DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

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VIA FACSIMILE AND U.S. MAIL

Jonathan W. Emord, Esq.
Emord & Associates, PC.
1050 Seventeenth Street, NW
Suite 600
Washington, D.C. 20036

Re: Petition for Health Claim: Antioxidants and Cancer (Docket No. 91N-0101)

Dear Mr. Emord:

This letter is in reference to the court decision directing the Food and Drug Administration (FDA or the agency) to reconsider the health claim "Consumption of antioxidant vitamins may reduce the risk of certain kinds of cancer" in dietary supplement labeling *(Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)). FDA previously sent to you replies on the three other health claims that the court directed FDA to reconsider, namely, folic acid and neural tube defects, fiber and colorectal cancer, and omega-3 fatty acids and coronary heart disease. We regret the delay in resppnding to you on this claim.

I. Procedure and Standard for Evaluating the Claim

In reconsidering this claim and the three other health claims that were the subject of *Pearson*, FDA has 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" (hereinafter "the October 6 notice"). 65 Fed. Reg. 59,855 (2000). As noted below in section IV., FDA first gathered new scientific evidence on the claims by contracting for a literature search and publishing two notices in the Federal Register soliciting comments and data. After reviewing the updated body of evidence on the claims, FDA applied the "significant scientific agreement" standard by which the health claim regulations require the agency to evaluate the scientific validity of claims. Under this 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.

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For claims that did not meet the significant scientific agreement standard, FDA next considered whether to exercise enforcement discretion for qualified claims about the substance-disease relationship. Consistent with the *Pearson* opinion, the agency considered whether consumer health and safety would be threatened by the claim, and, if not, whether the evidence in support of the claim was 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 outweighed the evidence against the dlaim and there was no health or safety threat, the agency went on to consider whether a qualified claim could 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. 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. *Id.*

Although the deadlines for FDA action in 21 C.F.R. § 101.70(j) apply to health claims that are submitted by petition, they do not apply to the four claims that were the subject of *Pearson.* FDA is reconsidering those claims under a court order that sets no specific deadlines but clearly contemplates prompt action because of First Amendment concerns and the agency's obligation to comply with court orders as soon as possible. FDA is issuing this decision letter on May 4,200 1.

II. Summary of Review

In the January 6, 1993 final rule concerning a health claim for antioxidant vitamins and cancer for conventional food (hereinafter "the 1993 final rule"), FDA considered the relationship between nutrients identified at that time as antioxidant vitamins (i.e., beta-carotene, vitamin C, and vitamin E) and cancer. 58 Fed. Reg. 2622 (1993). FDA authorized a health claim (codified at 2 1 CFR § 101.78) relating substances in diets that are low in fat and high in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A and vitamin C) to a reduced risk of cancer. *Id.* While FDA did conclude that evidence supported an association of reduced risk of cancer and diets low in fat and high in fruits and vegetables, FDA also concluded that the evidence available at

the time did not support an association of antioxidant vitamins, alone or in combination, and reduced risk of cancer. *Id.* at 2634. The available evidence did not resolve whether the observed protective effects of fruit and vegetable consumption against cancer risk are due to a single or combined effect of the antioxidant vitamins and other nutrients with antioxidant functions (i.e., selenium), to other nutritive components of such foods (e.g., dietary fiber), to unmeasured components of such diets (e.g., carotenoids, indoles or flavonoids), or to displacement of other known risk components (such as fats and calories) within the total diet. *Id.* Rather, FDA found that vitamins A and C and fiber are characteristic of protective foods and may serve as useful markers for identifying the types of foods which contribute to a dietary pattern that is associated with a reduced cancer risk. *Id.* at 2634-35.

Therefore, because of the limitations in the evidence, the authorized health claim for fruits and vegetables and cancer in 21 CFR § 101.78 characterizes the association between the reduced risk of cancer and consumption of fruits and vegetables, not the antioxidant vitamin component or some other components of those foods. *Id.* at 2635. The agency found that the scientific evidence was not sufficient to conclude that antioxidant vitamins are responsible for the protective effect of fruit and vegetable consumption against cancer risk. *Id.* FDA concluded that the scientific evidence did not provide the basis for significant scientific agreement among qualified experts that there is a relationship between antioxidant vitamins and a reduced risk of cancer and therefore did not authorize a health claim for that relationship. *Id.* at 2622. As explained in more detail in section IV. below, FDA also did not authorize a health claim for antioxidant vitamins and reduced risk of cancer for dietary supplements.'

In response to *Pearson,* FDA has reconsidered the scientific evidence on the putative relationship between antioxidant vitamins and the risk of certain kinds of cancer. Both the agency's original 199 1 -- 1993 scientific review and its evaluation of the evidence that has become available since that time were conducted 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 after January 6, 1993, FDA finds that: 1) The totality of the publicly available scientific evidence demonstrates a lack of significant scientific agreement among qualified experts as to the validity of a relationship between the intake of antioxidant vitamins (i.e., vitamin C and

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[1] A proposed rule for the dietary supplement health claim on antioxidant vitamins and reduced risk of cancer (58 Fed. Reg. 53,296 (1993)) became a final regulation by operation of law (59 Fed. Reg. 436 (1994)). FDA relied on the scientific review conducted as part of the antioxidant vitamin and cancer rulemaking for conventional foods, that concluded in January 1993, for the June 1993 dietary supplement proposed rulemaking for the same claim.

vitamin E)[2] and reduced risk of certain kinds of cancer in the general population, and 2) the weight of the scientific evidence against the relationship between vitamin C or vitamin E, alone or in combination, as antioxidants, and reduced risk of certain kinds of cancer is greater than the weight of the scientific evidence for the relationship.[3] Thus, the agency is not authorizing a health claim for a relationship between vitamin C or vitamin E, alone or in combination, and the risk of certain kinds of cancer or individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, stomach). Further, based on this review, FDA is not exercising enforcement discretion for a qualified claim for a relationship between vitamin C or vitamin E, alone or in combination, and the risk of certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, stomach).

III. Safety Review

Under 21 C.F.R. § 101.14(b)(3)(ii), which was not challenged in *Pearson* and still applies to FDA's review of a proposed dietary supplement health claim, the use of vitamin C and 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)!

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)(l)(A). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling. 21 U.S.C. 342(f)(l)(D). Ensuring the safety of a dietary supplement that may bear a qualified claim is also consistent with the

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[2] The definition of a "dietary antioxidant" is discussed in section IV. The National Academy of Science through the Institute of Medicine (IOM/NAS) has concluded that vitamins C and E function as dietary antioxidants, but beta-carotene does not. FDA agrees with the IOM/NAS conclusion and its basis for such conclusion. Thus, FDA has considered only vitamins C and E in this evaluation of the relationship between antioxidant vitamins and risk of certain kinds of cancer.

