DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

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VIA FACSIMILE AND U.S. MAIL

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RE: Health Claim: Vitamin E Dietary Supplements and Heart Disease
(Docket No. 99P-4375)

Dear Mr. Emord:

This letter is in further response to your petition of July 6, 1999, requesting the Food and Drug Administration (FDA) to authorize a health claim about the relationship between dietary supplements of vitamin E and reduced risk of heart disease. You identified in your petition the following three proposed model claims: (1) "*As part of a healthy diet low in saturated fat and cholesterol, 400 IU/day of Vitamin E (d-α-tocopherol or dl-α-tocopherol) may reduce the risk of heart disease. Individuals who take anticoagulant medicine(s) should consult their physicians before taking supplemental Vitamin E.*"; (2) "*As part of a healthy diet low in saturated fat and cholesterol, 100 – 400 IU/day of natural Vitamin E (d-α-tocopherol) may reduce the risk of heart disease. Individuals who take anticoagulant medicine(s) should consult their physicians before taking supplemental Vitamin E.*"; and (3) "*As part of a healthy diet low in saturated fat and cholesterol, 200 – 800 IU/day of synthetic Vitamin E (dl-α-tocopherol) may reduce the risk of heart disease. Individuals who take anticoagulant medicine(s) should consult their physicians before taking supplemental Vitamin E.*" FDA has reevaluated the petition, consistent with its strategy discussed below, in response to the court decision directing the agency to consider qualified health claims for dietary supplement labeling (*Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)) when the evidence in support of the claim does not meet the significant scientific agreement standard.

I. PROCEDURE AND STANDARD FOR EVALUATING THE CLAIM

In reconsidering this claim, FDA proceeded as described in the October 6, 2000, Federal Register notice entitled "Food Labeling; Health Claims and Label Statements for Dietary Supplements; Update to Strategy for Implementation of *Pearson* Court Decision." 65 Fed. Reg. 59,855 (2000) (the October 6 notice). FDA previously had evaluated your petitioned claim under the "significant scientific agreement" standard by which the health claim regulations require the agency to evaluate the scientific validity of claims. Under this

99P-4375

PDN 2

standard, FDA may issue a regulation authorizing a health claim only "when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence." 21 C.F.R. § 101.14(c). FDA informed you by a letter dated January 11, 2000 (the January 2000 letter) that the evidence in the petition did not meet the significant scientific agreement standard, and the agency denied the petition. A copy of that letter is enclosed.

For dietary supplement health claims that do not meet the significant scientific agreement standard, FDA must consider, under *Pearson*, whether to allow a qualified claim about the substance-disease relationship. Because current FDA regulations do not provide for qualified claims, FDA must also consider the circumstances under which it will exercise enforcement discretion for a qualified claim. Consistent with the *Pearson* decision, the agency considers whether consumer health and safety would be threatened by the qualified claim, and, if not, whether the evidence in support of the claim is outweighed by evidence against the claim, either quantitatively or qualitatively. See 164 F.3d at 650, 659 & n.10. If the evidence for the claim outweighs the evidence against the claim, and there is no health or safety threat, the agency considers whether a qualified claim can meet the general health claim requirements of 21 C.F.R. § 101.14, other than the requirement to meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. These requirements were not challenged in *Pearson* and therefore still apply.

In the October 6 notice, FDA explained that it would consider exercising enforcement discretion for a dietary supplement health claim that did not meet the significant scientific agreement standard if the scientific evidence for the claim outweighed the scientific evidence against the claim, if the claim included appropriate qualifying language, and if the other criteria listed in the notice were met. In that event, the agency explained, FDA would send a letter to the petitioner outlining the agency's rationale for its determination that the evidence did not meet the significant scientific agreement standard and stating the conditions under which the agency would ordinarily expect to exercise enforcement discretion for the claim. See 65 Fed. Reg. at 59,856. The agency also stated that, conversely, if the scientific evidence for the claim did not outweigh the scientific evidence against the claim, or the substance posed a threat to health, or the other criteria for the exercise of enforcement discretion were not met, FDA would issue a letter denying the claim and explaining its reasons for doing so. See 65 Fed. Reg. at 59,856.

The deadlines for FDA action in 21 C.F.R. § 101.70(j) apply to petitions for health claims. FDA initially responded to your petition within the prescribed 190 day time frame for issuing either a denial or a proposed regulation to authorize the health claim. In its January 2000 letter, the agency stated that after FDA completed a rulemaking to reconsider the general health claim regulations for dietary supplements, it would reconsider the petition. The agency subsequently agreed to decide by November 24, 2000, whether it would allow dietary supplement manufacturers to make the health claim with a qualifying statement. November 24 was the 540th day after submission of a separate health claim petition for Folic Acid, Vitamin B_6, and Vitamin B_{12} Dietary Supplements and Vascular Disease (Docket No.

99P-3029) (the B vitamin petition), pursuant to 21 C.F.R. 101.70(j). Following FDA's agreement to the November 24 date, a joint motion for a stay was filed in a lawsuit brought on your clients' behalf against the agency involving the B vitamin petition and the vitamin E petition that is the subject of this letter. The court granted the motion, and stayed the litigation until November 24, 2000. In November, FDA and your clients agreed to a further stay of the action. On November 30, 2000, the court granted this joint motion and stayed the litigation until January 12, 2001. On January 17, 2001, the court granted another motion to stay, and stayed the litigation until February 9, 2001. FDA is issuing this decision, consistent with its updated implementation strategy, on February 9, 2001.

II. SUMMARY OF REVIEW

FDA reviewed the evidence in your petition for a health claim about the relationship between dietary supplements of vitamin E and reduced risk of heart disease, and provided you with its decision in the January 2000 letter. FDA determined at that time that there was not significant scientific agreement (SSA) that the totality of publicly available scientific evidence supported the proposed claim.

In the January 2000 letter, FDA observed (at 2) that although the proposed health claim (as articulated in the three model claims) referred to heart disease, the information in the petition focused on a relationship of vitamin E supplements and cardiovascular disease (CVD). For example, the petition states, "In satisfaction of section 101.14(b)(1), the proposed health claim associates supplemental vitamin E with cardiovascular disease," (petition 99P-4375 at 7)). The petition also mentions (*id.*) that coronary heart disease (CHD) is the most common form of CVD. The agency interpreted in the January 2000 letter (at 2) the intent of the petition as addressing the relationship between vitamin E supplements and risk of CVD.

