to increased risk for CHD, it may have significant indirect effects. The agency stated that low fat diets facilitate reduction in the intake of saturated fat and cholesterol to recommended levels. Furthermore, the agency noted that obesity is a major risk factor for CHD, and dietary fats, which have more than twice as many calories per gram as proteins and carbohydrates, are major contributors to total calorie intakes. There have been several exceptions to this criterion in the past. Instead of the "low fat" criterion, fish and game meat are required to meet the "extra lean" criterion in the saturated fat and cholesterol and CHD health claim (21 CFR 101.75(c)(2)(ii)). 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 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 spread and dressing for salad 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.

FDA concurs with the 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, as a factor in the exercise of its enforcement discretion, that either dietary supplements or conventional foods that bear an omega-3 fatty acid qualified health claim meet the "low fat" criterion.

"Low saturated fat" and "low cholesterol" criteria

In regulations authorizing CHD health claims, FDA has also generally required that foods bearing the claims meet the "low saturated fat" criterion as defined by 21 CFR 101.62(c)(2), and the "low cholesterol" criterion as defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR sections 101.75, 101.77, 101.81, 101.82, and 101.83). FDA continues to believe that these criteria are important. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that conventional foods or dietary supplements that bear an omega-3 fatty acid qualified health claim meet the "low saturated fat" and "low cholesterol" criteria. However, there are some situations, as discussed below, when FDA does not believe that such a factor is important to a decision about the exercise of its enforcement discretion.

Low saturated fat

FDA intends to consider, as a factor in the exercise of its enforcement discretion, that individual foods other than fish that bear an omega-3 fatty acid qualified health claim, meet the "low saturated fat" criterion (21 CFR 101.62(c)(2)). This food category includes primarily foods enriched with EPA- and DHA-containing food ingredients. FDA intends to consider, as a factor in the exercise of its enforcement discretion for meal products as defined in 21 CFR 101.13(l) and main dishes as defined in 21 CFR 101.13(m) that such foods meet all criteria specified for the "low saturated fat" criteria (21 CFR 101.62(c)(2)). FDA believes that many foods would meet the "low saturated fat" criteria, as stated in the final rule for nutrient content claims (58 FR 2302 at 2339; January 6, 1993). The criteria, "no more than 15 percent of calories from saturated fat" for individual foods can be achieved due to calorie contribution from food ingredients other than fish oil in these foods. Later in this section, FDA defines fish as "products that are essentially all fish" and identifies nutrient content factors that it intends to consider in the exercise of its enforcement discretion for the qualified health claim.

FDA intends to exercise its enforcement discretion for EPA- and DHA-containing dietary supplements (whether softgels or liquid forms) that bear an omega-3 fatty acid qualified health claim, and that meet the low saturated fat criterion per reference amount customarily consumed (RACC). However, FDA does not intend to consider, as a factor in the exercise of its enforcement discretion, that "no more than 15 percent of calories be from saturated fat." In a fish oil, 20 - 30 percent of calories come from saturated fat (USDA National Nutrient Database for Standard Reference, Release 17). Because 100 percent fish oil dietary supplements usually have no other source of calories other than fish oil and reformulation is not possible to reduce percent of calories from saturated fat, fish oil dietary supplements would not be eligible for the qualified health claim if FDA decided to consider the 15 percent criterion in 21 CFR 101.62(c)(2) as a factor in the exercise of its enforcement discretion. FDA believes that not considering the 15 percent criterion as a factor in the exercise of its enforcement discretion is appropriate given that fish oils are derived from fish, which have been shown to be associated with a reduced risk of CHD in observational studies with healthy individuals. In the algal oil used in Martek's dietary supplements, 40 - 45 percent of the oil is DHA and 30 - 40 percent of calories

come from saturated fat.[56] Because the algal oil is diluted by high oleic sunflower oil by 7 - 10 percent or by 50 - 60 percent to make the final DHA concentration specific to Martek's products (either 20 percent or 40 percent DHA), calorie contribution from saturated fat will be either a little less than 30 - 40 percent (for the 40 percent DHA product) or about 15 - 20 percent of calories (for the 20 percent DHA product). In the final oil, calories from saturated fat exceed 15 percent; however, the level overlaps with that of fish oils. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements that bear an omega-3 fatty acid qualified health claim meet the "equal to or less than 1 g of saturated fat per RACC" criterion in 21 CFR 101.62(c)(2) but does not intend to consider the "no more than 15 percent of calories from saturated fat" criterion as a factor in the exercise of its enforcement discretion.

Low cholesterol

FDA intends to exercise enforcement discretion for an omega-3 fatty acid qualified health claim for individual foods, other than fish and dietary supplements, provided that such foods meet the low cholesterol criteria (21 CFR 101.62(d)(2)). The October 31, 2000 letter[57] and subsequent letters from FDA[58], [59] did not discuss the low cholesterol criteria for dietary supplements; however, most fish oil containing dietary supplements do not meet the low cholesterol criteria per 50 g. Most dietary supplements containing EPA and DHA omega-3 fatty acids (whether fish oils or algal oils) are in softgels, and the amount of these oils per RACC is very small. Serving sizes are usually in between 1 - 2 softgels. FDA estimates that 1 - 2 softgels may weigh about 1 - 3 g, containing about 0.5 - 2 g of fish oil or algal oil. This amount of fish oil would not exceed the "low cholesterol" criteria (20 mg) per RACC but would exceed the "low cholesterol" criteria per 50 g basis if the supplements contain 100 percent fish oil. Liquid forms of fish oil dietary supplements are much less common and provide usually one teaspoon as a serving size (containing 4.5 g of total fat). This amount of fish oil may contain about 22 - 34 mg of cholesterol (based upon USDA National Nutrient Database for Standard Reference, Release 17), but again such levels of consumption would not be common.