[3] The agency concluded that, for some antioxidant vitamin and cancer relationships it evaluated, there was an insufficient body of sound, relevant scientific evidence to support a qualified claim. The fact that there was a lack of a threshold level of scientific evidence supporting the purported substance-disease relationship to make a qualified claim was critical to the agency's conclusion about those relationships. The evidence that was available, on balance, was more against than in support of such a relationship. This finding, however, was secondary to the lack of a threshold level of evidence in the agency's conclusion.

[4] In this case, there is no proponent of the claim submitting safety data through a health claim petition. FDA is responding to instructions from the U.S. Court of Appeals for the D.C. Circuit to reconsider the health claim and is not responding to a petition. As discussed further in sections IV., V. and VI., FDA is not currently authorizing a health claim or exercising enforcement discretion for a qualified claim describing the relationship between antioxidant vitamins and certain kinds of cancer.

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 matter, FDA considered its 1991 proposed rule (56 Fed. Reg. 60,624; November 27, 1991) and its 1993 final rule on antioxidant vitamins and cancer, in which FDA addressed the safety of vitamins C and E. In the 1991" proposed rule, FDA noted that the Surgeon General's report stated that amounts of vitamin C in excess of the Recommended Dietary Allowances (RDAs) may cause rare adverse effects, including gastrointestinal disturbances, iron overload in susceptible individuals, altered metabolism of certain drugs, precipitation of calcium oxalate kidney stones, altered absorption of several minerals, and interference with clinical laboratory tests. 56 Fed. Reg. at 60,635. Regarding vitamin E, FDA noted that the National Research Councii's report entitled "Diet and Health" cited scientific evidence suggesting that large doses of vitamin E are relatively nontoxic. *Id.* at 60,637-38. However, as discussed below, vitamin E supplementation may increase the risk of prolonged bleeding time for some individuals.

FDA also considered the April 11, 2000 report of the Food and Nutrition Board, Institute of Medicine (IOM), National Academy of Sciences (NAS) on Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (hereinafter the April 2000 DRI Report). The April 2000 DRI Report (at 155) states that IOM's review of the scientific literature indicates that high vitamin C intakes generally are associated with low toxicity. IOM noted that adverse effects associated with very high vitamin C intakes include: diarrhea and other gastrointestinal disturbances, increased oxalate excretion and kidney stone formation, increased uric acid excretion, pro-oxidant effects, systemic conditioning (rebound scurvy), increased iron absorption leading to iron overload, reduced vitamin B_{12} and copper status, increased oxygen demand, and erosion of dental enamel.

With respect to vitamin E, the IOM reported, in the April 2000 DRI Report (at 253), that some uncontrolled studies have found various adverse effects to be associated with excess intake of vitamin E, including fatigue, emotional disturbances, thrombophlebitis (i.e., inflammation of the veins), breast soreness, creatinuria, altered serum lipid and lipoprotein levels, gastrointestinal disturbances, and thyroid effects. Side effects have been reported with extended intakes of 1,600 to 3,200 milligrams per day. However, the IOM noted that these effects are not severe and subside rapidly upon reducing the dosage or discontinuing use. The April 2000 DRI Report (at 253) notes that hemorrhagic effects have been seen in experimental animals with very high doses of vitamin E and are corrected with supplemental vitamin K. The IOM reported in the April 2000 DRI Report (at 253) that 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. The IOM noted that caution must be exercised in judgments regarding the safety of supplemental doses of vitamin E over multi-year periods, as available human data are based on small studies of relatively short duration.

Another potential concern about the safety of supplemental vitamin E raised by the IOM in its April 2000 DRI Report (at 254) was the apparent increase in mortality from hemorrhagic stroke seen in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study. However, the IOM considered the findings in the ATBC study preliminary and provocative but not convincing until the findings are corroborated or refuted in further large-scale clinical trials.

Based on its review, the IOM has established "Tolerable Upper Intake Levels" (ULs) for both vitamin C and vitamin E. A 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 IOM, in its April 2000 DRI Report (at 162), established the UL for adults for vitamin C at 2,000 milligrams per day from both food and supplement sources, based on the adverse effect of osmotic diarrhea. The April 2000 DRI Report (at 257) states that the UL for adults for vitamin E is 1,000 milligrams per day[5] from sources other than those that occur naturally in foods, based on the potential adverse effect of an increased, tendency to hemorrhage.

Finally, FDA notes unexpected increases in the incidence of some cancers in association with consumption of antioxidant vitamins, as reported in two of the studies identified in its current review. An intervention trial in Linxian, China found that there was an increased prevalence of gastric dysplasia and cancer among subjects receiving dietary supplements of 120 mg vitamin C and molybdenum (Wang et al., 1994). Because the supplement combined vitamin C and molybdenum, it is not clear that the increased prevalence of gastric cancer was a vitamin C effect; however, it cannot be ruled out that vitamin C contributed to this adverse finding. The incidence of bladder and stomach cancer, in the Alpha-Tocopherol, Beta-Carotene (ATBC) intervention trial in Finnish male smokers (ATBC Study Group, 1994), among subjects receiving vitamin E supplements, was reported to be above the incidence for subjects not supplemented with vitamin E. Based on a significant body of observational studies, this trial was designed to evaluate the effect of dietary supplement vitamin E on lung cancer; it was not designed to evaluate the effect of vitamin E on any other cancer. Thus, the enrollment protocols were not designed to evaluate and control for risks associated with cancers other than lung cancer, and therefore the occurrence of other cancers is subject to potential bias. Importantly, despite the availability of a significant body of human observational studies prior to this study, the vitamin E and lung cancer relationship was not supported. Moreover, the post-hoc analyses presented very mixed results at other cancer sites, with cancers at two sites appearing to benefit from vitamin E supplementation (i.e., prostate and colorectal) and two cancers appearing to have increased risk associated with vitamin E supplementation (i.e., bladder and stomach). The post-hoc findings are useful in generating hypotheses. The primary and post-hoc findings from this large, well-designed and well-conducted trial raise serious questions about the safety and

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[5] 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.

effectiveness of vitamin E supplementation on cancer risk and underscore the critical need for more research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real and that safe conditions of use of vitamin E supplementation can be ascertained.

