DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

January 11, 2000

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RE: Petition for Health Claim: Vitamin E Dietary Supplements and Heart Disease (Docket Number 99P-4375)

Dear Mr. Emord:

This responds to your health claim petition dated July 6, 1999, submitted to the Food and Drug Administration (FDA) on behalf of Julian M. Whitaker, M.D., Durk Pearson and Sandy Shaw, American Preventive Medical Association, and Pure Encapsulations, Inc., requesting that the agency authorize a health claim on the relationship between dietary supplements of vitamin E and reduced risk of heart disease.

FDA has carefully reviewed the scientific evidence submitted in the petition and is not able to conclude that, based on the totality of publicly available scientific evidence, there is significant scientific agreement among experts qualified by 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. The agency's conclusion is based on its evaluation of your petition and the information contained therein, and its own review of the available observational and interventional studies.

In your petition you requested that, consistent with the decision in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999), if the agency found that the proposed claim did not satisfy the standard of significant scientific agreement, the agency authorize the claim with such disclaimer or disclaimers as the agency deemed necessary to avoid a potentially misleading connotation. As explained in the notice that was published in the *Federal Register* on December 1, 1999 (64 FR 67289), until a rulemaking to reconsider the general health claims regulations for dietary supplements is complete, FDA intends to deny, without prejudice, any petition for a dietary supplement health claim that does not meet the significant scientific agreement standard in 21 CFR § 101.14(c). Once that rulemaking is complete, the agency will, on its own initiative, reconsider any petitions denied under this process. The agency will reconsider petitions in the order that it originally received them. Accordingly, the agency is not at this time authorizing the use of the proposed claim with disclaimers.

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At this time, consistent with 21 CFR § 101.14(c), based on the determination that significant scientific agreement does not exist, the agency is denying without prejudice your petition for a health claim on dietary supplements of vitamin E and reduced risk of heart disease. Below is the agency's rationale for its conclusions concerning significant scientific agreement.

I. Background: Petition for Vitamin E Dietary Supplements and Heart Disease and Preliminary Requirements

Your petition identifies dietary supplements of vitamin E as the substance that is the subject of the proposed claim. Although the petition identifies heart disease as the disease or health-related condition that is the subject of the proposed claim, there is other language in the petition which indicates that cardiovascular disease (CVD) is the subject of the proposed claim. For example, the petition states, "In satisfaction of section 101.14(b)(1), the proposed health claim associates supplemental vitamin E with cardiovascular disease," (p. 7). The petition also states that CVD includes diseases of the heart and circulatory system (p. 7). Although the petition does not provide an inclusive list of these diseases, it specifically mentions coronary heart disease (CHD) (p. 7) as the most common and serious form of cardiovascular disease and specifies stroke (p. 7) as another CVD that is a leading cause of death in the United States. Therefore, the agency is interpreting the term "heart disease", the disease endpoint which you identify in the petitioned claims, includes the broader spectrum of cardiovascular diseases. The specific claims for which authorization is sought are identified in three proposed model claims as follows: (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."

The petition also provides information with respect to the preliminary requirements for a health claim specified in 21 CFR § 101.14:

- that the substance conforms to the definition in § 101.14 (a)(2);
- that the substance contributes nutritive value and retains that attribute when consumed at levels that are necessary to justify the claim (§ 101.14 (b)(3)(i));
- that use of the substance at the levels necessary to justify the claim is safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (§ 101.14 (b)(3)(ii)); and

- that the substance is associated with a disease for which the general U.S. population is at risk (§ 101.14 (b)(1)).

II. Agency's Review of the Scientific Evidence for the Claim

On December 22, 1999, the FDA published in the Federal Register (64 FR 71794) a notice of availability of the guidance entitled, "Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (hereinafter "Guidance"). In this Guidance document, the FDA presented how it generally evaluates the scientific validity of a health claim. The agency's review of your health claim was performed in conformance to the principles enumerated in the Guidance. You are encouraged to consult this publicly-available Guidance document for detailed information on these matters.