The January 2000 letter explained FDA's evaluation, under the SSA standard, of the scientific data submitted in support of the proposed claim. The agency did not find a sufficient basis to establish a causal relationship between vitamin E supplements and CVD risk from its evaluation of the results of the clinical intervention trials. The agency noted that, overall, the results of the observational studies were inconsistent, i.e., a clear relationship between vitamin E intake and a reduction of risk of cardiovascular disease could not be discerned. The agency concluded, therefore, that the results from the totality of scientific evidence, considering the limitations of some of the study designs and the inconsistent results obtained, provided an inadequate basis to support a relationship between vitamin E supplements and reduced CVD risk.

Under its *Pearson* implementation strategy as set out in the October 6 notice, FDA has considered the scientific evidence on the putative relationship between vitamin E and reduced risk of CVD. FDA considered any new evidence from human studies that have become available since its January 2000 decision, including information in your submissions of October 17 and 19, 2000. We first evaluated new evidence derived from human studies for its potential impact on our original conclusion that there was no significant scientific agreement for the claim that dietary supplements of vitamin E may reduce the risk of CVD. We then considered the totality of evidence presented in the petition and in the new studies to determine if the evidence for the claim outweighed the evidence against the claim. We

conducted both the original and current scientific evaluations consistent with the principles and procedures articulated in FDA's *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (December 1999).

Based on its review of the scientific evidence, including evidence published subsequent to January 11, 2000, FDA has concluded that the totality of the publicly available scientific evidence demonstrates lack of significant scientific agreement about the validity of a relationship between dietary supplements of vitamin E and a reduction of risk of CVD. FDA has further concluded that the weight of the evidence against the relationship is greater that the weight of evidence for the relationship.

III. SAFETY REVIEW

Under 21 C.F.R. § 101.14(b)(3)(ii), which was not challenged in *Pearson* and which still applies to FDA's review of a proposed dietary supplement health claim, the use of vitamin E at levels to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (the act).[1]

The applicable safety provisions require, for example, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling or under ordinary conditions of use. 21 U.S.C. 342(f)(1)(A). Further, a dietary supplement must not contain a poisonous or deleterious substance that may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling. 21 U.S.C. 342(f)(1)(D). Ensuring the safety of a dietary supplement that may bear a qualified claim is also consistent with the *Pearson* decision, in which the court stated that the agency could be justified in banning certain health claims outright if, for example, consumer health and safety would be threatened. See *Pearson*, 164 F.3d 650 at 657-60.

In its safety review in this current matter, FDA considered earlier safety reviews summarized in a 1991 proposed rule (56 Fed. Reg. 60624; November 27, 1991) and a 1993 final rule (58 Fed. Reg. 2622; January 6, 1993) on antioxidant vitamins and cancer, in which the safety of vitamin E intake was addressed. In the 1991 proposed rule, FDA noted that the National Research Council's (NRC) report entitled "Diet and Health" cited scientific evidence suggesting that large doses of vitamin E are relatively nontoxic. 56 Fed. Reg. at 60637-38. However, vitamin E supplementation may increase the risk of prolonged bleeding time for individuals routinely ingesting non-steroidal anti-inflammatory drugs, such as aspirin, and anticoagulant drugs, or for individuals who have a vitamin K deficiency (IOM/NAS, 2000 at 253).

[1] As discussed further in sections V, VI and VII, FDA is not currently authorizing a health claim or exercising enforcement discretion for a qualified claim describing the relationship between vitamin E and risk of cardiovascular disease.

FDA also considered the April 11, 2000 report of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (IOM/NAS, 2000) on Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (hereinafter the April 2000 DRI report). Based on its review, the IOM has established "Tolerable Upper Intake Levels" (UL) for vitamin E. An UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals. The UL for adults for vitamin E is 1,000 milligrams per day[2] based on the potential adverse effect of an increased tendency to hemorrhage.

The agency recognizes that there are potential safety concerns with the use of supplemental vitamin E that are currently not well defined. However, FDA is not currently authorizing a health claim or exercising enforcement discretion for a qualified health claim for vitamin E and cardiovascular disease. Thus, FDA need not address these potential concerns in this letter. Should the scientific evidence change in the future, such that the agency would consider authorizing a health claim or exercising its enforcement discretion for a qualified health claim, FDA would consider the potential safety concerns with the use of supplemental vitamin E.

IV. Review of the Scientific Evidence

A. Previous (1999) Scientific Review

A full discussion of FDA's earlier decision on your petition about the relationship between dietary supplements of vitamin E and reduced risk of CVD is provided in the January 2000 letter (enclosed). FDA concluded at that time that, based on the totality of publicly available scientific evidence, there was not significant scientific agreement among experts qualified by scientific training and experience to evaluate such evidence that a relationship between dietary supplements of vitamin E and reduced risk of heart disease is supported by the available evidence.

B. Current Scientific Review

FDA first considered whether any significant new human study data had become available in the months since its January 11, 2000 decision. The agency conducted a literature search to ensure that all relevant recent scientific literature was included in the current review.

We conducted a search in Medline and Biological Abstracts for articles published subsequent to 1999 that contained human data on vitamin E and cardiovascular disease, heart disease or stroke. We did not include preclinical studies (studies not performed in humans) because there are human studies available, including several large clinical trials, and the usefulness of data from preclinical studies is limited in that such studies cannot fully simulate human physiology and disease. Additionally, preclinical studies cannot accurately estimate appropriate intake levels or magnitude of effects in humans.

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[2] Based upon conversion factors identified in the April 2000 DRI report (at 244), this equates to about 1500 IU of natural vitamin E or about 2200 IU of synthetic (all racemic) vitamin E.

The only relevant study on vitamin E supplementation and CVD captured by our literature search was an analysis of data from the Heart Outcomes Prevention Evaluation study (HOPE 2000). Subsequently, you submitted to the docket an intervention study (Boaz et al., 2000) published in October 2000 (Sup 5, Docket 99P-4375) and a prospective cohort study (Watkins et al., 2000) published in July 2000 (Sup 4, Docket 99P-4375, ref. 12).[3] We recently became aware of two other relevant intervention studies. One is a large cancer study published in 1993 that also collected data on vascular disease endpoints (Blot et al., 1993). The other is an intervention study on cardiovascular risk that just published in January 2001 (Roncaglioni et al., 2001).