Algal oil dietary supplements are sold as softgels and the RACC of the supplement is one softgel, containing 0.5 g of the mixture of algal oil and high oleic sunflower oil.[60] Both the 100 mg DHA softgel and the 200 mg DHA softgel contain less than 2 mg of cholesterol, which is below the "low cholesterol" criteria (20 mg) per RACC. The cholesterol content of algal oil will vary. The algal oil that Martek proposed to use for various food categories in its GRAS notification (GRAS No. 000137) contains higher levels of cholesterol (about 380 mg/100g without dilution) than does the algal oil currently used for dietary supplements (about 30 mg/100g without dilution). Even if the algal oil with the high cholesterol content were used for dietary supplements, the cholesterol content per RACC would be very small (about 2 mg of cholesterol) because the amount of oil per serving (0.5 g) is small, but the cholesterol content would exceed the "low cholesterol" criteria (20 mg) per 50 g basis.

FDA estimates that 50 g of fish oils would contain about 240 to 380 mg of cholesterol (USDA National Nutrient Database for Standard Reference, Release 17). The algal oil currently used for dietary supplements (without the addition of sunflower oil) contains about 15 mg of cholesterol per 50 g.[61] The algal oil that Martek proposed to use for foods in its GRAS notification (GRAS No. 000137) (without the addition of sunflower oil) contains about 190 mg of cholesterol per 50 g.

Since it is highly unlikely that individuals would consume 50 g of dietary supplements containing EPA and DHA per day, FDA has decided that it is not necessary to consider, as a factor in the exercise of its enforcement discretion, that EPA- and DHA-containing dietary supplements weighing equal to or less than 5 g per RACC contain no more than 20 mg of cholesterol on a 50 g basis. However, FDA has decided that it is necessary to consider, as a factor in the exercise of its enforcement discretion, that EPA- and DHA-containing dietary supplements that weigh more than 5 g per RACC contain no more than 20 mg of cholesterol on a 50 g basis.

"Extra Lean" criterion for fish

FDA has defined fish in 21 CFR 123.3(d) as "fresh or saltwater finfish, crustaceans, other forms of aquatic animal life (including, but not limited to, alligator, frog, aquatic turtle, jellyfish, sea cucumber, and sea urchin and the roe of such animals) other than birds or mammals, and all mollusks, where such animal life is intended for human consumption." For the purpose of omega-3 fatty acid qualified health claims about fish, FDA intends to consider certain factors in the exercise of its enforcement discretion for use of these claims on "products that are essentially all fish." This category includes fish without any added ingredients and fish with a small amount of added fat or carbohydrate that meets the definition of an insignificant amount in 21 CFR 101.9(f)(1). Examples of "products that are essentially all fish" are raw fish, boiled fish, and broiled fish.

In the past, fish was given an exception for the "low saturated fat" criterion and "the low cholesterol" criterion, along with game meat, in the health claim about diets low in saturated fat and cholesterol and reduced risk of CHD (21 CFR 101.75 (c)(2)(ii)). Instead of the "low saturated fat and low cholesterol" criteria, fish was required to meet the "extra lean" criterion as defined in 21 CFR 101.62(e)(3) (i.e, contains less than 5 g total fat, less than 2 g saturated fat, and less than 95 mg cholesterol per reference amount customarily consumed and per 100 g.).

In applying the "extra lean" criterion to fish, FDA was not thinking about oily fish that are rich in EPA and DHA omega-3 fatty acids. Most fish that are a rich source of EPA and DHA exceed the "extra lean" criterion for saturated fat (2 g of saturated fat per RACC) but do not exceed the saturated fat disqualifying level (4 g of saturated fat per RACC). One of the ways that FDA determines whether to consider nutrient content eligibility criteria as a factor in the exercise of its enforcement discretion is whether there are risk reduction data among healthy individuals that would suggest that there may be a benefit from consumption of the food, even though the food does not meet the nutrient content eligibility criteria. Such data, for purposes of this review, would include an association with a lower risk of CHD, shown in observational studies conducted in apparently healthy individuals. Because the following observational studies: Albert et al., 1998, 2002; Hu et al., 2002; Mozaffarian et al., 2003 showed an association of fish intake with reduced risk of CHD in apparently healthy individuals, FDA has decided that the agency does not need to consider, as a factor in the exercise of its enforcement discretion for products that are essentially all fish, that such products meet the "extra lean" criterion for saturated fat. However, FDA has decided to consider, as a factor in the exercise of its enforcement discretion for products that are essentially all fish, that such products meet the "extra lean" criterion for cholesterol (95 mg of cholesterol per RACC). Most fish that are rich sources of EPA and DHA do not exceed the "extra lean" criterion for cholesterol; thus, this approach should not disqualify many products that are essentially all fish. As discussed earlier, FDA now considers the "low fat" criterion not important here; therefore, FDA is not considering the "extra lean" criterion for total fat, as a factor in exercising its enforcement

discretion, which is not very different from how the agency approached its consideration of the "low fat" criteria as a factor for products that are essentially all fish.

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). Section 101.14 applies to all health claims regardless of types of diseases and health-related conditions. The disqualifying nutrient levels vary for individual foods, meal products, and main dishes. Disqualifying total fat levels are above 13.0 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 26.0 g per label serving size for meal products, and above 19.5 g per label serving size for main dish products. Disqualifying saturated fat levels are above 4.0 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 8.0 g per label serving size for meal products, and above 6.0 g per label serving size for main dish products. Disqualifying cholesterol levels are above 60 mg per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 120 mg per label serving size for meal products, and above 90 mg per label serving size for main dish products. Disqualifying sodium levels are 480 mg per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 960 mg per label serving size for meal products, and above 720 mg per label serving size for main dish products.