In addition, the Guidance specifically addresses a number of sequential threshold questions that need to be addressed in the agency's review of the scientific evidence for a health claim before significant scientific agreement can be assessed. These threshold questions include: (1) Have studies appropriately specified and measured the substance that is the subject of the claim?, (2) Have studies appropriately specified and measured the disease that is the subject of the claim?, and (3) Are any and all conclusions about the substance/disease relationship based on the totality of publicly available scientific evidence? After consideration of these questions, significant scientific agreement can be assessed. An assessment of significant scientific agreement considers whether there is a sufficient body of sound, relevant scientific evidence to permit the conclusion that a change in the dietary intake of the substance will result in a change in the disease endpoint. In the agency's review of your health claims, the usefulness, relevance, and generalizability of studies for the relationship between dietary supplements of vitamin E and reduced risk of CVD were carefully evaluated, in terms of specification and measurement of vitamin E, the substance of the claims, and reduction of risk of CVD, the disease or health-related condition that is the subject of the claims.

The summary of scientific data presents three lines of evidence regarding the proposed claims for a relationship between dietary supplements of vitamin E and the reduction of risk of CVD: evidence regarding the measurement of the substance, vitamin E; evidence regarding the measurement of the disease or health-related condition, reduction of the risk of CVD; and evidence regarding the association of vitamin E and reduction of the risk of CVD.

A. Measurement of the substance that is the subject of the petitioned claims

The proposed claims identify dietary supplements of vitamin E as the substance of the relationship. One of the initial determinations made in the agency's review of your health claims was whether or not a plausible relationship exists between the substance and the

disease. We therefore, considered studies with measures of vitamin E from both supplemental and/or food sources. If such a relationship appears tenable, later determinations would include an assessment of appropriate source and qualifying level of the substance that are found to reduce the risk of disease. However, the agency concludes that there is not a sufficient relationship between vitamin E and reduced risk of CVD at this time. Therefore, we did not assess, in our review of your petition, the appropriate source and qualifying level of vitamin E.

Only studies with measurement of vitamin E could be considered in the agency's review. Those considered included (a) interventional studies that controlled the intake of vitamin E; (b) observational studies based on estimates of vitamin E intake (food and/or supplemental sources); and (c) observational studies with estimates of vitamin E status, collected prospectively, as a surrogate measure of intake. Ecological studies were not considered in our review because population food supply or food disappearance data are less specific estimates of vitamin E intake than estimates from individuals. In addition, studies that examined antioxidants other than vitamin E (i.e., probucol) were submitted in the petition but were not relevant to the review.

Measurement of Substance: Controlled Intake of Vitamin E-Interventional Studies

The agency included, in its review, interventional studies (including both primary and secondary prevention studies) concerning the relationship between vitamin E that measured and/or controlled intake relative to CVD outcomes (Rapola et al., 1996; Takamatsu et al., 1995; The ATBC Study Group, 1994; Tornwall et al., 1997; Virtamo et al., 1998; DeMaio et al. 1992; Gillilan et al., 1977; GISSI Investigators, 1999; Rapola et al., 1997; Rapola et al., 1998; Stephens et al., 1996; and Williams et al., 1971). These studies provided the strongest measurement of vitamin E intake because the intervention was applied in a quantifiable and identifiable manner (i.e., the investigator controlled the form and amount of vitamin E consumed by subjects). These studies compared subjects receiving vitamin E (a dose ranging from 50 IU to 800 IU/day) to subjects not receiving a test dose of vitamin E. They assessed food intake at baseline in some of the studies, but alteration of diet during the supplemental intervention was not a design feature of the studies. Overall, these studies provided useful information on the measure of the substance that is the subject of the claim. In our review, we did not rely upon interventional studies of combination products because the effect of vitamin E alone could not be determined.

Measurement of Substance: Estimated Intake of Vitamin E- Observational Studies

The evidence presented in your petition included observational studies with estimates of vitamin E intake (total, from foods, or from supplements) (Ascherio et al., 1999; Bolton-Smith et al., 1992; Donnan et al., 1993; Keli et al., 1996; Klipstein-Grobusch et al., 1999; Knekt et al., 1994; Kritchevsky et al., 1995; Kushi et al., 1996; Losonczy et al., 1996; Meyer et al., 1996; Rimm et al., 1993; Sahyoun et al., 1996; and Stampfer et al., 1993). Compared to interventional studies, observational studies provide less definitive measures of vitamin E intake because measures of vitamin E intake in such studies are estimates of

intake based on self report and calculated amounts rather than more direct measures of controlled intake. The results of observational studies generally do not provide evidence for a causal relationship, that is, any association that is observed in these studies cannot necessarily be attributed to vitamin E because other factors may confound the relationship.

