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.

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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

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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.[65] 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[66]), 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[67]), 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 Mr. Emord submitted in response to the Martek petition, Mr. Emord 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. Mr. Emord disagreed with the Martek petition that mercury may diminish the protective effects of omega-3 fatty acids on heart health. Finally, Mr. Emord 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. Mr. Emord 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[68] 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 Mr. Emord's 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.[69] 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.[70] 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.[71] 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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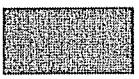

1. [1] "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" that published on July 10, 2003. http://www.cfsan.fda.gov/~dms/nuttf-e.html
2. [2] A letter from Christine J. Lewis, Ph.D., FDA to Jonathan W. Emord, Esq., Emord & Associates, 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

3. [3] 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
4. [4] 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
5. [5] See footnote 2
6. [6] See footnote 3
7. [7] See footnote 4
8. [8] This guidance published on July 10, 2003. http://www.cfsan.fda.gov/~dms/nuttf-b.html
9. [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. [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. [11] The physiology of animals is different than that of humans, thus animals often respond differently to dietary interventions compared to humans.
12. [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. [13] Angerer et al., 2002; Finnegan et al., 2003; Ghafoorunissa et al., 2002; Laidlaw and Holub 2003; Thies et al., 2003; Woodman et al., 2002
14. [14] Albert et al., 2002; Gillum et al., 2000; Hu et al., 2003; Lamaitre et al., 2003; Mozaffarian et al., 2003; Osler et al., 2003 ; Torres et al. 2000
15. [15] Baylin et al., 2003; Bemelmans et al., 2002; Djoussé et al., 2003; Forsyth et al., 2003; Singh et al., 2002
16. [16] Ascherio 2002; Bhatnagar and Durrington, 2003; Carroll and Roth, 2002; de Lorgeril and Salen, 2002; Grundy 2003; Harris et al., 2003; Holub 2002; Hu and Willet, 2002; Izzat and Avery, 2002; Leaf et al., 2003; Nordøy 2002; Sacks and Katan, 2002; Skerrett and Hennekens, 2003
17. [17] Bucher et al., 2002; Geleijnse et al., 2002
18. [18] Kris-Etherton et al., 2002
19. [19] Kris-Etherton et al., 2003; Lanzmann-Petithory et al., 2002; Morris, 2003; Siscovick et al., 2003
20. [20] Institute of Medicine, 2002
21. [21] Guallar et al., 2002; Yoshizawa et al., 2002
22. [22] Engler et al., 2002
23. [23] Burr et al., 1994 (also Burr et al., 1989); GISSI-Prevenzione Investigators,1999; Marchioli et al., 2002; Maresta et al., 2002; Singh et al., 1997
24. [24] Leng et al., 1998
25. [25] Nilsen et al. 2001
26. [26] Albert et al. 1998; Hallgren et al., 2001; Hu et al., 2002; Rissanen et al., 2000
27. [27] 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).
28. [28] Summary of all GRAS notices. http://www.cfsan.fda.gov/~rdb/opa-gras.html

29. [29] 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/
30. [30] Conventional foods enriched with EPA and DHA containing food ingredients are not included in the estimates.
31. [31] See footnote 2
32. [32]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)
33. [33] See footnote 32
34. [34] See footnote 2
35. [35] Albert et al., 1998; Burr et al., 1994 (also Burr et al., 1989); GISSI-Prevenzione Investigators,1999; Singh et al., 1997
36. [36] Angerer et al., 2002; Finnegan et al., 2003; Ghafoorunissa et al., 2002; Laidlaw and Holub 2003; Thies et al., 2003; Woodman et al., 2002
37. [37] Marchioli et al., 2002; Maresta et al., 2002
38. [38] Leng et al., 1998
39. [39] Nilsen et al. 2001
40. [40] Neither the patient/subject nor the investigator is aware of which treatment the patient/subject is receiving (Spilker, 1991).
41. [41] 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).
42. [42] 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).
43. [43] 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).
44. [44] Gillum et al., 2000; Hu et al., 2003; Mozaffarian et al., 2003; Osler et al., 2003
45. [45] Hu et al., 2002; Rissanen et al., 2000
46. [46] Albert et al., 2002; Lamaitre et al., 2003
47. [47] Hallgren et al., 2001
48. [48] Torres et al., 2000
49. [49] Gillum et al., 2000; Osler et al., 2003
50. [50] Not all fish contain significant amounts of EPA and DHA omega-3 fatty acids (see footnote 27)
51. [51] 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
52. [52] Quintiles are values that divide a sample of data into five groups containing (as far as possible) equal numbers of observations.
53. [53] DPA, docosapentaenoic acid, is formed from EPA and is converted to DHA
54. [54] Ischemic heart disease is a form of coronary heart disease (CHD)
55. [55] A method of dietary assessment in which subjects are asked to recall how frequently certain foods were consumed during a specified period of time.

56. [56] 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)
57. [57] 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).
58. [58] See footnote 2
59. [59] Telephone communication with Martin J. Hahn on August 24, 2004.
60. [60] See footnote 2
61. [61] See footnote 3
62. [62] See footnote 4
63. [63] See footnote 59
64. [64] See footnote 59
65. [65] See footnote 59
66. [66] See footnote 4
67. [67] See footnote 2
68. [68] See footnote 28
69. [69] 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
70. [70] 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.")
71. [71] 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.