The general requirements for health claims also provide for FDA to authorize a health claim for 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. 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 (21 CFR 101.14(e)(3)).

The application of these regulatory provisions to omega-3 fatty acid qualified health claims on dietary supplements and conventional foods is discussed below.

"Total fat" disqualifying level

In the previous section (Section IV A), FDA explained that the agency has decided not to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements and conventional foods that bear an omega-3 fatty acid 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 RACC is 30 g or less or 2 tablespoons or less. The total fat disqualifying level for individual foods is above 13 g per RACC, per label serving size and per 50 g if 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 total fat disqualifying level. In addition, the disqualifying levels of nutrients are a required element of all health claims (i.e., cancer claims, osteoporosis claims, CHD claims) under 21 CFR 101.14. Because FDA has not evaluated the implications of eliminating the total fat disqualifying level for all possible health claims, FDA believes that it would be appropriate to consider, as a factor in the exercise of its enforcement discretion that conventional foods and dietary supplements that bear an omega-3 fatty acid qualified claim

meet the total fat disqualifying level. However, there are some situations, as discussed below, when FDA does not believe that such a factor is important to a decision about the exercise of its enforcement discretion.

Products that are essentially all fish

Based upon the data the agency has (USDA National Nutrient Database for Standard Reference, Release 17), FDA believes that total fat content of almost all fish that are a rich source of EPA and DHA are below the total fat disqualifying level (13.0 g of total fat per RACC). A few fish including halibut, herring, and mackerel contain total fat exceeding 13 g but contain less than 16.0 g of total fat per RACC. Because the observational studies that showed an association of fish intake with reduced risk of CHD do not distinguish fish species, FDA has no basis to discriminate one type of fish from any other type. In addition, the amount of total fat exceeding the disqualifying total fat level by these fish is small (about 3 g); therefore, FDA has decided to consider, as a factor in the exercise of its enforcement discretion, that products that are essentially all fish not exceed a total fat content per RACC of 16.0 g. If the total fat level of products that are essentially all fish exceeds the disqualifying level as defined by 21 CFR 101.14(a)(4), the disclosure statement (i.e., "See nutrition information for total fat, saturated fat, and cholesterol content") required by §101.14(e)(3) 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. Under 21 CFR 101.9(j)(10), if raw fish bears a health claim, nutrition labeling of the fish must be presented to the public in accordance with 21 CFR 101.45. Nutrition labeling of fish other than raw fish must follow the regulations specified in 21 CFR 101.9.

Other conventional foods and dietary supplements

Unlike fish, other EPA- and DHA-containing conventional foods that contain high levels of total fat have not been shown to have an association with a reduced risk of CHD in a population free of CHD. Therefore, FDA intends to consider the "total fat" disqualifying levels as defined in 21 CFR 101.14(a)(4) for all conventional foods, other than products that are essentially all fish, in the agency's consideration for the exercise of enforcement discretion for the omega-3 qualified health claim.

A comment suggested that FDA apply 6.5 g or less of total fat per RACC and per labeled serving instead of the "low fat" criterion as an eligibility criterion for spreads and mayonnaise-type dressings and requested an exemption for these foods from the "low fat" criterion and the total fat disqualifying level per 50 g. As explained earlier in this letter (Section IV A), FDA does not intend to consider the "low fat" criterion as a factor in the exercise of its enforcement discretion for the omega-3 qualified health claim. The 50 g weight-based criterion was developed, in part, to deal with foods with small serving sizes (e.g., foods with 15-30 g RACCs) that are dense in nutrients such as fat or sodium. As the agency noted in the final rule for general requirements for health claims, foods with small serving sizes may be consumed more frequently than once a day (58 FR 2478 at 2496; January 6, 1993). Health claims on foods such as spreads (RACC is 15 g) and mayonnaise-type dressings (RACC is 15 g) would promote their consumption, and could contribute to large intakes of total fat and calories that might not help to maintain healthy dietary practices. In addition, the level of scientific evidence linking EPA and DHA omega-3 fatty acids to reduced risk of CHD does not reach the significant scientific evidence standard; therefore, there is a fair amount of uncertainty as to whether frequent

consumption of EPA and DHA enriched spreads and mayonnaise-type dressings that contribute a large amount of total fat and calories would maintain healthy dietary practices, compared to other foods that do not contain such high amounts of fats and calories in such small serving sizes. Also, there are many foods that are naturally lower in total fat on a weight basis than spreads and mayonnaise-type dressings to which EPA and DHA containing food ingredients could be added; therefore, consumers would have many foods to choose from to obtain the purported health benefit of EPA and DHA. Therefore, FDA has decided to not accept the comment's suggestion, and instead, considers compliance with the "total fat" disqualifying levels as a condition of its enforcement discretion for spreads and mayonnaise-type dressings.