The observational studies that the agency reviewed and evaluated employed several dietary assessment techniques to estimate vitamin E intake. These techniques ranged from diet history interviews to food frequency questionnaires. The methodology for assessing supplemental intakes of vitamin E also varied. In some studies, qualitative information on the use of vitamin E supplements (e.g., yes/no response to a query about participants' consumption of vitamin E supplements) was obtained; in other studies consumer reports of dose, duration, and frequency of supplemental vitamin E use was also ascertained. The dietary assessment techniques presented in these studies are limited in that they cannot be relied upon to estimate dietary intake accurately because of self reports of intakes and are further limited by the lack of availability of valid and complete composition databases for nutrients.

We, therefore, use and interpret such data cautiously and such data carried less weight in our review of your health claims than the measures of controlled vitamin E intake obtained from interventional studies. Within these limitations, the agency considered these observational studies because they provided information under actual consumer conditions of use and provided additional information for our assessment about the evidence for the relationship between vitamin E and reduction of risk of CVD.

You identified several prospective studies, in which investigators recruited subjects and estimated vitamin E intake prior to occurrence of CVD (Keli et al., 1996; Knekt et al., 1994; Kushi et al., 1996; Losonczy et al., 1996; Meyer et al., 1996; Rimm et al., 1993; Sahyoun et al., 1996; and Stampfer et al., 1993). Several prospective observational studies which ascertained total, food source, or supplemental intakes of vitamin E by quintile or other ranking (Ascherio et al., 1999; Keli et al., 1996; Klipstein-Grobusch et al., 1999; Knekt et al., 1994; Kushi et al., 1996; Rimm et al., 1993; Sahyoun et al., 1996; and Stampfer et al., 1993) provided the more useful estimates of vitamin E intake among the observational studies because they measured intake prior to the occurrence of disease.

Measurement of Substance: Vitamin E Status as Surrogates for Intake- Observational Studies

You included observational studies with measures of vitamin E status as surrogates of vitamin E intake, primarily measures of plasma or serum concentrations of vitamin E (Eichholzer et al., 1992; Evans et al., 1998; Hense et al., 1993; Kok et al., 1987; Salonen et al., 1985; and Street et al., 1994). In these studies, cases and controls were drawn from the population in a cohort or longitudinal study and blood or tissue samples were obtained prospectively.

Measures of vitamin E status as a surrogate for intake in these observational studies may be influenced by factors other than vitamin E intake. Therefore, an association found in an observational study generally does not provide evidence for a causal relationship. We therefore, use and interpret such data cautiously and such data carried less weight in our review of your health claims than the measures of controlled vitamin E intake obtained from interventional studies.

B. Measurement of the disease that is the subject of the petitioned claims

Measurement of Disease: Cardiovascular Disease Endpoints

In the petition, you state that the studies submitted demonstrate that "(1) LDL oxidation increases cardiovascular disease risk, (2) increased consumption of vitamin E inhibits LDL oxidation, and (3) increased consumption of vitamin E, with attendant inhibition of LDL oxidation and platelet adhesion, lowers cardiovascular disease risk." Your petition, therefore, identifies CVD as the disease or health-related condition that is the subject of the proposed claims, even though the claims submitted identify "heart disease" as the disease or health-related condition. Accordingly, of your submitted studies that have measures of CVD, we have included studies in our review with either mortality or morbidity measures (e.g., prevalence or incidence) of the following CVD endpoints: CHD, stroke, myocardial infarction (MI), peripheral artery disease, ischemic heart disease, coronary artery disease (CAD), vascular disease, intermittent claudication, restenosis, and angina pectoris. We also considered carotid artery ultrasound measurements, ankle brachial pressure index (ABPI), and treatment procedures, such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, for which CVD is the underlying cause, as CVD endpoints which were relevant to our review.

Measurement of Disease: LDL oxidation and other endpoints

In your petition, you assert that the studies submitted support a relationship of increased consumption of vitamin E with a corresponding inhibition of LDL oxidation. Some studies have also hypothesized LDL oxidation as having a role in progression of atherosclerosis, a precursor to clinical CVD endpoints.

However, at this time there is insufficient evidence in humans establishing a causal relationship between oxidized LDL and risk of CVD. As such, biochemical indicators of oxidized LDL are not acceptable surrogate biomarkers of CVD, and cannot be considered as substitutes for direct measures of the disease. In short, a causative role for oxidatively modified-LDL in CVD has not been established. The agency recognizes that you submitted some studies suggesting that oxidation of LDL or autoantibodies to LDL were associated with the risk of CVD (Boyd et al., 1989; Haberland et al., 1988; Halevy et al., 1997; Liu et al., 1992; Salonen et al., 1992). However, these studies have at most only provided circumstantial evidence of this occurrence and they are insufficient to establish a causal relationship between LDL oxidation and the risk of CVD.