The agency recognizes that there are potential safety concerns with the use of supplemental vitamins C and E that are currently not well defined. FDA is not currently authorizing a health claim nor exercising enforcement discretion for a qualified health claim for vitamin C or vitamin E, alone or in combination, and their relationship to certain kinds of cancer or to any individual cancers. As a result, FDA does not have to evaluate the safety of vitamin C or vitamin E dietary 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.

IV. Review of the Scientific Evidence

A. 199 1- 1993 Scientific Review

Congress enacted the health claims provisions of the Nutrition Labeling and Education Act of 1990 (the NLEA) to help consumers maintain good health through appropriate dietary patterns and to protect consumers from unfounded health claims. The NLEA specifically required the FDA to determine whether claims respecting 10 nutrient/disease relationships met the statutory requirements for health claims. Pub. L. No. 101-535, § 3(b)(l)(A), 104 Stat. 2353, 2361. 'The relationship between antioxidant vitamins and cancer was one of these 10 claims the agency was required to evaluate.

FDA began its review of these 10 claims by publishing a notice in the March 28, 1991, Federal Register (56 Fed. Reg. 12,932) requesting scientific data and-information relevant to the claims. The agency also contracted with the Life Sciences Research Office (LSRO) of the Federation of American Societies of Experimental Biology (FASEB) for an independent scientific review of recent evidence on antioxidant vitamins and cancer. In November 1991, FDA published, in the Federal Register, a proposed rule (the 1991 proposed rule) setting forth its review of available scientific evidence and tentative conclusions with respect to authorization of a health claim for the relationship between antioxidant vitamins and cancer risk. 56 Fed. Reg. 60,624. In the 1991 proposed rule, the agency proposed not to authorize the use on foods, including dietary supplements, health claims relating to the association between antioxidant vitamins and cancer. The agency found that the data on the relationship between vitamin C and cancer risk were not consistent and had mostly been obtained in studies of consumption of foods containing high levels of vitamin C. *Id.* at 60,635-36. Regarding vitamin E, FDA found that the evidence for an effect of vitamin E on cancer risk was limited and inconclusive. *Id.* at 60,625. FDA tentatively concluded that there was not significant scientific agreement to support the use of a health claim relating to antioxidant vitamins and cancer. *Id.* at 60,624 and 60,638. The agency found that strong epidemiologic evidence

existed that showed that consumption of fruits and vegetables, which tend to be rich in the carotenoids and vitamin C, were associated with reduced risk of cancers in some sites. *Id.* at 60,63 1 and 60,636. However, the agency found that, in most studies, it was not possible to determine from the available data whether a protective effect was due to the presence of vitamin C, beta-carotene, other nutrients, or combined effects of both vitamins and other dietary factors, such as fiber. *Id.* at 60,635-36.

While the proposed rule was pending, Congress passed the Dietary Supplement Act of 1992 (the DSA). Pub. L. No. 102-571, 106 Stat. 4500. The DSA imposed a moratorium on FDA's implementation of the NLEA with respect to dietary supplements until December 15, 1993. The DSA also directed FDA to repropose implementing regulations for dietary supplements by June 15, 1993, and provided that the proposed regulations would become final by operation of law if final rules were not issued by December 3 1, 1993.

In the 1993 final rule, FDA concluded that diets rich in fruits and vegetables, which are low in fat and generally are good sources of vitamin A (as beta-carotene), vitamin C, and dietary fiber, are associated with a reduced risk of cancer. 58 Fed. Reg. at 2634. However, the agency found that there was not significant scientific agreement as to whether the observed protective effects of fruit and vegetable consumption against cancer risk are due to a single or combined effect of the antioxidant vitamins and other nutrients with antioxidant functions (i.e., selenium), to other nutritive components of such foods (such as dietary fiber), to unmeasured components of such diets (for example, nonnutritive components such as carotenoids, indoles or flavonoids), or to displacement of other known risk components (such as fats and calories) within the total diet. *Id.* Regarding vitamin C, FDA found that the data were not sufficient to identify vitamin C, from among other substances in these foods, as being responsible for the observed protective effect against cancer and therefore, the data did not support a relationship between vitamin C and a protective effect against cancer. *Id.* at 2634-35. With respect to vitamin E, FDA found that the data were not sufficient to associate vitamin E's antioxidant effects with protection against cancer. *Id.* at 2633. The agency concluded that the scientific evidence does not provide the basis for significant agreement among qualified experts that there is a relationship between antioxidant vitamins (i.e., beta-carotene, vitamin C, or vitamin E) and a reduced risk of cancer. *Id.* at 2633. Therefore, FDA did not authorize a health claim for a relationship between intake of antioxidant vitamins and a reduced risk of cancer. *Id.* at 2634-35.

Because of the DSA's moratorium on implementation of the NLEA with respect to dietary supplements, the 1993 final rule applied only to health claims for conventional foods, not for dietary supplements. In response to the DSA's directive to issue proposed regulations specific to dietary supplements, FDA proposed, on October 6, 1993, not to authorize a health claim for antioxidants and cancer in the labeling of dietary supplements. 58 Fed. Reg. 53,296 (1993). The October 1993 proposal relied on the scientific review conducted as part of the antioxidant-cancer health claim rulemaking that concluded in January 1993. Because FDA did not issue a final rule by December 3 1,

1993, the October 1993 proposal became final by operation of law. 59 Fed. Reg. 436 (1994). Therefore, the only authorized'health claim related the substances in diets that are low in fat and high in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, and vitamin C) to a reduced risk of cancer.

B. Current Scientific Review

FDA considered the antioxidant vitamins to include vitamins C and E and beta-carotene when the agency published the 199 1 proposed rule and 1993 final rule concerning a health claim for antioxidant vitamins and cancer. 56 Fed. Reg. at 60,625 and 58 Fed. Reg. at 2622. Recently, the IOM/NAS evaluated the nutritional requirements for antioxidant-related nutrients. In its April 2000 DRI Report (at 42), the IOM defined a dietary antioxidant as "a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on normal physiological function in humans." The IOM concluded in its April 2000 DRI Report (at 43-44) that although beta-carotene and other carotenoids display antioxidant activity *in vitro,* there is inadequate evidence that they have antioxidant activity *in vivo* when consumed in food by humans and, therefore, do not meet the definition of a dietary antioxidant. The IOM considered only vitamins C and E and the mineral selenium to be dietary antioxidants. FDA concurs with the IOM definition of "dietary antioxidant" and the rationale expressed in the April 2000 DRI Report for why beta-carotene and other carotenoids do not meet that definition. Therefore, FDA does not now believe that it is appropriate to consider beta-carotene as an antioxidant vitamin in its review of the proposed health claim for a relationship between antioxidant vitamins and a reduced risk of certain kinds of cancer. Consequently, FDA is considering only vitamins C and E in this review and will refer to them as the "antioxidant vitamins" throughout the remainder of this letter.[6]

FDA's initial step in reconsidering the health claim for antioxidant vitamins and reduced risk of certain kinds of cancer in response to Pearson was to gather the relevant scientific evidence that had become available since the previous rulemaking on this topic. To update its previous review, the agency reviewed comments' and data submitted in

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[6] Since selenium is a mineral and not a vitamin, FDA did not include selenium in its evaluation of a health claim for antioxidant vitamins and reduced risk of certain cancers.