However, FDA does believe that it would be appropriate to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements that weigh equal to or less than 5 g per RACC that exceed the per 50 g total fat disqualifying level (i.e., above 13.0 g of total fat per 50 g), be eligible to bear an omega-3 fatty acid qualified health claim. As explained earlier, most EPA- and DHA-containing dietary supplements are in softgel forms. A serving of fish oil or algal oil dietary supplements in softgels normally contain extremely small amount of total fat (about 0.5 - 2 g of total fat). Liquid forms of fish oils are rare and the serving size is labeled as a teaspoonful. A teaspoonful of fish oil contains about 4.5 g of total fat. FDA is not aware of algal oil dietary supplements in a liquid form. In either softgel or liquid forms, one serving of an EPA- and DHA-containing dietary supplement that weighs equal to or less than 5 g per RACC would provide a very small amount of total fat. It is highly unlikely that individuals would consume 50 g of dietary supplements per day. Therefore, FDA believes that it would be appropriate to consider the exercise of its enforcement discretion for the use of an omega-3 fatty acid qualified health claim for dietary supplements that weigh equal to or less than 5 g per RACC but that exceed the disqualifying level for total fat per 50 g. If the total fat level of dietary supplements that weigh equal to or less than 5 g per RACC exceeds the per 50 g disqualifying level, the disclosure statement (i.e., "See nutrition information for total fat content") required by 21 CFR 101.14(e)(3) 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. FDA does not intend to exercise its enforcement discretion with respect to all other applicable labeling requirements that apply to dietary supplements, including 21 CFR 101.36(b)(2) that requires dietary supplements to declare the amount of nutrients when the level exceeds the amount that can be declared as zero. Please note that dietary supplements that are not subject to FDA's enforcement discretion that weigh more than 5 g per RACC are subject to the per 50 g total fat disqualifying level, consistent with 21 CFR 101.14(a)(4).

"Saturated fat" disqualifying level

In exercising enforcement discretion for the omega-3 qualified health claim, FDA intends to consider, as a factor in the exercise of its enforcement discretion, the disqualifying saturated fat level, as defined in 21 CFR 101.14(a)(4), for all conventional foods including products that are essentially all fish. FDA believes that almost all products that are essentially all fish do not exceed the saturated fat disqualifying level. FDA also believes that many other conventional foods to which EPA and DHA could be added do not exceed the saturated fat disqualifying level.

The EPA- and DHA-containing dietary supplements generally exceed the saturated fat disqualifying level per 50 g (i.e., above 4.0 g of saturated fat per 50 g). Fish oils contain 10 - 15 g of saturated fat per 50 g (USDA National Nutrient Database for Standard Reference, Release

17). The algal oil used for dietary supplements contains 15 - 20 g of saturated fat per 50 g.[62]

A serving of EPA- and DHA- containing dietary supplements in softgels normally contain about 0.5 - 2 g of total fat. This amount of fish oil or algal oil does not contain more than 1 g of saturated fat. Also, a teaspoon of fish oil contains about 0.9 - 1.4 g of saturated fat, a level that is below the saturated fat disqualifying level per RACC (4 g). Given that the suggested consumption level is so low, it is highly unlikely that individuals would consume 50 g of dietary supplements, which might contain about 10 - 20 g of saturated fat. Because the amount of saturated fat consumed through dietary supplements which weigh equal to or less than 5 g per RACC is small, FDA has decided not to consider, as a factor in the exercise of its enforcement discretion, that such dietary supplements bearing an omega-3 fatty acid qualified health claim meet the per 50 g saturated fat disqualifying level. If the saturated fat level of dietary supplements that weigh equal to or less than 5 g per RACC exceeds the per 50 g disqualifying level, the disclosure statement (i.e., "See nutrition information for saturated fat content") required by §101.14(e)(3) 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. Dietary supplements that weigh more than 5 g per RACC must comply with the per 50 g saturated fat disqualifying level, consistent with 21 CFR 101.14(a)(4).

"Cholesterol" disqualifying level

Products that are essentially all fish

As discussed earlier, FDA applies the "extra lean" criterion for cholesterol as a factor in the exercise of its enforcement discretion for the omega-3 fatty acid qualified health claim. The "extra lean" criterion allows more cholesterol per RACC (95 mg per RACC) than does the cholesterol disqualifying level (60 mg per RACC) for products that are essentially all fish. The agency has decided not to consider, as a factor in the exercise of its enforcement discretion, that these products bearing an omega-3 fatty acid qualified health claim meet the cholesterol disqualifying level because, as discussed earlier, observational studies (Albert et al., 1998, 2002; Hu et al., 2002; Mozaffarian et al., 2003) conducted among healthy individuals showed an association of fish intake with reduced risk of CHD. If the cholesterol level of products that are essentially all fish exceed the cholesterol disqualifying level, the disclosure statement (i.e., "See nutrition information for cholesterol content") required by §101.14(e)(3) 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.

Other conventional foods and dietary supplements

FDA intends to consider, as a factor in the exercise of its enforcement discretion, the disqualifying cholesterol level, as defined in 21 CFR 101.14(a)(4), for all conventional foods other than products that are essentially all fish and dietary supplements. FDA does not intend to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements weighing equal to or less than 5 g per RACC that bear an omega-3 fatty acid qualified health claim meet the cholesterol disqualifying criteria on a per 50 g basis for the same reasons discussed in the "low cholesterol" criteria in section IV A. If the cholesterol level of dietary supplements that weigh equal to or less than 5 g per RACC exceeds the per 50 g disqualifying level, the disclosure statement (i.e., "See nutrition information for cholesterol content") required by §101.14(e)(3) 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. Dietary supplements that weigh more than 5 g per RACC must comply with the per 50 g cholesterol disqualifying level, consistent with 21 CFR 101.14(a)(4).

"Sodium" disqualifying level

FDA intends to consider, as a factor in the exercise of its enforcement discretion for the use of an omega-3 fatty acid qualified health claim, the sodium disqualifying nutrient level as specified in 21 CFR 101.14(a)(4) for dietary supplements and conventional foods, including products that are essentially all fish.