You have submitted a number of studies evaluating the role of vitamin E as protection against LDL-cholesterol oxidation (Sup 4, Docket 99P-4375). These studies provide information relative to hypothetical mechanisms potentially linking vitamin E intake and risk of CVD. In a brief critical review, Meydani (2000) also cites reports on similar mechanisms whereby vitamin E may reduce the risk of CVD. However, there are persuasive intervention studies, as discussed below, that evaluate the relationship between intake of dietary supplement vitamin E and direct measures of CVD events and mortality. These studies provide sufficient data on which FDA can base its decision about whether there is significant scientific agreement for a relationship between dietary supplement vitamin E intake and reduced risk of CVD, and on whether the weight of the evidence is more for or against such a relationship. Therefore, the information from studies on potential intermediate mechanistic links between vitamin E intake and CVD does not alter FDA's decision that the totality of the publicly available scientific evidence does not support a health claim or a qualified health claim for this relationship.

As noted in Section III above, the NAS/IOM, published a report in April 2000 on Dietary Reference Intakes for antioxidant vitamins, including vitamin E. We also considered the information and views presented in that report because it represents the views of experts on the state of the science for vitamin E.

1. INTERVENTION STUDIES

In an intervention study, the investigator controls whether the subjects receive an exposure (the intervention), whereas in an observational study, the investigator does not have control over the exposure. Therefore, intervention studies generally provide the strongest evidence for an effect. Unlike observational studies, which provide evidence of an association--but not necessarily a cause and effect relationship--between the substance and disease of interest, intervention studies can provide evidence of causal relationships or the lack thereof. Randomized, double-blinded, placebo-controlled clinical trials are considered the most

[3] You also submitted a "Supplemental Submission" discussing the economic impacts of the significant scientific agreement (SSA) guidance standard in August 2000 (Sup 2, Docket 99P-4375) and a "Supplemental Submission" of alleged ramifications of the SSA standard in October 2000 (Sup 3, Docket 99P-4375). The agency considered these submissions to be not relevant to its evaluation of the health claim about vitamin E dietary supplements and risk of CVD. Moreover, the submissions are immaterial because FDA is considering this health claim not only in light of the SSA guidance, but also in conformance with the Pearson implementation strategy. Under that strategy, the agency considers whether the weight of the scientific evidence supports an exercise of the agency's enforcement discretion for the use of an appropriate qualified claim that does not meet the SSA standard.

persuasive studies. When the results of such studies are available, they will be given the most weight in the evaluation of the totality of the evidence. See *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*, at 5.

Three randomized controlled clinical intervention trials evaluating the impact of vitamin E on the risk of cardiovascular disease have been published since our January 2000 letter (HOPE 2000; Boaz et al., 2000; Roncaglioni et al., 2001). In addition, we have become aware of a large clinical intervention trial, published in 1993, in which cerebrovascular mortality (a measure of CVD risk) was a secondary endpoint (Blot et al., 1993).

(a) *HOPE 2000*

The HOPE 2000 study is a 19 country, multi-center randomized, placebo-controlled, double-blinded clinical intervention trial designed to investigate the effects both of vitamin E supplements and of an angiotensin-converting-enzyme inhibitor drug (ramipril) on coronary heart disease and atherosclerosis in high-risk patients. The study was conducted as a two-by-two factorial design, in which subjects were randomly assigned to receive a vitamin E supplement and ramipril, vitamin E and the ramipril placebo, ramipril and the vitamin E placebo, or both placebos. The vitamin E groups took a daily supplement of 400 IU/day vitamin E from natural sources. The follow-up period was from 4 to 6 years. The subject population included a total of 9,541 male and female subjects, 55 years and older, who had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, in addition to at least one other CVD risk factor (hypertension, hypercholesterolemia, low serum HDL-cholesterol, cigarette use, or microalbuminuria). Mean age of the subjects was 66 ± 7 years. The primary outcome measure was a composite that included the sum of myocardial infarctions, strokes, and deaths from cardiovascular causes. Other measured outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer. For statistical analysis, the two groups receiving vitamin E supplementation were combined, and the two groups receiving the vitamin E placebo were combined.

There were no differences between the combined vitamin E group and the combined vitamin E placebo group for any of the outcome measures. The primary CVD outcome (myocardial infarction, stroke, or death from cardiovascular causes) occurred in 16.2 percent of the patients receiving vitamin E, and in 15.5 percent of patients receiving the vitamin E placebo (relative risk (RR), 1.05; 95 percent confidence interval (95% CI), 0.95 to 1.16; $p = 0.33$). There were no significant differences between the combined vitamin E group and the combined vitamin E placebo group in number of deaths from cardiovascular causes (7.2% and 6.9%; RR, 1.05; 95% CI, 0.90 - 1.22; $p = 0.54$); myocardial infarctions (11.2% and 11.0%; RR, 1.02; 95% CI, 0.09 - 1.15; $p = 0.74$); stroke (4.4% and 3.8%; RR, 1.17; 95% CI, 0.95 - 1.42; $p = 0.13$); or in number of deaths from any cause (11.2% and 11.2%; RR, 1.00; 95% CI, 0.89 - 1.13; $p = 0.99$). There were no significant differences between the combined vitamin E group and combined vitamin E placebo group for any of the other outcome measures; these included hospitalizations for unstable angina, hospitalizations for heart failure, revascularizations or limb amputations, angina of new onset, microvascular complications of diabetes, or total proportion of patients having any primary or secondary

event. There was consistency (i.e., no heterogeneity) of results among subjects defined according to sex, age, previous CVD, or use of other drugs.

In this large, well-controlled intervention study in high risk patients, there was a consistent lack of vitamin E effect in all measured outcomes, with a large number of cardiovascular events being included in the statistical analysis.