In your petition, you also implied that vitamin E has other biologic functions that have been hypothesized to influence CVD risk, such as inhibition of platelet adhesion and aggregation, inhibition of the expression and function of adhesion molecules, and attenuation of the synthesis of leukotrienes (Chan, 1998). The agency did not consider these other biologic functions because there is insufficient evidence at this time to demonstrate a causal relationship between any of the above mentioned biologic functions of vitamin E and development of CVD. Therefore, measures of these biologic functions cannot be considered surrogate biomarkers of the disease endpoint.

C. Evidence for the Relationship Between Vitamin E and Cardiovascular Disease

The agency included, in its review, the interventional studies you submitted in your petition concerning the relationship between vitamin E that measured and/or controlled intake relative to CVD outcomes. Interventional trials for reduction of the risk of a chronic disease such as CVD may be divided into two categories: 1) primary prevention trials designed to test reduction of the first occurrence of a disease in generally healthy subjects with or without risk factors for the disease, and 2) secondary prevention trials designed to test reduction of recurrence or progression of a disease in a patient population already diagnosed with the disease. Dietary interventions in secondary prevention trials for the reduction of risk of CVD generally act to prevent, slow, or reverse the disease process. The results of both types of interventional trials can provide insight on the causal relationship between substance and disease. The results of secondary prevention trials are useful to establish whether, in high risk populations with high doses of vitamin E, a relationship exists, but do not answer the question about appropriate doses for a reduction of risk in the general population. FDA reviewed secondary prevention studies in its evaluation of the evidence because they provide information on the causal relationship between the substance and disease under sensitive research conditions. The results of primary prevention trials, however, are most applicable to evaluating the reduction of risk of disease in the general population.

Interventional Studies

The agency concludes that the outcomes from the available primary prevention studies are not sufficient to establish the relationship between vitamin E and reduction of risk of CVD. Furthermore, the outcomes of secondary prevention studies did not provide sufficient information on the causal relationship between vitamin E and CVD.

Primary Prevention Studies: Based on the primary prevention studies (Rapola et al., 1996; Takamatsu et al., 1995; The ATBC Study Group, 1994; Tornwall et al., 1997; and Virtamo et al., 1998), we conclude that there is insufficient evidence to support a relationship between vitamin E and reduction of risk of CVD.

One reason for the insufficient evidence from the primary prevention studies is that none of the studies were designed to measure the association between vitamin E and reduced

risk of CVD. The ATBC Study was designed to intervene on lung cancer (Rapola et al., 1996; The ATBC Study Group, 1994; Tornwall et al., 1997; and Virtamo et al., 1998) and the study by Takamatsu et al., was designed to intervene on blood parameters, including LDL oxidation, as well as to measure the prevalence of any illness (Takamatsu et al., 1995).

In the case of the ATBC study (The ATBC Study Group, 1994), several secondary analyses were considered (Rapola et al., 1996; Tornwall et al., 1997; and Virtamo et al., 1998). The original study reported that the vitamin E supplemented group had lower ischemic heart disease and ischemic stroke death rates, but higher hemorrhagic stroke and other CVD death rates compared to the group not receiving vitamin E supplementation (The ATBC Study Group, 1994). However, statistical analysis of these relationships was not provided in the study results. The CVD death rate differential between the group receiving vitamin E and the group not receiving vitamin E, therefore, may not be statistically significant. Of the secondary analyses, only Rapola et al. (Rapola et al., 1996) showed a statistically significant beneficial effect for vitamin E on a CVD endpoint, which was incidence of angina pectoris; no beneficial effects were observed for incidence of major coronary events (Virtamo et al., 1998) or intermittent claudication (Tornwell et al., 1997). The angina pectoris (Rapola et al., 1996) and intermittent claudication (Tornwell et al., 1997) CVD endpoints, however, may be viewed as questionable because the assessment of these CVD endpoints were obtained solely through the use of a questionnaire without confirmatory clinical diagnostic criteria. This may compromise the validity of the disease endpoint measurement.