[7] FDA received four submissions from you after the close of the comment period. You submitted a "Supplemental Submission" discussing the economic impacts of the significant scientific agreement (SSA) guidance standard in August 2000 (Sup 2, Docket 91N-0101) and a "Supplemental Submission" of alleged ramifications of the SSA standard in October 2000 (Sup 4, Docket 91N-0101). The agency was not obligated to consider these two late comments and, moreover, found these submissions to be not relevant to its evaluation of the health claim about dietary supplements of antioxidant vitamins and risk of certain cancers. Further, 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. You also submitted a supplemental submission containing comments and "additional scientific

response to two Federal Register notices requesting scientific data and information, as well as data identified in a literature search. See 64 Fed. Reg. 48,841 (1999); 65 Fed. Reg. 4,252 (2000). The literature search covered publications that were issued after 1992.

During its 1991-93 review, FDA considered preclinical studies (studies not performed in humans) because such studies are useful for developing hypotheses or investigating mechanisms of putative relationships between food substances and physiological changes associated with disease risk. The available clinical data at the time of FDA's 1991-1993 review specifically relating to antioxidant vitamins, as opposed to data for foods containing antioxidant vitamins, were limited. However, the usefulness of data from preclinical studies is limited in that such studies cannot fully simulate human disease and physiology. Additionally, such studies cannot accurately estimate appropriate intake levels or the magnitude of effects in humans. Since FDA's 1991-93 review, results from a number of new human studies with antioxidant vitamin data have become available. In the current review, therefore, FDA focused its attention on human studies that quantitatively measured or estimated the intakes of vitamin C and vitamin E (alone or in combination) and that were specifically designed to test the effect of these antioxidant vitamins on cancer risk. The threshold criteria for selection of human studies as part of the evaluation were the same as those used in the 1991-93 FDA review of this health claim topic. See 56 Fed. Reg. at 60,629.

1. Intervention Trials

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 exposure. Therefore, intervention studies generally provide the strongest evidence for an effect. Unlike observational studies, which provide evidence of an association between the substance and disease of interest, but not necessarily a cause and effect relationship, intervention studies can provide evidence of causal relationships or the lack thereof. Randomized controlled clinical trials are considered the most 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.

A number of randomized, controlled, clinical intervention trials of vitamin C and vitamin E alone and in combination have been published since 1992 (Blot et al., 1993; Li et al., 1993; Roncucci et al., 1993; Zaridze et al., 1993; ATBC Study Group, 1994 (and

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evidence" (Sup 3, Docket 91N-0101), and a "Motion for leave to supplement comments" (Sup 5, Docket 91N-0101). Both submissions contained reports that were not available prior to the end of the comment period. Although FDA was not obligated to consider these additional late comments, it considered these reports in its review.

other reports based on this study population); Dawsey et al., 1994; Greenberg et al., 1994; Kaugars et al., 1994; Wang et al., 1994; Hofstad et al., 1998; Liede et al., 1998; Mackerras et al., 1999; and Correa et al., 2000). These trials were most useful when they provided specificity regarding measurement of the substance (i.e., antioxidant vitamin), measurement of the disease or health-related condition, and evidence for evaluating a relationship between the substance and the disease or health-related condition. For example, some of these trials directly addressed the intake of dietary supplements of vitamin C, vitamin E, or a combination of both and a cancer endpoint (e.g., ATBC Study Group, 1994 (lung cancer)). However, some trials included other substances with vitamin C or vitamin E and thus lacked specificity of substance (e.g., Blot et al. (1993) and Wang et al. (1994): beta-carotene and selenium; and Li et al. (1993) and Dawsey et al. (1994): multivitamin and mineral dietary supplements). FDA also considered evidence from post-hoc analysis of intervention trials (e.g., Hartman et al., 1998 and Heinonen et al., 1998). A post-hoc analysis of an intervention trial is an analysis of data on an endpoint other than the primary endpoint tested in the intervention trial. Such a post-hoc analysis must be interpreted cautiously. Because the original' 'intervention trial was not specifically designed to look at post-hoc endpoints, factorsthat may affect the results may not be controlled in the original intervention trial, thus potentially introducing bias into the results.

A number of clinical intervention cancer trials that investigated the relationship between vitamin C and vitamin E and the risk of colon cancer used a surrogate marker of cancer risk. A surrogate marker is a biological parameter that is associated with a disease, and for which there is evidence that altering the parameter can reduce the risk of the disease. A surrogate marker for cancer must be validated by evidence demonstrating that altering the surrogate marker does, in fact, affect the risk of developing cancer. Several studies used colorectal adenomatous polyp recurrence as a surrogate marker of colorectal cancer risk (e.g., McKeown-Eyssen et al., 1988; DeCosse et al., 1989; Roncucci et al., 1993; Greenberg et al., 1994; and Hofstad et al., 1998). Development of colorectal cancer is a multi-step process beginning with adenomatous polyps. Most colorectal adenomatous polyps remain as small non-malignant tubular polyps, but a small proportion grow into larger, more dysplastic polyps, which in turn evolve into malignant adenocarcinomas. Because all colorectal cancers are believed to develop from adenomatous polyps, polyp appearance is considered to be a surrogate marker for the cancer endpoint (Einspabr et al., 1997). Further, it has been established that removal of adenomatous polyps prevents the development of colorectal cancer (Winawer et al., 1993); that is, colorectal cancer does not develop in the absence of adenomatous polyps. Thus, the link between adenomatous polyps and subsequent colorectal cancer risk in humans has been established.

In a study of cervical cancer, Mackerras et al. (1999) used the rate of progression in cervical intraepithelial neoplasia (CIN) lesions as a surrogate marker for invasive cervical cancer risk. CIN is a precursor of cervical cancer. CIN lesions are pre-malignant tumors typically localized in the cervical epithelium. Some CIN lesions progress to more dysplastic stages and grow through the epithelial layer to become invasive cervical

cancer. Development of invasive cervical cancer is a continuum from pre-invasive CIN stages to the invasive cancer stages that have spread through the epithelial wall (Rock et al., 2000). Therefore, the risk of developing invasive cervical cancer is directly related to the rate of progression of existing CIN lesions.