(b) *Boaz et al., 2000*

The secondary prevention study by Boaz et al. (2000) (SPACE study), with end-stage renal disease patients who were on renal dialysis and who had pre-existing CVD disease, was designed to test the effects of high dose vitamin E supplementation on the prevention of secondary CVD events in these patients. This was a double-blinded, placebo-controlled, intervention trial in 196 patients conducted at six hemodialysis centers in Israel. Subjects received either 800 IU/day of a vitamin E dietary supplement, or a matching placebo. The subjects were followed for a median of 519 days (about 1.5 years). The primary endpoint was a composite that included the sum of myocardial infarction, ischemic stroke, peripheral vascular disease, and unstable angina. Secondary endpoints were the individual components of the primary endpoint, total mortality, and cardiovascular mortality. Among the vitamin E supplemented-group subjects, with sudden death excluded, 16% (15/97) experienced a primary endpoint, while 33% (33/99) of the placebo group experienced a primary endpoint; the figures when sudden death was included were 19% (18/97) and 34% (34/99), respectively. The relative risk, with sudden death excluded, was 0.46 (95% confidence interval (CI): 0.27 - 0.78; $p = 0.014$), and with sudden death included was 0.54 (CI: 0.33 - 0.89; $p = 0.016$). When the components of the primary endpoint and other secondary endpoints were analyzed, only myocardial infarction (MI) displayed a significant difference; the two groups were not statistically significantly different for all other endpoints, including cardiovascular disease mortality. Among the supplemented group (sudden death excluded), 5% (5/97) experienced an MI, while 17% (17/99) of the placebo group did so. When sudden death was included, the figures were 8% (8/97) and 18% (18/99), respectively. The relative risk ratios were 0.30 (CI: 0.11 - 0.78; $p = 0.016$) with sudden death excluded, and 0.45 (CI: 0.20 - 0.99; $p = 0.04$) with sudden death included. Differences between the intervention and placebo groups in fatal and non-fatal MIs were not statistically significant; however, the study was not designed, and lacked the power, to detect a difference in this secondary endpoint.

This study was of relatively limited duration (median, 519 days) and of small size ($n = 196$). It was conducted in an unique population (end-stage renal disease patients with pre-existing CVD who were undergoing dialysis). It is unknown whether these results can be generalized to the general population. Total mortality was not different in the group receiving supplemental vitamin E (31/97 among the vitamin E supplemented subjects and 29/99 among placebo subjects). Of particular concern is the observation of excess deaths due to hemorrhage, pulmonary edema, mesenteric thrombosis, and post-surgery intestinal necrosis among the vitamin E supplemented group. Although the study lacked statistical power to determine the statistical significance of these adverse effects, these results are consistent with the known adverse effect of hemorrhagic toxicity associated with high doses of vitamin E.

(c) *Roncaglioni et al., 2001*

The study by Roncaglioni et al. (2001) (termed the Primary Prevention Project, or PPP) was a randomized, open-label (i.e., the subjects knew if they were treated or not, and if treated what the treatment was) clinical intervention trial. The study was conducted as a two-by-two factorial design intended to test whether chronic treatment with aspirin or vitamin E reduces the risk of major fatal and non-fatal cardiovascular events. The study was conducted by a cooperative group of 315 general practice physicians in Italy. Subjects were randomly assigned to receive either aspirin (100 mg enteric-coated aspirin per day) or no aspirin, and either vitamin E (one capsule of 300 mg synthetic alpha-tocopherol per day) or no vitamin E. The mean follow-up period was 3.6 years. The subject population included a total of 4,495 male and female subjects, 50 years and older, who had at least one recognized major cardiovascular disease risk factor, but no history of cardiovascular disease. Risk factors included: age (>65 years), hypertension, hypercholesterolemia, diabetes, obesity, and family history of myocardial infarction before 55 years of age. Mean age of the subjects was 64.4 ± 7.6 years. The primary outcome was a composite that included endpoints of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

The primary composite outcome occurred in 2.5 percent of the subjects receiving vitamin E and in 2.3 percent of the subjects not receiving vitamin E (RR = 1.07; 95% CI = 0.74 – 1.56). Thus, vitamin E had no effect on the primary outcome. There also were no vitamin E effects on overall mortality (RR = 1.07; 95% CI = 0.77 – 1.49), on CVD-related death alone (RR = 0.86; 95% CI = 0.49 – 1.52), on overall myocardial infarction (RR = 0.89; 95% CI = 0.52 – 1.58), or on overall stroke (RR = 1.24; 95% CI = 0.66 – 2.31). Subjects receiving vitamin E had a lower incidence of peripheral artery disease than did controls (RR = 0.54; 95% CI = 0.30 – 0.99; $p < 0.05$). There were no significant vitamin E effects on any other secondary endpoint measures analyzed; these included non CVD deaths, non-fatal myocardial infarctions alone, non-fatal stroke alone, angina pectoris, transient ischemic attack, and revascularization procedures.

In this randomized clinical trial in 4495 subjects without pre-existing cardiovascular disease, there was a consistent lack of vitamin E supplement effect on all primary and secondary outcomes with the exception of incidence of new peripheral vascular disease. We note that this result occurred despite the unblinded nature of the study, which could potentially have biased the study toward finding an effect. As is discussed further in section V below, this study was halted early, and therefore must be interpreted with caution. However, it is noteworthy that the lack of any suggestion of an effect of vitamin E on reduction of CVD risk was one factor contributing to the halting of the study. Unlike the secondary prevention vitamin E intervention clinical trials conducted in subjects with existing CVD, this was a primary prevention study conducted in subjects with CVD risk factors but without pre-existing CVD. Thus, the study by Roncaglioni et al. (2001) is relevant to an evaluation of the relationship between dietary supplement vitamin E intake and reduction of CVD risk in the general population.

(d) *Blot et al., 1993*

A large (29, 584 subjects at risk for stomach cancer, but who were not identified as being at risk for CVD) multifactorial, randomized, placebo-controlled, intervention study of 5.25 years duration was conducted in Linxian, China to evaluate the effect of various nutrients on various cancer endpoints. Data were also collected on cerebrovascular mortality and total mortality. The authors reported finding little or no reduction in mortality from cardiovascular disease among subjects receiving the supplement combination that included vitamin E (no data provided), and a 10% reduction in mortality from cerebrovascular disease (RR = 0.90, 95% CI = 0.76-1.07). Although this study must be interpreted with caution because it was not designed to evaluate the independent effect of vitamin E on CVD, it is suggestive that in a such a large population there was little or no effect of vitamin E on risk of CVD mortality (a measure of CVD risk).

2. OBSERVATIONAL STUDIES

Several types of observational, or epidemiological, studies can provide information on the association between a substance and a disease; however, these studies often do not provide a sufficient basis for determining whether a substance-disease association reflects a causal, rather than a coincidental, relationship. In prospective, or cohort, studies, disease-free subjects are recruited within a specified group of people, such as female nurses (the cohort), and the dietary habits of the subjects are determined. The study tracks the subjects over an extended period of time to see whether they develop the disease being investigated. At the end of the follow-up period, the dietary patterns of subjects who developed the disease during the follow-up period are compared to those of the subjects who did not develop the disease to discern dietary patterns that are associated with risk of the disease. In case-control studies, subjects with existing diagnosed disease (the cases) are enrolled in a study. These subjects are matched by identifiable characteristics (i.e., age, race, gender) to disease-free subjects (the controls). The diets of the two groups are then compared to discern dietary habits associated with risk for the disease. Population, or correlational, studies use grouped data to examine the relationship between dietary exposure and health outcomes among populations. Such studies do not examine relationships for individuals and have traditionally been regarded as useful for generating, rather than testing, hypotheses regarding diet-disease relationships. As such, population studies are generally accorded little weight.