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 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.

Dietary Supplements. The 10 percent minimum nutrient content requirement does not apply to dietary supplements (21 CFR 101.14(e)(6)).

"Products that are essentially all fish." The 10% minimum nutrient content requirement per RACC for protein is 5 grams. Products that are essentially all fish contain more than 5 grams of protein per RACC. Thus, FDA believes that such products would qualify for the requirement. FDA intends to consider, as a factor in the exercise of its enforcement discretion, that products that are essentially all fish that bear an omega-3 fatty acid qualified health claim meet the 10 percent minimum nutrient content requirement.

Other conventional foods. FDA intends to consider, as a factor in the exercise of its enforcement discretion, that other conventional foods meet the 10 percent minimum nutrient content requirement. A comment requested that FDA eliminate the minimum nutrient content requirement for dressings for salad and mayonnaise-type dressings. These foods are almost completely devoid of the nutrients that are required to be present at 10 percent or more of reference daily intake as specified in 21 CFR 101.14(e)(6). These foods are the type of foods that FDA had in mind when it required the 10 percent minimum nutrient content as a general requirement for health claims because nutritional values are low while fat and calories are high. FDA considers that the presence of an omega-3 qualified health claim on salad dressings and mayonnaise-type dressings that do not meet the 10% minimum nutrient content requirement would be inconsistent with the principle of health claims, i.e., that health claims should be used on foods that help maintain healthy dietary practices. Since there are many conventional foods enriched with EPA and DHA omega-3 fatty acids that could meet the 10 percent minimum nutrient content requirement, FDA believes that there is no need to consider enforcement discretion for a qualified claim on dressings for salad and mayonnaise-type dressings that do not meet the 10 percent minimum nutrient content requirement.

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 the 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 coronary heart disease that are authorized by regulation (e.g., health claims about fruit, vegetables and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease (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 the risk of CHD.

However, in FDA's previous letter, regarding omega-3 fatty acids and CHD qualified health claims (February 8, 2002 letter[63]), the agency decided that its exercise of enforcement discretion was not contingent on the use of the sentence (i.e., "It is known that diets low in saturated fat and cholesterol may reduce the risk of heart disease.") in connection with the claim. FDA made this decision because the scientific data that the agency relied on did not specifically evaluate whether the potential benefit of consuming EPA and DHA omega-3 fatty acids on CHD risk depends upon subjects consuming diets low in saturated fat and cholesterol. Because FDA is not aware of any new scientific data that might shed light on this subject, the agency has decided to take the same position discussed in the February 8, 2002 letter. Thus, FDA will not consider the exercise of its enforcement discretion to be contingent upon the use of the phrase or sentence relating diets low in saturated fat and cholesterol in the claim.

E. Daily Dietary Intake Needed to Achieve the Claimed Effect

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)). Several comments stated that 0.5 to 1 g of EPA and DHA are the effective daily dietary intake levels of EPA and DHA in reducing the risk of CHD, and that about one fourth of the amount (100 to 250 mg of EPA and DHA) should be the minimum level of EPA and DHA per RACC necessary to bear the qualified health claim. One comment suggested 32 mg of EPA and DHA as the minimum level of EPA and DHA necessary to bear the qualified health claim.

The minimum daily dietary intake level is based on the total amount of substance consumed in a day (g/day) and is calculated by summing the amount consumed through supplementation with the amount consumed in the diet. However, as concluded in FDA's previous review on omega-3 fatty acids and CHD (October 31, 2000 letter[64]), the agency finds that this provision cannot be applied to the qualified claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD because the scientific evidence for this relationship is not conclusive and does not support the establishment of a recommended daily dietary intake level or even a possible level of effect for the general U.S. population. Therefore, the agency continues to consider any label or labeling suggesting a level of omega-3 fatty acids to be useful in achieving a reduction in the risk of CHD for the general healthy population to be false and misleading under Section 403(a) of the Act.

FDA concludes that the use of EPA and DHA omega-3 fatty acids as dietary supplements and as an ingredient in conventional foods is safe and lawful under 21 CFR 101.14, provided that the daily intakes of EPA and DHA omega-3 fatty acids do not exceed 3 grams per person per

day from conventional foods and dietary supplement sources. Further, in order to help ensure that a consumer does not exceed an intake of 3 grams per person per day of EPA and DHA omega-3 fatty acids from consumption of a dietary supplement with the qualified health claim, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that an EPA- and DHA- containing dietary supplement bearing a qualified claim not recommend or suggest in its labeling a daily intake exceeding 2 grams of EPA and DHA.

As previously stated, the agency is encouraging manufacturers to limit the products that bear the qualified health claim for omega-3 fatty acids and reduced risk of CHD to a daily intake of 1 gram. Further, the agency would consider dietary supplements that bear the qualified claim that encourage intakes (in labeling or under ordinary conditions of use) above 2 grams per day to be outside the scope of the agency's consideration of its enforcement discretion. FDA expects EPA and DHA levels of conventional foods enriched with EPA and DHA containing food ingredients not to exceed the maximum use level specified in the menhaden oil GRAS affirmation or the GRAS notifications (to which FDA did not object) specific to their oil and food category. Also, as explained in the section on safety of foods containing EPA and DHA (see section I.C.), FDA intends to consider, as a factor in the exercise of its enforcement discretion, that conventional foods and dietary supplements that bear an omega-3 fatty acid qualified health claim declare the amount of EPA and DHA per serving in the claim.