The other primary interventional study (Takamatsu et al., 1995) observed that the frequency of coronary disorders was higher in the control group compared to the group receiving vitamin E. This was a small study, the objective of which was to intervene on various blood parameters including measures of LDL oxidation, and therefore less relevant for assessing the association between vitamin E and reduced risk of CVD. Overall the primary prevention studies did not provide evidence for the relationship between vitamin E and reduced risk of CVD.

Secondary Prevention Studies: Based on the available secondary prevention studies (DeMaio et al. 1992; Gillilan et al., 1977; GISSI Investigators, 1999; Rapola et al., 1997; Rapola et al., 1998; Stephens et al., 1996; and Williams et al., 1971), we conclude that there is not sufficient evidence to support a relationship between vitamin E and CVD. Of the five randomized, placebo-controlled interventional studies (DeMaio et al. 1992; GISSI Investigators, 1999; Rapola et al., 1997; Rapola et al., 1998; and Stephens et al., 1996), only the Stephens et al., study showed a statistically significant beneficial effect for vitamin E on the primary CVD endpoint. The relative risk (RR) for the combination endpoint, cardiovascular death, nonfatal MI and nonfatal stroke, was 0.53 (95% confidence interval (CI) 0.34-0.83) in this study (Stephens et al. 1996). However, a suggestion that randomization was not complete in the study is given because the investigators found

small, but statistically significant differences in the distribution of five conventional coronary risk factors between active and placebo groups: sex ratio, total serum cholesterol, systolic blood pressure, presence of diabetes, and proportion taking beta-blockers. Among these factors, only the presence of diabetes and proportion taking beta-blockers were controlled for in multivariate models. Controlling for sex ratio, total serum cholesterol, and systolic blood pressure could have impacted the multivariate findings and perhaps influenced the conclusions of the study.

It was possible to consider secondary prevention analyses in the ATBC study because the original study was designed as a cancer prevention study and, thus, CVD endpoints were not criteria for exclusion from the study. Two secondary analyses from the ATBC study found no effect of vitamin E on either major coronary events or recurrence of angina pectoris (Rapola et al., 1997; Rapola et al., 1998, respectively). The ATBC study, however, was not designed to intervene on CVD. It is interesting to note that in both the study by Stephens et al., (Stephens et al., 1996) and the ATBC study (Rapola, et al., 1997), vitamin E showed statistically significant beneficial effects for nonfatal MI (as a secondary endpoint in the ATBC Study), but nonsignificant increased risk of CV or CHD deaths, respectively, suggesting a potential adverse effect on CVD deaths that needs to be monitored in ongoing trials (Ness et al., 1999). The GISSI study found no benefit from 330 IU/day of Vitamin E (GISSI Investigators, 1999). A small randomized clinical study did not find a statistically significant association between vitamin E (1200 IU/day) and recurrent stenosis, but a trend toward an inverse association between vitamin E and restenosis was observed (DeMaio et al., 1992).

One small nonrandomized clinical study performed in the 1970's showed benefit for intermittent claudication (Williams et al., 1971). The absence of randomization makes interpretation of this study difficult. Additionally, a few patients were switched from the placebo to the vitamin E group during the study, thereby altering the prevention design (Williams et al., 1971). A small double blind crossover study did not find a relationship between 1600 IU/day of vitamin E and symptoms of angina (Gillilan et al., 1977). The agency is also aware that data from the Heart Outcomes Prevention Evaluation (HOPE) Study, planned to be published in the January 20, 2000 issue of the New England Journal of Medicine, showed a neutral impact for vitamin E (400 IU/day with 5 years of follow-up) on a range of CVD outcomes. Overall, the results from the secondary prevention studies are mixed, and thus they did not provide a sufficient basis to support the hypothesized relationship between vitamin E and CVD.

The agency concludes that the findings of the available interventional studies are insufficient to establish a relationship. Therefore, based on the totality of available interventional studies the evidence does not support a relationship between vitamin E and reduced risk of CVD.

Observational studies

Although a few large prospective observational studies suggest benefit from vitamin E (Kushi et al., 1996; Rimm et al., 1993; Stampfer et al., 1993; and Knekt et al., 1994), overall data from observational studies are inconsistent and, thus, do not help to establish the relationship between vitamin E and reduction of risk of CVD. Taken as a group and coupled with the outcomes from the interventional studies, there is insufficient evidence to support the relationship.