An inherent limitation of dietary observational studies is the extent to which intake of a specific substance can be assessed. There is considerable uncertainty in the quantitative measurement of habitual food intake over long periods of time. Some studies typically use a retrospective food frequency questionnaire in which the study subjects are asked to recall their typical diets (in terms of foods eaten, frequency of eating, and serving sizes) over several previous years. Such techniques are subject to recall bias, particularly for dietary factors thought possibly related to the disease. Further, there can be uncertainty in the translation of food intake data, by calculation from food composition tables, into data on intake of a specific substance. The natural variability of foods, the effects of processing, compositional complexities that may be associated with the substance, and the consequential inconsistencies in analytical methods together can make it difficult or impossible to accurately calculate substance intake from food intake data. These and other considerations can make it difficult

to establish whether the substance or some other component of the diet is responsible for any observed benefit. Therefore, there are significant limitations to assessing substance intake data from observational studies and relating intake to the disease. Since the primary variable assessed in these studies is food consumption, and there is uncertainty involved in the computation of substance intake from such data, the usefulness of these types of studies to differentiate effects of the substance in the food from effects of other components of the food is limited.

One prospective cohort study (Watkins et al., 2000), evaluating vitamin use and the risk of cardiovascular disease, has been published since our January 2000 letter. This was an analysis of data from the Cancer Prevention Study II (CPS-II), which was a nationwide, prospective mortality study of about one million men and women aged 30 years and older. The subjects were followed from enrollment in 1982 until 1989. The analysis by Watkins et al. (2000) included about 1 million men and women from the CPS-II population who reported usable data on vitamin use on enrollment. The authors initially stratified the analyses by the presence of diagnosed disease at baseline, but subsequently excluded persons with a history of the disease of interest (i.e., ischemic heart disease, stroke or cancer). However, all-cause mortality analyses included all subjects, regardless of preexisting disease at baseline. Vitamin use stratification was by: no vitamin use (referent group); multivitamin use; use of vitamin A, C or E; and use of multivitamins and vitamin A, C or E. The analyses were not intended to be informative for vitamin A, C or E separately, and data on these vitamins were combined into a single exposure variable (Watkins et al., 2000, at 153).

Multivitamin users had heart disease and CVD mortality risks similar to nonusers when persons reporting preexisting heart disease or stroke were excluded from the analysis. Persons reporting use of multivitamins together with vitamin A, C or E had lower mortality risks than nonusers. Among this latter group, persons who reported at entry into the study that they had taken the combination of vitamins for greater than five years tended to have lower risk than those who reported having used the combination for five years or less.

This study does not allow an evaluation of the specific relationship that is the subject of the claim, namely the relationship between vitamin E intake and reduced risk of CVD. Any putative protective effect of vitamin E cannot be parsed out from the data on combined vitamin use presented in the study report. Furthermore, the information about vitamin use was only gathered at entry into the study. No follow-up data on vitamin E intake were gathered to assure continued use of the vitamin, and there is no information about the level of vitamin E intake. The study cannot differentiate between effects from supplemental vitamin E use *per se,* and effects wherein supplemental vitamin E use is simply a marker for other life-style or dietary intakes that may be affecting the disease risk. For these reasons, FDA did not consider this study further.

3. OTHER CONSIDERATIONS: *April 2000 DRI report*

The IOM/NAS April 2000 DRI report included a section on the relationship of vitamin E to chronic diseases, including cardiovascular disease. The report concluded that available data do not adequately substantiate the premise that increasing the intake of vitamin E will reduce the risk of coronary heart disease. The Food and Nutrition Board recognized that some

that in a population with risk factors for CVD but with no prior history of CVD, vitamin E provides no reduction of risk for CVD.

The usefulness of the recent results reported by Boaz et al. (2000) are questionable. This study was relatively short term (about 1.5 years), was small (196 subjects), and was conducted in an unique patient population (end-stage renal disease patients with pre-existing CVD who were on dialysis) from whom extrapolation of results to the general population is very uncertain. Renal disease patients, particularly those on dialysis, often exhibit significant differences in measures of nutritional status when compared to the general population or patients with other types of diseases. Moreover, despite a favorable effect on the primary CVD endpoints, CVD-related and total mortality were not different in the vitamin E supplemented group. Of particular concern are the excess deaths due to hemorrhage, pulmonary edema, mesenteric thrombosis, and post-surgical intestinal necrosis in the vitamin E treated group. Given recognized concerns of adverse effects of high vitamin E intakes on hemorrhagic tendencies, these observations underscore the need for more study in this patient population.

The prospective cohort study by Watkins et al. (2000) is not helpful in our evaluation of the relationship between vitamin E intake and reduced risk of CVD. That is because no independent effect of vitamin E can be discerned from this study.

The IOM/NAS April 2000 DRI report concluded that there are insufficient data to recommend supplemental vitamin E as a heart disease preventative for the general population.

FDA has evaluated the totality of publicly available scientific evidence, including the studies newly discussed in this letter, the April 2000 DRI report, and the studies discussed in the January 2000 letter. The agency concludes from this evaluation that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and risk of cardiovascular disease.

VI. AGENCY'S CONSIDERATION OF A QUALIFIED CLAIM

The agency stated, in its October 6, 2000 notice, that it would consider exercising enforcement discretion for a dietary supplement health claim when the following conditions are met:

1) The claim is the subject of a health claim petition that meets the requirements of 20 C.F.R. § 101.70;
2) the scientific evidence in support of the claim outweighs the scientific evidence against the claim, the claim is appropriately qualified, and all statements in the claim are consistent with the weight of the scientific evidence;
3) consumer health and safety are not threatened; and
4) the claim meets the general requirements for health claims in 21 C.F.R. § 101.14, except for the requirement that the evidence supporting the claim meet the significant scientific agreement standards and the requirement that the claim be made in accordance with an authorizing regulation.

Thus, in the absence of significant scientific agreement, FDA has considered, under *Pearson*, whether the weight of the scientific evidence in support of the claim outweighs the scientific evidence against the claim.