V. Fish and Mercury

FDA received a few comments specific to the safety of fish and fish oils. The Martek petition stated that the presence of mercury in fish can harm the developing nervous systems of unborn children, infants, and young children, and therefore, the presence of mercury in fish and fish derivatives needs to be addressed in the health claim. The Martek petition referenced the March 2004 FDA advisory that cautions pregnant women, women who might become pregnant, nursing mothers and young children against the consumption of certain fish, and that suggests limits to weekly intake of other fish and shellfish. Specifically, the Martek petition stated that certain fish (including shark, swordfish, king mackerel, and tile fish) and other fish that similarly become included in a future FDA advisory should be ineligible to bear the proposed health claim. The Martek petition further suggested that when the health claim appears on other fish, it should be accompanied by an advisory statement suggesting a limited weekly intake for a vulnerable population of pregnant women, women of childbearing age, nursing mothers, and young children. In addition, the Martek petition stated that sources of omega-3 fatty acids derived from fish (such as fish oils) should be ineligible for the health claim unless the oil has been tested and found to contain less than 0.025 ppm of mercury. Finally, the Martek petition stated that the presence of mercury may offset the cardio-protective effects of omega-3 fatty acids, and therefore, that the claim would be misleading if it appeared on fish that contained elevated levels of mercury. The Martek petition stated that the mercury specific limitations and the advisory language would be needed to ensure that the claim is truthful and not misleading under sections 403(a) and 201(n) of the Act.

In a comment that you submitted in response to the Martek petition, you concurred with the suggested prohibition of the use of the proposed health claim on shark, king mackerel, swordfish, and tile fish and with the need for an advisory as part of the claim on other fish, but only for those fish that contained 1 ppm total mercury or less. You disagreed with the Martek petition that mercury may diminish the protective effects of omega-3 fatty acids on heart health. Finally, you presented modified language for the proposed advisory statement on other

fish and provided a statement for use on omega-3 fatty acid dietary supplements, containing 1 ppm total mercury or less, stating that intake of omega-3 fatty acids from such supplements should be limited to no more than 3000 mg/day. You suggested setting 1 ppm mercury as an eligibility criterion for qualified health claims for all foods and dietary supplements.

Yet another comment asserted that most of the refining techniques ensure the removal of contaminants, such as mercury, from fish oil products, and often achieve levels below the level of detection. The comment asserted that highly refined fish oils are safe to ingest at the recommended levels when consumed as conventional foods or as dietary supplements. FDA is not aware of any contrary information.

However, FDA does question the basis of the Martek petition's assertion that in order to bear omega-3 fatty acid qualified health claims, fish oils have to be tested and confirmed to contain less than 0.025 ppm of mercury, a level the Martek petition claims is the limit of detection for the most sensitive test accepted as standard by the Association of Official Analytical Chemists. Top selling fish oil dietary supplements have been reported not to contain any significant amount of mercury (Foran et al., 2003 and Consumer Reports, 2003) and FDA is not aware of any data that has shown otherwise. Further, FDA notes that in order for conventional foods to bear omega-3 fatty acid qualified health claims, EPA- and DHA-containing food ingredients have to be generally recognized as safe (GRAS). The determination of GRAS includes an evaluation of possible contaminants including mercury. For instance, the menhaden oil GRAS affirmation (21 CFR 185.1472(a)(2)(ix)) sets a limit on mercury content (0.5 ppm) and GRAS notifications for other EPA and DHA containing food ingredients[65] did not raise FDA's concerns for mercury. Given that there are no data showing that the mercury content of fish oils are high and that the Martek petition's reason for setting 0.025 ppm was based upon detection limit rather than effect on health, FDA is not persuaded to adopt the Martek petition's request.

With regard to your comment suggesting setting 1 ppm as an eligibility criterion for conventional foods and dietary supplements, as mentioned previously, FDA does not expect that the mercury content of dietary supplements would be close to 1 ppm. Also, the GRAS notification process for conventional foods ensures that the mercury level specifications for EPA and DHA containing food ingredients are low enough to protect the public health. Therefore, FDA concludes that there is no need for the agency's exercise of enforcement discretion for the omega-3 fatty acid qualified health claim on fish oils to be contingent on additional specifications for mercury.

FDA disagrees with the petitioners' contention that the omega-3 fatty acid qualified health claim should be accompanied by a product label statement about mercury content of fish and possible harmful health effects to the vulnerable population of pregnant women, women who might become pregnant, nursing mothers, and young children. For some time, FDA has been addressing the issue of reducing the exposure to the harmful effects of mercury by communicating with this target population (pregnant women, women who might become pregnant, nursing mothers, and parents of young children) through the use of consumer advisories. The latest consumer advisory was issued in March 2004 jointly by FDA and the Environmental Protection Agency.[66] This advisory includes information about mercury and makes recommendations about the kinds and amount of fish to eat and to avoid.

Agencies are granted broad discretion in determining the means by which to pursue policy goals.[67] Furthermore, the agency believes that the consumer advisory is a preferable method

to educate the target population about mercury in fish, for several reasons. First, consumer advisories are communicated to the target population directly.[68] Second, FDA believes that the advisory approach is more effective than a product label statement in relaying the complex messages about mercury in fish and shellfish. For example, the current advisory distinguishes the mercury content in the fish by identifying specifically which fish to eat and not eat and how much fish to eat of the different types. The advisory also identifies which common fish are low in mercury. This level of clarity and detail would be difficult to provide on a product label statement, due to the limited space. Furthermore, confusion could take place when different kinds of label statements are put on different species of commercial fish and not on locally caught fish. Third, a label statement that reaches the public at large can also have unintended adverse public health consequences. FDA focus group results suggest that people who are not in the target audience (i.e., women who are not nursing and not likely to become pregnant, and men) might eat less fish or refrain from eating fish altogether when they receive information about the mercury content of fish and possible harmful health effects to pregnant women, women who might become pregnant, nursing mothers, and young children (ORC Macro, 2003).