You submitted several studies in your petition that investigated the association between estimates of vitamin E intake and risk of CVD (Bolton-Smith et al., 1992; Keli et al., 1996; Knekt et al., 1994; Kushi et al., 1996; Losonczy et al., 1996; Meyer et al., 1996; Rimm et al., 1993; Sahyoun et al., 1996; Stampfer et al., 1993). These studies were included in the agency's review of the evidence. Based on these studies, the agency concludes that the evidence concerning a relationship between vitamin E and reduction of risk of CVD is inconclusive at this time. In addition, the agency included observational studies of vitamin E intake not included in your submission (Ascherio et al., 1999; Donnan et al., 1993; Klipstein-Grobusch et al., 1999; Kritchevsky et al., 1995). These studies did not change the agency's conclusion based on its evaluation of your petition.

Three large prospective observational studies which ascertained total, dietary (from foods), and supplemental intakes of vitamin E by quintile found a significant association between either dietary (Kushi et al., 1996) or supplemental (Rimm et al., 1993 and Stampfer et al., 1993) estimates of vitamin E intake and reduced risk of CVD endpoints. Although vitamin E intake from diet alone was significantly associated with reduced risk of CHD mortality, Kushi et al., also found that total and supplemental vitamin E intakes were not significantly inversely associated with CHD mortality (Kushi et al., 1996). Although several risk factors for CVD were considered in multivariate models, total serum cholesterol, LDL- and high density lipoprotein-cholesterol levels were not considered as confounders in this study. This is a limitation of this study because high blood levels of total and LDL cholesterol are known risk factors for CVD. Rimm et al., showed that total intake and supplemental intake, but not dietary intake of vitamin E was inversely associated with a composite coronary heart disease endpoint (Rimm et al., 1993). Although several CVD risk factors were controlled for in the analysis, these investigators also did not control for serum lipids.

In the study by Stampfer et al., total, but not dietary, vitamin E intake was associated with decreased risk of the CVD endpoint (Stampfer et al., 1993). These results were significant after adjustment for age, smoking and energy. The multivariate-adjusted relative risk for major coronary disease associated with the use of specific vitamin E supplements was 0.63 (95% CI, 0.45- 0.88). Risk factors adjusted for in the vitamin E supplement use multivariate analysis included the known risk factors for CVD and/or variables known to be associated with intake of vitamin E.

Conversely, another large prospective study which also assessed the relationship between vitamin E intake and a CVD endpoint by quintile of intake did not find an association between intake (for both total and supplemental intakes of vitamin E) and stroke (Ascherio et al., 1999). Measures for serum lipids were not included in multivariate analyses. The authors note, however, that baseline information on history of hypercholesterolemia did not differ by quintile of vitamin E intake and therefore this variable was not included in multivariate analysis.

A prospective study assessed the relationship between plasma concentrations of vitamin E as well as total (dietary plus supplemental) intake of vitamin E and mortality from heart disease (Sahyoun et al., 1996). Plasma vitamin E was not associated with mortality from heart disease. Furthermore, there was not a significant association between total (from foods and supplemental sources) intake of vitamin E and mortality from heart disease. No analysis for supplemental intake alone could be performed because few in the cohort used vitamin E supplements, thus raising the possibility that intakes were too low to show a relationship. Risk factors adjusted for in multivariate analysis included age, sex, serum cholesterol (in plasma vitamin E analyses), disease status, and disabilities affecting shopping (an indicator of health status). Some of the more classical CVD risk factors, i.e., relative weight, exercise, smoking, were not addressed in this study.

Two of three prospective studies that analyzed total intake of vitamin E, essentially from food sources because supplement use was rare, in relation to CVD endpoints found no benefit from vitamin E on stroke (Keli et al., 1996) or MI (Klipstein-Grobusch et al., 1999). The study by Knekt found a significant benefit for women but not for men on risk of CHD death in the highest vitamin E tertile; trends across tertiles, however, showed a significant benefit for vitamin E on the risk of CHD death for both men and women (Knekt et al., 1994).