A. Weight of the Scientific Evidence

1) *Intervention studies*

We evaluated, as summarized in the January 2000 letter and earlier in this letter, eleven clinical intervention trials that addressed vitamin E intake and CVD risk (HOPE 2000; GISSI-Prevenzione, 1999; Blot et al., 1993; Roncaglioni et al., 2001; ATBC study (ATBC Study Group, 1994; Rapola et al., 1997; Virtamo et al., 1998); Stephens et al., 1996; Boaz et al., 2000; Takamatsu et al., 1995; DeMaio et al., 1992; Williams et al., 1971; and Gillilan et al., 1977). These eleven trials, however, are not weighted equally. Among these intervention trials, we regard the results from the HOPE 2000 study to be the most persuasive, for the reasons outlined below.

The most persuasive scientific evidence comes from randomized, double-blinded, placebo-controlled clinical intervention trials. The hypothesis that high doses of supplemental vitamin E can reduce the morbidity and mortality of CVD has been tested directly in several such trials. Of these trials, there are several reasons for relying most heavily upon the results of the HOPE 2000 study to evaluate whether there is a relationship between vitamin E and CVD risk.

The HOPE 2000 study was a large study (9541subjects) and of relatively long duration (about 4.5 years). It was designed to measure the effect of 400 IU vitamin E daily on a CVD composite outcome (a summation of myocardial infarction, stroke and death from cardiovascular causes as primary outcome events). It had a large number of the primary outcome cardiovascular events (1,511) occurring during the study duration. Because of these factors (size, duration, and number of primary outcomes), FDA considered the results of the HOPE 2000 study to be the most persuasive. The HOPE 2000 study was conducted in about 280 medical centers in the western hemisphere and in Europe. Thus, the HOPE 2000 study tested the hypothesis at issue in a large and diverse range of the high-risk patient population. The HOPE 2000 study consistently found a lack of effect of vitamin E on all primary and secondary outcomes, even among diabetics, a patient population at particularly high risk of CVD events. Because of the absence of any impact on the event outcomes in this study of high risk patients, it is very unlikely that vitamin E would have any effect in the general population.

The HOPE 2000 study has been critiqued, for example, with respect to lack of collection of dietary data and use of natural vitamin E (Jialal & Devaraj, 2000), and to possible differences in risk factor distribution between study groups (Boaz et al., 2000). Specifically, the study was criticized for not reporting baseline dietary intakes of vitamin E, for not using plasma levels to confirm compliance, for using a natural rather than a synthetic source of vitamin E, and for misinterpreting available observational studies. The criticism of absence of baseline dietary data is common to many available studies. It is difficult, however, to obtain accurate data on dietary vitamin E intakes. (IOM/NAS, 2000). Moreover, randomization procedures

would be expected to "equalize" effects of varying dietary intake levels across study groups. Although the absence of plasma levels to confirm treatment compliance is unfortunate, the authors did report high and comparable compliance between treatment and placebo groups. Criticism of vitamin E source materials and misinterpretation of observational studies have been rebutted by one of the HOPE 2000 authors (Yusuf, 2000).

All the intervention studies evaluated in this current review have design or conduct factors that may subject the studies to criticisms. We note some of these factors in our summaries of the studies in earlier sections of this letter and below in this section, and have considered such factors in our weighting of the evidence for or against a relationship between intake of vitamin E and reduced risk of CVD. FDA believes that the HOPE 2000 study, despite the criticisms, remains the most persuasive study because, overall, it is the one most well-designed (i.e., in terms of factors cited above as examples) to address whether vitamin E intake can reduce the risk of CVD in a broad spectrum of subject populations.

The Gruppo Italiano per lo Sudio della Sopravvivenza nell'Infarto miocardio trial (GISSI-Prevenzione, 1999) was a large (11,324 subjects) randomized intervention trial, conducted for 3.5 years, and designed to investigate supplemental vitamin E effects on CVD. Although this study was non-blinded, and therefore subject to the possibility of bias toward finding an effect, the authors document evidence of similarity in dietary habits and other relevant measures across the four study groups. Even with this potential for bias in favor of an effect, the GISSI-Prevenzione Study found no relationship between vitamin E supplements and risk for any of the CVD outcomes evaluated in the study.

The large (29,584 subjects), long duration (5.25 years) multifactorial intervention study by Blot et al. (1993) was discussed in Sections IV and V. As noted there, this study must be interpreted with caution because it was not designed to evaluate the independent effect of vitamin E on CVD. However, although it involved a combination intervention (i.e., beta-carotene, selenium and vitamin E), this combination of substances had no effect on the risk of CVD. This study is suggestive that none of the component substances of the intervention had an effect. Therefore, the study is also suggestive that in a large population vitamin E alone has no effect on the risk of CVD mortality, consistent with the HOPE 2000 study.

The 3.6-year, 4495 subject primary intervention study by Roncaglioni et al. (2001) was discussed in Section IV and V. As noted there, although this study was halted early for ethical reasons and therefore must be interpreted with caution, there was no hint that vitamin E reduces the risk of CVD. This result is consistent with the HOPE 2000 study, even though the unblinded nature of the Roncaglioni study could potentially have biased it toward finding an effect.

The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study (ATBC Study Group, 1994; Rapola et al, 1997; Virtamo et al, 1998) was a large (29,133 subjects) randomized, double-blinded, placebo-controlled vitamin E intervention trial that had lung cancer, rather than CVD, as its primary outcome. It did, however, include some information on CVD endpoints and risk factors. Rapola et al. (1997) conducted a post-hoc analysis of the ATBC study data for a small subset of the study population in which subjects had had a