2. Observational Studies

FDA also reviewed observational studies in humans that specifically estimated the intake of antioxidant vitamins from food sources (e.g., fruit and vegetable or dietary supplement consumption), or that measured the level of antioxidant vitamins in the body (e.g., serum levels), and the impact on certain kinds of cancer. Though less persuasive than intervention studies, particularly with regard to the quantitative measure of antioxidant vitamins and to attribution of any relationship to antioxidant vitamins *per se*, observational studies can provide evidence of an association between the intake of the dietary substance and the disease or health-related condition. However, these studies often do not provide a sufficient basis to determine if this association is causal or coincidental. In general, observational studies (also commonly called "epidemiological" studies) include, in descending order of persuasiveness, cohort studies, nested case-control studies, case-control studies, cross-sectional studies, and population or ecological studies. In the prospective studies (cohort and some nested case-control), investigators recruit subjects and observe them prior to the occurrence of the outcome. In retrospective studies (case-control), investigators review the records of subjects and interview subjects after the outcome has occurred. Retrospective studies are usually considered to be more vulnerable to recall bias (error that occurs when subjects are asked to remember past behaviors) and measurement error (e.g., measurement of the substance using intake data or serum or plasma levels). Temporal association between dietary exposure and disease outcome is also difficult to establish. Accordingly, prospective studies are generally more persuasive than retrospective studies.

In prospective cohort studies disease-free subjects are recruited within a specified group of people (the cohort) and the intakes of the subjects are determined. The study tracks the subjects over an extended period of time to see whether they develop the disease under investigation. At the end of the follow-up period, the intakes of subjects who developed the disease during the follow-up period are compared to those subjects who did not develop the disease to discern intake patterns that are associated with the risk of the disease. FDA generally weighted the prospective cohort studies more heavily than other types of observational studies because prospective studies are generally considered the most persuasive type of observational study. Nested case-control studies are case-control studies that are embedded in prospective cohort studies. Nested case-control studies may be more like prospective or more like retrospective studies, depending on when and how the intake estimates were performed.

In retrospective case-control studies, subjects with existing diagnosed disease are enrolled in the study (the cases) and are matched by identifiable characteristics (e.g., age, race, gender) to disease-free subjects (the controls). The intakes of the two groups are

compared to identify differences in intake patterns associated with risk for the disease. In cross-sectional studies, at a single point in time the individuals with a disease who have received a specific exposure are compared to the individuals without the disease who did not receive the exposure. Population (ecological) studies use grouped data to examine the relationship between dietary exposure and health outcome among populations. In these studies, the rate of a disease is compared across different populations and the investigators seek to identify population traits that may cause the disease. In this evaluation, FDA focused its attention on the more persuasive types of observational studies that evaluated the association of vitamin C or vitamin E, alone or in combination, with certain kinds of cancer in individuals. *See Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements.*

One of the inherent limitations of observational studies is the extent to which vitamin C or vitamin E intake of the subjects can be accurately assessed. Also, it often is not possible to isolate effects from vitamin C or E intake from the intake of other dietary components, as we noted in our 1993 review of these issues (see section II. above). These difficulties are encountered whether intake is assessed from dietary data, or from serum or plasma data as a surrogate for dietary data.

Intake of vitamins C and E based on food or supplement recall is difficult to accurately estimate. In general, there is considerable uncertainty in the quantitative measurement of habitual intake over long periods of time. Some studies typically use a retrospective food frequency or supplement questionnaire in which the study subjects are asked to recall their typical intakes (in terms of foods eaten, frequency of eating and serving sizes, and information about supplements used) during prior time periods. Such techniques are subject to recall bias, particularly for dietary factors thought possibly related to the disease. Further, there is uncertainty in the translation of food intake-data into antioxidant vitamin intake data by calculation from food composition tables. The natural variability of foods and the effects of processing, storing, and preparation of the food on vitamin content make it impossible to accurately calculate antioxidant vitamin intake from food intake data. Moreover, it is not possible to isolate the effect of the nutrients of interest from the effects of other components in foods or dietary supplements. Problems also are encountered with obtaining data on composition of any supplements used, including data that reflect actual levels of nutrient intake. This makes it difficult to establish whether antioxidant vitamins or some other component of the diet is responsible for any observed benefit. In short, there are significant limitations to assessing dietary antioxidant intake data from observational studies and associating intake with the disease. Because the variable assessed in these studies may include the diet, dietary supplement intake, or a biological marker of dietary patterns and there is uncertainty involved in the estimates of antioxidant vitamin exposures from such data, the usefulness of these types of studies to differentiate effects of the dietary antioxidant vitamin component of the food from effects of other components of the food is limited.

In the case of vitamin E, dietary intake estimates from observational studies are particularly prone to difficulties in obtaining accurate measurements (see, for example, the April 2000 DRI Report at 245 and 247-8). Most nutrient data bases and analytical methods do not distinguish among the alpha-, beta-, gamma-, and delta- forms of tocopherols that occur in food. Only one tocopherol (i.e., alpha-tocopherol) is retained in the body and is the most bioactive form. Additionally, vitamin E intakes are dependent on the types and amounts of oils in the diet; some vegetable oils contain more gamma- than alpha-tocopherol. Accurate information on both amounts and composition of oils used in food processing and preparation is often not asked in interviews nor known by most study respondents.

A serum or plasma level of either vitamin C or E is difficult to interpret as a surrogate marker for intake unless frank deficiency is present. Vitamin C deficiency is rare in developed countries such as the United States, and vitamin E deficiency is so rare in humans generally that medical indications of deficiency cannot be compared with vitamin E intake (April 2000 DRI Report at 101,202 and 210). In retrospective observational studies (and some prospective cohort studies), the serum or plasma measure is taken in subjects with existing disease. When such a measure is taken, it is not possible to determine whether a low plasma vitamin E or C level in a cancer patient is due to a lower nutritional status or is low as a result of the disease process itself, Hence, predictions based on such findings of higher or lower serum levels of a nutrient in test subjects versus controls are not scientifically credible because the nutrient may either be a contributing cause or a consequence -of the disease.