Therefore, the statement about possible harmful effects of mercury accompanying the qualified health claim would likely have the effect of negating the qualified health claim. In summary, FDA has decided that it is preferable not to use a label statement about mercury and possible harmful effect to pregnant women, women who might become pregnant, nursing mothers and young children as a condition for the agency's enforcement discretion for the omega-3 fatty acid qualified health claims.

FDA also disagrees with petitioners' suggestion that FDA not allow the use of omega-3 fatty acid qualified health claims on the four fish the FDA advisory warns the target population not to consume. FDA has not issued any advice about the consumption of these fish for the general public, particularly the non-target population (i.e., men, adolescents, women who are not nursing and not likely to become pregnant) and the agency does not believe that it is necessary to prohibit labels of these fish from bearing omega-3 fatty acid qualified health claims.

Finally, FDA disagrees with the assertion in the Martek petition that it would be misleading not to have a statement about mercury's effects on the cardio-protective effects of EPA and DHA omega-3 fatty acids from fish. There are only a few studies on this subject and results are inconsistent. A case-control study by Guallar et al. (2002) showed an association between mercury levels in toenails and increased risk of myocardial infarction. A case-control study within a large prospective cohort, conducted by Yoshizawa et al. (2003) found no association between mercury levels in toenails and CHD risk. After excluding dentists, who were found to have higher levels of mercury in toenails than other study participants, the analysis did not find a significant association between mercury levels in toenails and CHD risk. A cohort study by Salonen et al. (1995) did find an association between mercury levels in hair and increased risk of acute myocardial infarction. But, a case-control study within an ongoing community intervention program on cardiovascular disease and diabetes prevention, conducted by Hallgren et al. (2001), found an association between the concentration of mercury in erythrocytes and decreased risk of CHD. Thus, these observational studies showed inconsistent results regarding the relationship between mercury and CHD. FDA believes that whether mercury has any role in CHD risk is an unanswered scientific question. Consequently, it is not possible to determine whether mercury counteracts the cardio-protective effects of EPA and DHA omega-3 fatty acids from fish. In summary, FDA finds that the Martek assertion that mercury can counteract the

beneficial effect of omega-3 fatty acids as speculative, and FDA will not consider, as a factor in the exercise of its enforcement discretion, that foods that bear an omega-3 fatty acid qualified health claim also bear the suggested label statement, "At high levels, mercury may diminish the protective effects of omega-3 fatty acids on heart health."

VI. Conclusions

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

> Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [Name of the food] provides [ ] gram of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat, and cholesterol content.]

Dietary supplements may declare the amount of EPA and DHA per serving in "Supplement Facts," instead of making the declaration in the claim.

FDA intends to consider exercising enforcement discretion for the above qualified 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 claim, or that may raise safety concerns about the substance that is the subject of the claim.

Sincerely,

William K. Hubbard
Associate Commissioner for Policy and Planning

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[1] A letter from Christine J. Lewis, Ph.D., FDA to Jonathan W. Emord, Esq., Emord &

Associates, P.C., "Letter Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease" (Docket No. 91N-0103), October 31, 2000. http://www.cfsan.fda.gov/~dms/ds-ltr11.html

[2] A letter from Christine J. Lewis, Ph.D., FDA to Jonathan W. Emord, Esq., Emord & Associates, P.C., "Letter Clarifying Conditions for a Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease" (Docket No. 91N-0103), February 16, 2001. http://www.cfsan.fda.gov/~dms/ds-ltr20.html

[3] A letter from Christine J. Taylor, Ph.D., FDA to Jonathan W. Emord, Esq., Emord & Associates, P.C., "Letter Responding to a Request to Reconsider the Qualified Claim for Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease" (Docket No. 91N-0103), February 8, 2002. http://www.cfsan.fda.gov/~dms/ds-ltr28.html

[4] "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" that published on July 10, 2003. http://www.cfsan.fda.gov/~dms/nuttf-e.html

[5] See footnote 1

[6] See footnote 2

[7] See footnote 3

[8] This guidance published on July 10, 2003. http://www.cfsan.fda.gov/~dms/nuttf-b.html

[9] 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, 1991). FDA uses meta-analyses to identify relevant primary reports, which the Agency then evaluates individually.

[10] 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).

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

[12] *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.

[13] Angerer et al., 2002; Burr et al., 1989; GISSI et al., 1999; Marchioli et al., 2002; Maresta, et al., 2002; Singh et al., 1997

[14] Albert et al., 1998; Albert et al., 2002; Hallgren et al., 2001; Hu et al., 2002; Hu et al., 2003; Lamaitre et al., 2003; Mozaffarian et al., 2003; Rissanen et al., 2000

[15] Connor, 2000; de Lorgeril et al., 2002; Leaf et al., 2003

[16] Kris-Etherton et al., 2002

[17] Siscovick et al., 2003

[18] Bucher et al., 2002

[19] Bang et al., 1980

[20] Dyerberg et al., 1978; Goel et al., 2002; Pepe and McLennan, 2002

[21] Finnegan et al., 2003; Ghafoorunissa et al., 2002; Laidlaw and Holub 2003; Thies et al., 2003; Woodman et al., 2002

[22] Leng et al., 1998

[23] Nilsen et al. 2001

[24] Gillum et al., 2000; Osler et al., 2003; Torres et al., 2000

[25] Institute of Medicine, 2002

[26] U.S. Department of Agriculture, Agricultural Research Service. 2004. USDA National Nutrient Database for Standard Reference, Release 17 (http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/sr17.html).