previous myocardial infarction (1,862 men). Among these men, there was an apparent beneficial effect of vitamin E on non-fatal myocardial infarction incidence at a median followup of 5.3 years in those who were receiving vitamin E (multivariate adjusted RR = 0.62, 95% CI = 0.41-0.96; 40 treated cases v. 55 placebo cases), but an apparent adverse vitamin E effect on fatal coronary heart disease incidence (multivariate adjusted RR = 1.33, 95% CI = 0.86-2.05; 54 treated cases v. 39 placebo cases) and no effect on all major coronary events (multivariate adjusted RR = 0.90, 95% CI = 0.67-1.22; 94 cases in both treated and placebo groups). In a separate post-hoc analysis of the ATBC study data which included all the ATBC subjects who had not had a previous myocardial infarction (27,271 subjects), Virtamo et al. (1998) found, at a median follow-up of 6.1 years, no effect of vitamin E alone on non-fatal myocardial infarctions (RR = 1.04, 95% CI = 0.89-1.22; 307 treated cases v. 296 placebo cases), no effect on fatal coronary heart disease incidence (RR = 0.90; 95% CI = 0.75-1.08; 212 treated cases v. 238 placebo cases), and no effect on all major coronary events (RR = 0.98; 95% CI = 0.87-1.10; 519 treated cases v. 534 placebo cases). When multiple treatments were taken into account in a 2 X 2 factorial analysis, vitamin E treatment provided no effect on reducing nonfatal myocardial infarction (-1%, 95% CI = -12% to +10%; 596 treated cases v. 608 non-treated cases), a slight reduction in all major coronary events (-4%, 95% CI = -12% to +4%; 1030 treated cases v. 1081 non-treated cases), and a small reduction in fatal coronary heart disease (-8%, 95% CI = -19% to +5%; 434 treated cases v. 473 non-treated cases). Although vitamin E supplementation was associated with fewer deaths from ischemic heart disease and ischemic stroke (ATBC Study Group, 1994), there was a 50% increase in deaths from hemorrhagic stroke in the vitamin E supplemented group (66 in the vitamin E supplemented group v. 44 in the control group, out of a total of 3,570 deaths in the study). The vitamin E supplemented group also had an increased incidence of deaths associated with certain cancers. Overall mortality was slightly increased (2%) in the vitamin E supplemented group. This study was not designed to evaluate the effect of vitamin E on CVD risk, and the analyses of CVD were post-hoc analyses. Therefore, the results of the study with respect to vitamin E and reduction of CVD risk cannot be considered conclusive, and its findings for this relationship therefore must be interpreted with caution. However, the study results are suggestive that vitamin E does not reduce the risk of CVD, and the results raise the need for caution until the relationship between vitamin E and these disease endpoints is better understood.

The CHAOS study (Stephens et al., 1996) was relatively small (2,002 subjects) and of short duration (1.4 years). It found a significant vitamin E effect on the composite major cardiovascular event outcome and on non-fatal myocardial infarctions, but no effect on deaths from cardiovascular causes. This study is suggestive that vitamin E may reduce the risk of CVD. However, although the study was not designed to have adequate statistical power to detect an effect of vitamin E supplementation on all-cause mortality, the finding of a non-significant vitamin E effect on increased overall mortality suggests that there may be potential safety concerns about vitamin E that should be addressed in future studies.

The recently reported SPACE study (Boaz et al., 2000) was a small (196 subjects), double-blinded, placebo-controlled study of short duration (median, 519 days). It found that high intakes of vitamin E (800 IU/day) by end-stage renal disease dialysis patients with pre-existing CVD, a particularly unique high-risk group, afforded a reduction in risk of some CVD endpoints. The SPACE study found a significant vitamin E effect on the composite

major cardiovascular event outcome (i.e., the sum of incidences of myocardial infarction, ischemic stroke, peripheral vascular disease, and unstable angina), and on myocardial infarctions separately as a secondary endpoint, but no effect on other secondary cardiovascular endpoints (including, individually, stroke, peripheral vascular disease, unstable angina pectoris, and cardiovascular disease mortality) and a slight increase in total mortality. As with the CHAOS study, the effect of vitamin E varied across CVD endpoints. This patient population (i.e., end-stage renal patients with pre-existing CVD who were on hemodialysis) differs significantly from populations in other studies evaluated by FDA. For this reason, it is unclear whether the results from this patient population can be extrapolated to a broader patient population or the general population, or to safe long-term use.

We commented in the January 2000 letter on the small (147 subjects), double-blinded, placebo-controlled, six year study reported by Takamatsu et al. (Takamatsu, et al., 1995) for subjects without evident disease at entry into the study. The frequency of coronary disorders was reported to be higher in the control group than in the group receiving vitamin E; however, this difference was based on a total of 7 cases of coronary disorders among subjects withdrawing from the study prior to completion, and the study did not report the frequency of CVD-related illness among subjects remaining in the study. Because the study objective was intervention on blood parameters, we maintained in the January 2000 letter that the study was less relevant for evaluating the association between vitamin E and reduced risk of CVD. We suggest here that there are other reasons to interpret these results with caution. This study was not designed for and does not have the statistical power to evaluate effects of vitamin E supplementation on CVD (only 7 cases over 6 years). The CVD morbidity data presented by the authors are for subjects withdrawing from the study for medical reasons. The study report does not explicitly indicate whether the list of all 15 subjects (intervention and placebo groups) withdrawing from the study for medical reasons captures all of the CVD-related illness in the study group. There is no other discussion of CVD illness in the study population. Among the seven in the control group who withdrew for medical reasons, "myocardial damage," as assessed by certain electrocardiogram (ECG) measures, was the reason given. The authors did not present data on the natures of the illnesses of those subjects who remained in the study and were "treated successfully." Finally, we note that while the frequency of reported disorders was higher in the control group, the authors report that the morbidity rate for myocardial infarction or angina pectoris was not different. Thus, the results are difficult to interpret and provide little help in further assessing the relationship between vitamin E intake and reduction of CVD risk.

We also commented in the January 2000 letter on intervention studies by DeMaio et al. (1992), Williams et al. (1971) and Gillilan et al. (1977). These three studies evaluated endpoints not generally observed in the newer and larger studies. The small, randomized study by DeMaio et al. (1992) found no association between vitamin E intake (1200 IU/day) and recurrent stenosis, but a trend toward an association for restenosis. Williams et al. (1971) found a benefit for intermittent claudication; however, the study was not randomized, and some subjects were switched between the groups during the study. A small double-blind, cross-over study by Gillilan et al. (1977) did not find a relationship between a vitamin E intake of 1600 IU/day and symptoms of angina.

The available intervention studies evaluated the effect of vitamin E on CVD in populations of widely varying sizes, and with a range of risk for CVD from no known risk to very high risk. A variety of CVD endpoints were measured. The results of the most persuasive study (HOPE 2000) showed no relationship between dietary supplement vitamin E intake and reduction of risk of CVD. The other large intervention studies (GISSI-Prevensione, 1999; Blot et al., 1993; Roncaglioni et al., 2001; and the ATBC study) were consistent with the results of the HOPE 2000 study. FDA concludes, with particular consideration to the most persuasive study (HOPE 2000), that the weight of the scientific evidence against the claim about the relationship between vitamin E dietary supplements and reduced risk of CVD outweighs the scientific evidence in support of a claim about this relationship.

2) *Observational studies*

FDA has concluded above that the weight of the scientific evidence against the claim about the relationship between vitamin E dietary supplements and reduced risk of CVD outweighs the scientific evidence in support of a claim about this relationship. An intervention study is the more persuasive type of study because it directly evaluates the impact of an intervention on a measured outcome. Observational studies are indirect, less persuasive types of studies. We summarize below our conclusions about available observational studies that examined the effect of vitamin E on risk of CVD.