In addition to the generic concerns with the use of plasma or serum values to estimate dietary intake of vitamin E or C, a plasma or serum vitamin E level is not a reliable surrogate measure of dietary intake. The correlation, if any, between dietary vitamin E intake and normal vitamin E plasma concentrations is not strong (April 2000 DRI Report at 2 10). Consequently, results from observational studies based on blood measurement of vitamin E intakes are not reliable and are particularly difficult to interpret. Predictions based on outcomes of such vitamin E observational studies are problematic and clinical intervention trials, that quantitatively measure actual vitamin E intakes, are needed to meaningfully evaluate a possible relationship between vitamin E intake and a reduced risk of cancer.

Serum or plasma measures of vitamin C also pose interpretive problems when intake is outside of typical dietary ranges. Dose-dependent absorption and renal regulation limit plasma levels when intakes are high and conserve body stores when intakes are low (April 2000 DRI Report at 100). Nonetheless, there is a direct relationship between serum or plasma vitamin C levels and recent vitamin C intake when that intake is within the range typically obtained from the diet. Thus, the scientific credibility of prospective studies of a possible association between vitamin C and cancer risk will depend on study design and subject population.

As a consequence of these and other inherent limitations, observational studies are much less useful than intervention studies in resolving the key issue from the 1993 evaluation; that is, whether the vitamin C or vitamin E, alone or in combination, is responsible for reducing the risk of some kinds of cancer that is observed with diets low in fat and high in fruits and vegetables, and that may contain dietary fiber, vitamin A, and vitamin C. The agency gave greater weight to well-designed and well-conducted intervention trials that directly addressed the intake of vitamin C or vitamin E, alone or in combination, in relation to a cancer endpoint. The agency gave the observational studies relatively low weight.

C. Evaluation of the Scientific Evidence

As with the agency's review of the available data in the 1993 final rule, the more recently available studies that the agency evaluated concerned the putative relationship between antioxidant vitamins and certain kinds of cancer. Because associations between intake patterns* and cancer risk appear to be site related, the data from the 199 1 - 1993 review and the current review are summarized by cancer sites: cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, and stomach. Because of the sheer number of relationships between the antioxidant vitamins and types of cancer to be evaluated, FDA included the data used in its 1991-1993 review in the current scientific review.

1. Bladder Cancer

a. Vitamin C

FDA's review of the available scientific evidence did not identify any intervention trials that evaluated a possible relationship between vitamin C and the reduced risk of bladder cancer. Without relevant data from intervention trials, the agency must evaluate the results of observational studies to determine whether there is a potential relationship between vitamin C and bladder cancer risk. Regarding the relevant observational studies, FDA identified two prospective cohort studies (Shibata et al., 1992 and Enstrom et al., 1992) and two retrospective case-control studies (La Vecchia et al., 1989 and Vena et al., 1992).

No statistically significant association between vitamin C intake (both dietary and supplemental intake) and bladder cancer risk was found in a ten-year follow-up of the First National Health and Nutrition Examination Survey (NHANES I) cohort of 11,348 adults (Enstrom et al., 1992). Similarly, an eight-year follow up of 11,580 elderly subjects in a California retirement community cohort found no statistically significant

[8] Certain dietary patterns, e.g., reduced total fat and increased fruit and vegetable consumption, have been shown to reduce the risk of certain types of cancer. To determine whether antioxidant vitamins exhibit a similar effect, FDA reviewed data concerning vitamin C and vitamin E and each of the cancer sites listed in this discussion.

association of dietary vitamin C intake and bladder cancer incidence among elderly men; too few cancer cases occurred among the females in the cohort to evaluate cancer risk (Shibata et al., 1992). Shibata et al. (1992) did find, however, a statistically significant inverse association between use of vitamin C-containing multivitamin/mineral dietary supplements and bladder cancer incidence in elderly men. No statistically significant association between vitamin C and bladder cancer risk was found in either case-control study (La Vecchia et al., 1989 and Vena et al., 1992).

i. Consideration of Significant Scientific Agreement

Without relevant intervention trials to evaluate whether there is a relationship between vitamin C and bladder cancer risk, the agency considered whether the data from the observational studies are sufficient to establish such a relationship. Of the available evidence, one prospective cohort study (Enstrom et al., 1992) found no statistically significant association of bladder cancer risk with dietary or supplemental vitamin C intake. Another prospective cohort study found no statistically significant association of bladder cancer risk in elderly men with dietary vitamin C intake, but found a statistically significant inverse association with use of vitamin C-containing multivitamin/mineral dietary supplements in such men (Shibata et al., 1992). Neither of the retrospective case-control studies found any association between vitamin C and bladder cancer risk (La Vecchia et al., 1989 and Vena et al., 1992).

The lone finding of an association in a prospective cohort study (Shibata et al., 1992) provides insufficient scientific evidence to support a relationship between vitamin C and reduced bladder cancer risk. A single non-replicated result from an observational study does not provide a sufficient body of scientific evidence to permit a determination of whether a change in the dietary intake of the substance will result in a change in a disease endpoint. (See memorandum to the file in Docket 91N-0101 - "Replication of research findings" April 30, 2001.) Further, Shibata et al. (1992), which found a statistically significant inverse association between the use of vitamin C-containing multivitamin/mineral dietary supplements and bladder cancer incidence in elderly men, could not isolate the effect of vitamin C from other substances in the supplement products as being responsible for a possible association. In addition, the association found in Shibata, et al. (1992) with the use of vitamin C-containing multivitamin/mineral dietary supplements and bladder cancer incidence was not consistent with the findings with dietary vitamin C intake in that same study. Moreover, an association between dietary or supplemental vitamin C intake was not found in either the prospective cohort study (Enstrom et al., 1992) or the retrospective case-control studies (La Vecchia et al., 1989 and Vena et al., 1992). Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C intake and a reduced risk of bladder cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of bladder cancer.

ii. Weight of the Evidence

The agency noted that the available evidence consisted of only four observational studies; two prospective and two retrospective studies. One prospective cohort study (Enstrom et al., 1992) found there was not a statistically significant association of bladder cancer risk with dietary or supplemental vitamin C intake. Another prospective cohort study found no statistically significant association between dietary vitamin C intake but a statistically significant inverse association between vitamin C-containing multivitamin/mineral dietary supplement use and reduced bladder cancer risk in elderly men (Shibata et al., 1992). Neither of the retrospective case-control studies found any association between vitamin C and bladder cancer risk (La Vecchia et al., 1989 and Vena et al., 1992).