The above discussion describes the findings from prospective observational studies. To briefly summarize, there are prospective observational studies that suggest that (1) total vitamin E intake is associated with a reduced risk of CVD endpoints (Rimm et al., 1993; Stampfer et al., 1993), (2) supplemental vitamin E intake is associated with reduced risk of CVD endpoints (Rimm et al., 1993), and (3) dietary vitamin E intake is associated with reduced risk of CVD endpoints (Knekt et al., 1994; Kushi et al, 1996). On the other hand, there are prospective observational studies that found: (1) total vitamin E intake is not associated with reduced risk of CVD endpoints (Ascherio et al., 1999; Kushi et al, 1996), (2) supplemental vitamin E intake is not associated with reduced risk of CVD endpoints (Ascherio et al., 1999; Kushi et al, 1996), and (3) dietary vitamin E intake is not associated with reduced risk of CVD endpoints (Keli et al., 1996; Klipstein-Grobusch et al., 1999; Rimm et al., 1993). Although each study has its own strengths and weaknesses, the overall results are contradictory.

Furthermore, two prospective studies, which measured the association between qualitative measures of vitamin E intake from supplements (users versus nonusers) and risk of CVD, found significant associations for users of vitamin E supplements and reduced risk of CVD endpoints (Losonczy et al., 1996 and Meyer et al., 1996). However, the agency considered studies without quantitative measures of vitamin E intake and studies that did not control for confounders to be of less weight compared to studies which ascertained total, dietary, and supplemental intakes of vitamin E by quintile or other ranking method.

Results of the few case-control (Bolton-Smith et al., 1992) or cross-sectional studies (Donnan et al., 1993 and Kritchevsky et al., 1995) also report mixed results for the association between vitamin E intake and CVD endpoints. As previously noted, these studies carried less weight compared to the prospective studies. In the case-control study, the higher intakes of vitamin E in diagnosed cases were thought to be due to post-diagnosis dietary advice (Bolton-Smith et al., 1992). For controls compared to undiagnosed CHD cases, risk estimates were significantly lower in the 4th quintile of vitamin E for men, but not for women. There was no trend across quintiles for men or women. Overall, the results of this study do not support a strong association. In a cross-sectional study of men and women aged 55-74, dietary vitamin E intake was positively associated with ankle brachial pressure index (ABPI) (Donnan et al., 1993). A higher ABPI is indicative of less extensive peripheral artery disease. This association was independent of smoking and intake of other nutrients. A limitation of the study is that additional CVD risk factors were not considered.

Your petition included another cross-sectional study in which associations between vitamin E intake and average carotid artery wall thickness were found to vary by age and sex (Kritchevsky et al., 1995). A significant trend across quintiles of vitamin E intake was observed for men aged 55-64 years, $P= 0.04$ after multivariate adjustment, but not for women in the same age category. Interestingly, when subjects who started a special diet were omitted from the analysis the opposite trend was observed; that is, a significant trend across quintiles was observed for women aged 55-64 years, $P= 0.033$ after multivariate adjustment, but not for men in the same age category. No significant relationships were seen in participants less than 55 years of age. A limitation of this study is that semi-quantitative information on supplement use was obtained by these investigators. For example, users of multivitamins were reassigned intake levels assuming users took 1 tablet containing 100% of the RDA for vitamin E. Those taking single source vitamin E were reassigned to the highest quintile of vitamin E.

In addition to the limitations mentioned above, observational studies may be subject to considerable bias, such as vitamin E consumers more often adopting other healthy lifestyle changes, e.g., increased exercise or nonsmoking. It is therefore possible that the degree of benefit apparent from vitamin E intake may be overestimated by these nonrandomized studies. One example of lifestyle factors potentially confounding the relationship can be observed in the Health Professionals Follow-up study (Ascherio et al., 1999 and Rimm et

al., 1993). These investigators report that men who were in the highest quintile of total vitamin E intake were more likely to use supplemental vitamin E, were less likely to smoke, more likely to use aspirin, and more physically active compared to men in the lowest quintile of total vitamin E intake. The participants in this study were a self-selected group of health professionals, and their lifestyles and diets were healthier than those of average men; these lifestyle differences may not be completely controlled for in multivariate regression techniques. Because men with high intake of vitamin E have healthier risk profiles than men with lower intakes of vitamin E, it may be that a significant association is due to confounding by other aspects of lifestyle that were not measured or adequately controlled. Therefore, cause and effect relationships cannot be established from observational data because confounding from some unmeasured variable may account for the results.

Another limitation of observational studies of diet-disease relationships is the possibility of colinearity among dietary variables. That is, intakes of specific nutrients tend to be intercorrelated so that associations of disease endpoints with one nutrient may be confounded by other aspects of the diet. It cannot be ruled out that associations observed between the intake of vitamin E and CVD in observational studies were due to confounding caused incomplete control of various dietary factors closely correlated with the intake of vitamin E. One potential confounder is polyunsaturated fatty acid intake, which is closely associated with vitamin E intake from foods and has been hypothesized to reduce the risk of CVD.