We observed in the January 2000 letter (at 11) that, overall, the results of prospective observational studies have been inconsistent with respect to an association between vitamin E intake and CVD risk. Our summary of the prospective observational studies available at that time showed that, of the seven studies evaluated, two supported an association between vitamin E intake and reduced risk of CVD (Stampfer et al., 1993; Knekt et al., 1994), three did not support an association (Asherio, et al., 1999; Keli et al., 1996; Klipstein-Grobusch et al., 1999), and two yielded results that depended upon the nature of the vitamin E intake parameter being assessed (total, supplemental or dietary) (Rimm et al., 1993; Kushi et al., 1996).

In section IV of this letter, we reviewed a new prospective cohort study that was not available to us in January 2000 (Watkins et al., 2000), and that suggested that persons using multivitamins together with vitamins A, C or E had lower mortality risks. We noted the reasons why FDA did not consider this study useful, including the fact that any putative effect of dietary supplement vitamin E alone cannot be parsed out from the data.

Intervention studies provide sufficient scientific evidence on which FDA can base its conclusion that the weight of the scientific evidence is more against than in support of a claim about the relationship between dietary supplement vitamin E intake and reduced risk of CVD. Therefore, we have relied upon the intervention studies in our consideration of a qualified claim.

3) *Summary*

The HOPE 2000 study is the most persuasive in evaluating the claim about the relationship between dietary supplements of vitamin E and reduced risk of CVD. The HOPE 2000 study,

a large (9,541 subjects) study of relatively long duration, was conducted across multiple centers in high-risk patient populations and consistently found no effect across a number of primary and secondary CVD endpoints. Because of the absence of any impact on the event outcomes in this study of high risk patients, it is very unlikely that vitamin E would have any effect in the general population.

The GISSI-Prevenzione study (1999) and the study by Blot et al. (1993) were also large (11,324 and 29, 584 subjects, respectively) and of relatively long duration (3.3 years, on average, and 5.25 years, respectively). They also found no effect.

The 4,495-subject PPP study by Roncaglioni et al. (2001) was of relatively long duration (a mean of 3.6 years). Although its open label design favored finding an effect, no effect of vitamin E on risk of CVD was seen. Because the study was stopped early for ethical reasons, including the fact that there was no evidence of vitamin E benefit, it was underpowered.

The ATBC study, also of large sample size (27,271 subjects) and relatively long duration (6.1 years of follow-up in the report by Virtamo et al., 1998), also showed no effect on the relationship between vitamin E and reduced risk of CVD, and it suggested possible safety concerns. Although this study was not designed to study CVD, its large sample size, duration, and suggestion either of no effect or a perhaps increased risk, particularly for hemorrhagic stroke, highlight the need for further research, and warrant caution about the relationship between vitamin E intake and CVD risk.

The CHAOS and SPACE trials are of low persuasiveness compared with the five studies cited above, as they are small in size and of short duration. They showed an effect on some CVD endpoints, but no effect on others. Further, it is questionable whether the findings of the SPACE study can be extrapolated from the study population (endstage renal patients on hemodialysis) to the general population. Moreover, indications of possible increased risk in all-cause mortality in both studies suggest a need for further research.

The study by Takamatsu et al. (1995), while superficially suggestive of a possible relationship, was a small study with design features that make it difficult to interpret, including the fact it is unclear if the list of subjects withdrawing from the study for medical reasons captures all of the CVD-related illnesses in the study group. Other questions surrounding the results of this study are discussed earlier in this section under intervention studies. Gillilan et al. (1977) found no relationship between vitamin E intake and symptoms of angina. DeMaio et al. (1992) found no association for recurrent stenosis, but a trend toward an association for restenosis. The study by Williams et al. (1971), as noted earlier in this section under intervention studies, is not useful because of errors in conduct of the study.

Having considered all the evidence in its previous (as summarized in the January 2000 letter) and current scientific reviews, FDA concludes that the weight of the scientific evidence against a claim relating intake of vitamin E dietary supplements and reduced risk of cardiovascular disease outweighs the scientific evidence for a claim about such a relationship. All of the most scientifically persuasive intervention studies, i.e., the large, long-term intervention studies, found no effect of vitamin E on risk of CVD. Intervention studies that showed an effect on some CVD endpoints (but not on others), were smaller, of shorter

duration, and the scientific evidence from these smaller studies did not outweigh the scientific evidence from the larger, longer-term intervention studies. Further, for the reasons previously stated in this letter, the scientific evidence from the observational studies did not outweigh the evidence from the larger, longer-term intervention studies. Therefore, a claim for a relationship between vitamin E supplements and CVD risk cannot be qualified in such a way as not to mislead consumers.

B. Consumer Health and Safety

FDA has concluded that there is no significant scientific agreement for a relationship between vitamin E supplements and CVD risk, and that the scientific evidence for a relationship is outweighed by the scientific evidence against the relationship. Since FDA does not intend to exercise enforcement discretion with respect to the use of a qualified claim on vitamin E supplements, FDA did not have to evaluate the safety of vitamin E with respect to the use of a health claim or a qualified claim. The agency has noted in section III of this letter that there are potential safety concerns with the use of vitamin E supplements. Should the scientific evidence change in the future, such that the agency would consider authorizing a health claim or exercising its enforcement discretion for a qualified health claim, FDA would consider these potential safety concerns at that time.

VII. CONCLUSION

FDA has determined that health claims relating vitamin E supplements and reduced risk of cardiovascular disease are inherently misleading and cannot be made non-misleading with a disclaimer or other qualifying language. See *Pearson*, 164 F.3d at 659. The use of such health claims is therefore prohibited by the Federal Food, Drug, and Cosmetic Act. A dietary supplement that bears a claim about vitamin E supplements and reduced risk of cardiovascular disease will be subject to regulatory action as a misbranded food under 21 U.S.C. § 343(a)(1) and (r)(1)(B); as a misbranded drug under 21 U.S.C. § 352(a) and (f)(1); and as an

unapproved new drug under 21 U.S.C. § 355(a). FDA does not intend to exercise enforcement discretion with respect to the use of a qualified health claim relating dietary supplement vitamin E intake and reduced risk of CVD.

Sincerely,

Virginia L. Wilkening

for Christine J. Lewis, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Attachments (2)
Reference list
January 2000 letter