The available evidence is limited and of low persuasiveness. This evidence includes one non-replicated observational study that suggests a relationship between vitamin C and reduced bladder cancer risk, with another similar type of observational study and a few other less persuasive observational studies that show no such relationship. The single finding of a suggested benefit is both unconfirmed and inconsistent with the results of the other available studies. The agency finds that there is an insufficient body of sound, relevant scientific evidence to support even a qualified claim[9] about a relationship between supplemental vitamin C and reduced risk of bladder cancer in the general population. In order to make suggestions about any benefit of ingesting a substance to reduce the risk of cancer, without being false or misleading, there must be a credible scientific basis to do so. Thus, a certain threshold level of scientific evidence supporting the purported substance-disease relationship must be met to make a claim about such a relationship, even with a disclaimer that the available evidence is inconclusive or suggestive." Below this threshold, the agency would deem any qualified claim about such a relationship to be inherently misleading because there would be an insufficient scientific basis for the claim.

Thus, the agency concludes that the available observational data do not provide a sufficient body of sound, relevant scientific evidence to support the use of a qualified claim for a relationship between vitamin C and bladder cancer risk. Therefore, the

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[9] The term "qualified claim" includes within its meaning both the use of a qualified statement and the use of a claim with a disclaimer.

[10] Just as one cannot weigh an amount of material or measure a distance an order of magnitude smaller than the unit increments marked on a scale or a ruler, one needs a sufficient body of evidence before one can use the "weight" of information to support a qualified claim. For example, one would not expect to weigh milligram amounts of a material using a kitchen scale that is only sensitive to the nearest five grams. Likewise, in considering the bbdy of evidence available for evaluation of a qualified claim, one must consider the factors that contribute to the "weight" of the evidence. These include not only the number of available studies that bear in the issue, but also the nature of the studies (e.g., what kind of information the studies provide) and the quality of the studies (e.g., were the studies designed to answer the questions being asked in a qualified claim evaluation).

agency is not providing for the use of a qualified claim about the use of vitamin C and a reduced risk of bladder cancer.

b. Vitamin E

FDA's review of the available scientific evidence identified a single intervention trial that evaluated, on a post-hoc basis, a possible relationship between vitamin E and bladder cancer risk (ATBC Study Group, 1994). The agency also identified three relevant prospective cohort studies (Shibata et al., 1992; Comstock et al., 1991; and Wald et al., 1987) and two retrospective case-control studies (Vena et al., 1992 and Riboli et al., 1991).

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention intervention trial (ATBC Study Group, 1994) was designed to investigate the effects of beta-carotene and 50 milligrams of vitamin E daily on lung cancer risk among male Finnish smokers; incidences of cancers at other sites were also recorded. This 1994 ATBC study report states that there was a higher incidence of cancers of the bladder (9.6 versus 8.7 cases per 10,000 person-years) in the participants who received vitamin E supplements than in participants who received a placebo. Because this trial was designed to evaluate the effect of vitamin E on lung cancer, the enrollment protocols were not designed to evaluate and control for risks associated with other cancers, nor systematically to screen for and diagnose other cancers. Thus, the results with respect to bladder cancer risk must be interpreted with caution. With this caution in mind, FDA notes that the observation of a higher cancer incidence at two sites other than the lung (i.e., bladder and stomach), despite observation of a lower cancer incidence at two other sites (i.e., prostate and colorectal), suggests that there may be potential safety concerns. The results from the ATBC lung cancer prevention trial raise concerns about the safety of vitamin E supplementation and the ability of observational studies to predict benefit. These results underscore the critical need for more clinical research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real, and that safe conditions of use for vitamin E supplementation can be ascertained.

No statistically significant association between vitamin E and reduced risk of bladder cancer was found in any of the three prospective cohort studies (Shibata et al., 1992; Comstock et al., 1991; and Wald et al., 1987). One retrospective case-control study (Vena et al. 1992) found no statistically significant association between vitamin E and bladder cancer risk. Conversely, the other retrospective case-control study (Riboli et al. 199 1) reported a marginally significant reduction of bladder cancer risk associated with vitamin E intake. However, the Riboli et al. study may have introduced bias by including prevalent cancer cases (approximately 40 percent of the cancer cases). Prevalent cases include both patients who have survived the disease for a period of time and newly diagnosed patients. Case-control studies typically rely upon incident cases (newly diagnosed) rather than prevalent cases because the characteristics that contribute to survival of the prevalent cases may modify potential risk factors for the disease. Therefore, although the results of the two relevant case-control studies were mixed, the

study finding an association (Riboli, et al., 1991) had design limitations which produced questionable results.

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence was sufficient to establish a relationship between vitamin E and reduced risk of bladder cancer. Because the ATBC trial was designed as a lung cancer prevention trial, the results cannot be relied upon to support any effect of vitamin E supplements other than those on lung cancer incidence. However, as already noted, the results from the ATBC trial do raise safety concerns about vitamin E supplementation and the ability to predict effectiveness of vitamin E supplementation on cancer risk. Thus, more research is needed to ascertain conditions of safe use and whether such use is associated with benefit or risk for certain cancers.

None of the three prospective cohort studies reported a statistically significant association between vitamin E and bladder cancer risk (Shibata et al., 1992; Comstock et al., 1991; and Wald et al., 1987). One retrospective case-control study also found no statistically significant association between vitamin E and bladder cancer risk (Vena et al., 1992). The single case control study (Riboli et al., 1991) that suggested an association between vitamin E intake and reduced bladder cancer risk was the least persuasive evidence available, and also had design limitations resulting in questionable results. Moreover, Riboli et al. (1991) could not isolate vitamin E from other substances in the diet as being responsible for a possible association.

A single non-replicated result from an observational study does not provide a sufficient body of scientific evidence to permit a determination of whether a change in the dietary intake of the substance will result in a change in a disease endpoint. The results from the ATBC intervention tial underscore the difficulty of predicting the safety or effectiveness of vitamin E supplementation on cancer risk. This study not only failed to support the hypothesized effect based on a body of observational studies, but also suggested that vitamin E supplementation is associated both with reduced cancer incidence at some sites and increased cancer incidence at other sites, including bladder cancer. This low predictability and confusion about the role of vitamin E dietary supplements in modifying cancer risk can be resolved only by further clinical intervention research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real and that safe conditions of use from such supplementation can be ascertained. Thus, there is no strong, relevant, consistent body of observational evidence to support a causal relationship between vitamin E and bladder cancer. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E intake and a reduced risk of bladder cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of bladder cancer.

ii. Weight of the Evidence

The agency first considered the only available intervention trial evidence (ATBC Study Group, 1994). The ATBC Study Group (1994) results raise concerns about the safety of vitamin E supplementation, including bladder cancer, and the ability of observational studies to predict benefit. These results underscore the critical need for more research to ensure both that any suggestion of benefit or increased risk from vitamin E supplementation is real and that safe conditions of use for vitamin E supplementation can be ascertained.