[27] Summary of all GRAS notices. http://www.cfsan.fda.gov/~rdb/opa-gras.html

[28] Institute of Medicine of the National Academies. Dietary Reference Intakes. Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Part 2. Pages E-13, E-14. http://www.nap.edu/books/0309085373/html/

[29] Conventional foods enriched with EPA and DHA containing food ingredients are not included in the estimates.

[30] See footnote 1

[31]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)

[32] See footnote 1

[33] Albert et al., 1998; Burr et al., 1994 (also Burr et al., 1989); GISSI-Prevenzione Investigators,1999; Singh et al., 1997.

[34] Angerer et al., 2002; Marchioli et al., 2002; Maresta et al., 2002

[35] Finnegan et al., 2003; Ghafoorunissa et al., 2002; Laidlaw and Holub 2003; Thies et al., 2003; Woodman et al., 2002

[36] Leng et al., 1998

[37] Nilsen et al. 2001

[38] Neither the patient/subject nor the investigator is aware of which treatment the patient/subject is receiving (Spilker, 1991).

[39] FDA considers the subjects in this study to be representative of the general population because they did not have CHD and the physiological responses to omega-3 fatty acids is the same in hyperlipidemics and normolipidemics (reviewed in the 2000 letter).

[40] FDA considered this study relevant to its review because the bioavailability and distribution of EPA ethyl ester and DHA ethyl esters are equivalent to the natural forms of EPA and DHA from fish oil (Krokan, et al., 1993).

[41] Diabetes is a risk factor for CHD (What Makes a Heart Attach More Likely? National Institutes of Health, National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/health/dci/Diseases/HeartAttack/heartattack_risk.html). FDA considers this study on diabetics relevant to its review for establishing the substance-disease relationship because: (1) the diabetic study population did not have CHD and; (2) omega-3 fatty acids affect blood pressure in diabetics and healthy individuals similarly (Evidence Report/Technology Assessment: Number 94, Effects of Omega-3 Fatty Acids on Cardiovascular Disease, Agency for Healthcare Research and Quality, March 2004, page 63-64, http://www.ahrq.gov/clinic/evrptfiles.htm#o3cardio).

[42] Hu et al., 2002; Hu et al., 2003; Mozaffarian et al., 2003; Rissanen et al., 2000

[43] Gillum et al., 2000; Osler et al., 2003

[44] Albert et al., 2002; Hallgren et al., 2001; Lamaitre et al., 2003

[45] Torres et al., 2000

[46] Gillum et al., 2000; Osler et al., 2003

[47] Not all fish contain significant amounts of EPA and DHA omega-3 fatty acids (see footnote 26)

[48] Albert et al., 1998, 2002 ; Hallgren et al., 2001; Hu et al., 2002 ; Hu et al., 2003; Lamaitre et al.,2003; Mozaffarian et al., 2003 ; Rissanen et al., 2000; Torres et al., 2000

[49] Quintiles are values that divide a sample of data into five groups containing (as far as possible) equal numbers of observations.

[50] DPA, docosapentaenoic acid, is formed from EPA and is converted to DHA

[51] Ischemic heart disease is a form of coronary heart disease (CHD)

[52] A method of dietary assessment in which subjects are asked to recall how frequently certain foods were consumed during a specified period of time.

[53] Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, Part 2, Chapter 11, Page 11-40 (Institutes of the Medicine of the National Academies, 2002)

[54] 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).

[55] See footnote 1

[56] Telephone communication with Martin J. Hahn on August 24, 2004.

[57] See footnote 1

[58] See footnote 2

[59] See footnote 3

[60] See footnote 56

[61] See footnote 56

[62] See footnote 56

[63] See footnote 3

[64] See footnote 1

[65] See footnote 27

[66] U.S. Department of Health and Human Services and U.S. Environmental Protection Agency, "What You Need to Know About Mercury in Fish and Shellfish, 2004 EPA and FDA Advice For: Women Who Might Become Pregnant, Women Who are Pregnant, Nursing Mothers, Young Children." March 2004. http://www.cfsan.fda.gov/~dms/admehg3.html

[67] See, e.g., *UAW v. Chao*, 361 F.3d 249 (3rd Cir. 2004), (court deferred to OSHA's decision to pursue various non-regulatory measures, such as non-mandatory guidelines and educational programs, rather than to promulgate a rule limiting worker exposure to metalworking fluids, which were acknowledged by the court to have debilitating health effects); *CFA v. CPSC*, 990 F.2d 1298 (DC Cir. 1993), (court deferred to CPSC's decision to negotiate a comprehensive consent decree with vehicle manufacturers and dealer monitoring agreements, rather than to promulgate a rule banning the sale of all-terrain vehicles for use by children under the age of sixteen. The court stated: "We accord due respect, moreover, to an agency's selection of means for pursuing policy goals. Such choices implicate the allocation of scarce administrative resources; they involve forecasts about the consequences of proposed regulatory actions and other matters the agency ordinarily is best equipped to judge.")

[68] For instance, with regard to the mercury in fish advisory, the agency is targeting mailings about the advisory to appropriate health professionals, e.g., obstetrician - gynecologists. The agency is also targeting the appropriate media, e.g., women's magazines, as well as professional health organizations that deal with pregnant women, women who might become pregnant, nursing mothers and young children.

FDA Announces Qualified Health Claims for Omega-3 Fatty Acids September 8, 2004

Letter Responding to Health Claim Petition dated November 3, 2003 (Martek Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease September 8, 2004

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