Although a few large prospective observational studies suggest benefit from vitamin E, overall data from observational studies of vitamin E intake are inconsistent and results must be used with caution, thus, they do not establish a relationship between vitamin E and reduced risk of CVD.

Several studies that investigated the association between vitamin E status as a surrogate measure of vitamin E intake and risk of CVD were submitted in the petition. Studies with serum or plasma alpha-tocopherol concentrations that were measured prospectively were reviewed by the agency (Eichholzer et al., 1992; Evans et al., 1998; Hense et al., 1993; Kok et al., 1987; Salonen et al., 1985; and Street et al., 1994). It has been shown that plasma or serum alpha-tocopherol levels can, if adjusted for blood lipids, represent long-term vitamin E intake to a modest degree (Hunter, 1998) and, thus, the studies that adjusted for blood lipids were given greater weight in the agency's evaluation of the evidence than those that did not make this adjustment. Based on the case-control studies with prospective measures of vitamin E status (Eichholzer et al., 1992; Evans et al., 1998; Hense et al., 1993; Kok et al., 1987; Salonen et al., 1985; and Street et al., 1994), the agency concludes that there is no evidence to support a relationship between vitamin E and reduction of risk of CVD at this time. This conclusion is consistent across the studies. In Street et al., lower serum vitamin E levels were significantly associated with decreased risk of MI, but when serum vitamin E was adjusted for serum cholesterol, the relationship

was reversed and this result was not adjusted for other confounders (Street et al., 1994). Therefore, the results of this study were mixed and did not provide evidence for the association between vitamin E status and risk reduction of CVD. None of the studies evaluated provided information on dietary or supplemental intakes of vitamin E; thus, the vitamin E status measures could not be evaluated as a direct surrogate measure of intake in the populations studied. Furthermore, a few studies suggested that they were unable to observe an association between vitamin E status and reduced risk of CVD due to limitations of statistical power (Evans et al., 1998, Hense et al., 1993, and Kok et al., 1987). Although, this may be due to the small number of CVD cases in the populations studied, these results within the context of all other data, are not sufficient to establish an association between vitamin E and reduced risk of CVD. From the description of the results of these studies, the agency does not consider them to provide evidence for the relationship between vitamin E and reduced risk of CVD.

Summary of review of the evidence

The primary prevention studies did not provide evidence for the relationship between vitamin E and reduced risk of CVD. Considered collectively, the results from the secondary prevention studies are mixed and they also did not provide a sufficient basis to establish a relationship between vitamin E intake and CVD. Although a few large prospective observational studies suggest benefit from vitamin E, overall data from observational studies are inconsistent. The agency concludes, therefore, that the results from the totality of studies, considering the limitations in the designs used and conflicting results obtained, provided an inadequate basis to support a relationship between vitamin E and reduced risk of CVD.

D. Other Reviews

The petition included a review by the Nutrition Committee of the American Heart Association that prepared a science advisory for healthcare professionals based on a critical review of the data on vitamin C, vitamin E, and beta-carotene and risk of coronary heart disease (Tribble et al., 1999). The committee concluded that the most prudent and scientifically supportable recommendation for the general population is to consume a balanced diet with emphasis on antioxidant-rich fruits, vegetables, and whole grains. The committee stressed that in the absence of efficacy and safety data from randomized trials, population-wide recommendations regarding vitamin E supplementation are not warranted at this time. The agency finds this conclusion to be consistent with the conclusions of our evaluation of the evidence.

E. Significant Scientific Agreement for the Relationship of Vitamin E and Cardiovascular Disease

The agency finds that, based on the data evaluated, there is not significant scientific agreement that the proposed claims for a relationship between vitamin E dietary supplements and reduced risk of cardiovascular disease is supported by the available evidence.

Sincerely,

for Elizabeth A. Yetley, Ph.D.
Director
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition

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Memo

To: Dockets Management Branch (HFA-305)
From: Sharon Ross, Nutritionist (HFS-456)
Date: January 12, 2000
Subject: RE: Petition for Health Claim: Vitamin E Dietary Supplements and Heart Disease (Docket Number 99P-4375)

Attached please find the agency's response to the Petition for Health Claim: Vitamin E Dietary Supplements and Heart Disease for submission to Docket Number 99P-4375.

Thank you.

(202-205-5843)