In evaluating the observational evidence, the agency noted that the results from all three of the prospective cohort studies are consistent in finding no association between vitamin E and bladder cancer risk (Shibata et al., 1992; Comstock et al., 1991; and Wald et al., 1987). Concerning the less persuasive observational data, the results of the retrospective case-control studies were mixed. One retrospective case-control study found no statistically significant association (Vena et al., 1992), while another retrospective case-control study reported a marginally significant association between vitamin E and reduced bladder cancer risk (Riboli et al., 1991). The agency placed less weight on Riboli et al. (1991), compared to Vena et al. (1992), because of a limitation in the Riboli et al. (1991) study design. Therefore, the only evidence suggesting an association is a single retrospective case-control study with design limitations (Riboli et al., 1991), the results of which were marginally significant and questionable at best.

The results from the ATBC intervention trial, which suggest that vitamin E supplementation might be associated with both reduced cancer incidence or increased cancer incidence depending on the cancer site, raises serious questions and cause confusion about the role, if any, of vitamin E dietary supplements in modifying cancer risk, such that no disclaimer could render a claim for a relationship of vitamin E and reduced risk of cancer non-misleading. Further, FDA explained earlier in section IV.B.2. the difficulties in interpreting the results of observational studies of vitamin E and cancer. After reviewing the available data, including the post-hoc results from the ATBC intervention tial and the limitations associated with observational data on vitamin E, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin E and reduced bladder cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin E and reduced risk of bladder cancer.

2. Breast Cancer

a. Vitamin C

FDA's review of the available scientific evidence did not identify any intervention trials that evaluated a possible relationship between vitamin C and the reduced risk of breast cancer. Without relevant data from intervention trials, the agency must evaluate the results of observational studies to determine whether there is a potential relationship

between vitamin C and breast cancer risk. Regarding the relevant observational studies, FDA identified seven prospective cohort studies (Hunter et al., 1993; Kushi et al., 1996; Jarvinen et al., 1997; Verhoeven et al., 1997; Shibata et al., 1992; Zhang et al., 1999; and Enstrom et al., 1992), one prospective nested case-control study (Rohan et al., 1993), thirteen retrospective case-control studies (Landa et al., 1994; Ronco et al., 1999; Freudenheim et al., 1996; Rosenblatt et al., 1999; Bohlke et al., 1999; Ramaswamy et al., 1996; Yuan et al., 1995; Gerber et al., 1991; Graham et al., 1991; Katsouyanni et al., 1988; Toniolo et al., 1989; Zaridze et al., 1991; and Mannisto et al., 1999), and one meta-analysis (Howe et al. 1990).[11]

Six of the seven prospective cohort studies found no statistically significant association between vitamin C and breast cancer risk (Enstrom et al, 1992; Hunter et al., 1993; Kushi et al., 1996; Jarvinen et al., 1997; Shibata et al., 1992 and Verhoeven et al., 1997). The single prospective cohort study (Zhang et al., 1999) that found a statistically significant association between total dietary vitamin C and reduced breast cancer risk also found no such statistically significant association with use of vitamin C-contain&g multivitamin/mineral dietary supplements. These findings from Zhang et al. (1999), that vitamin C in the diet but not vitamin C in supplements was associated with breast cancer risk, suggest that dietary components of the types of foods that are high in vitamin C, but not vitamin C itself, affected the breast cancer risk, and that dietary vitamin C may have been a marker for those other dietary components. Similar to the findings of the majority of the prospective cohort studies, the results of the prospective nested case-control study also found no association between vitamin C and breast cancer risk (Rohan et al., 1993).

Most of the retrospective case-control studies also reported no statistically significant association between vitamin C and breast cancer risk (Katsouyanni et al., 1988; Toniolo et al., 1989; Graham et al., 1991; Gerber et al., 1991; Freudenheim et al., 1996; Rosenblatt et al., 1999; Ramaswamy et al., 1996; Bohlke et al., 1999; and Mannisto et al., 1999). The remaining studies reported a statistically significant decreased risk of breast cancer associated with vitamin C intake (Zaridze et al., 1991; Landa et al., 1994; Yuan et al., 1995; and Ronco et al., 1999). A 1990 meta-analysis of 12 retrospective case-control studies was identified in FDA's 1991 proposal (56 FR 60,624 at 60,633-34) as having found an association between estimated vitamin C intakes and breast cancer risk (Howe et al., 1990). However, meta-analyses must be reviewed with caution because such analyses are potentially subject to publication biases[12] and can also magnify biases that are present in individual studies. Moreover, the results of this meta-analysis of pre- 1990 case-control studies are not consistent with more recent evidence, including many prospective studies, showing no association between vitamin C and breast cancer risk.

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[11] Meta-analysis is a systematic approach to identifying, appraising, synthesizing, and (if appropriate) combining the results of relevant studies to arrive at conclusions about a body of research (Stroup et al., 2000).

[12] Publication bias is the selective publication of studies based on the magnitude and direction of their findings (Stroup et al., 2000).

values. There is no strong, relevant, consistent body of observational evidence to infer a causal relationship between vitamin E and breast cancer risk. In fact, the relevant, consistent body of evidence from prospective observational studies supports a conclusion that a relationship is not likely. Therefore; based‘on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E and reduced breast cancer risk. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of breast cancer.

ii. Weight of the Evidence

In evaluating the observational evidence, the agency noted that most of the prospective studies (Knekt et al., 1988; Comstock et al., 1991; Shibata et al., 1992; Hunter et al., 1993; Kushi et al., 1996; Jarvinen et al., ‘1997; Verhoeven et al., 1997; Russell et al., 1988; Rohan et al., 1993; and Dorgan et al., 1998) consistently show no association between vitamin E and breast cancer risk. The results of the prospective cohort study by Zhang et al. (1999), which report an association of dietary vitamin E intake and breast cancer risk, but not an association of vitamin E-containing dietary supplements and breast cancer risk, suggest that it was not vitamin E in the diet responsible for the protective association. The results of the retrospective case-control studies were consistent with the results of prospective studies. Most of the retrospective case-control studies reported no association between vitamin E and breast cancer risk (Basu et al., 1989; Toniolo et al., 1989; Gerber et al., 1989 and 1991; Richardson et al., 1991; Yuan et al., 1995; Freudenheim et al., 1996; Rosenblatt et al.,’ 1999; Van’t Veer et al., 1996; Ronco et al., 1999; and Bohlke et al., 1999). ‘Only four retrospective case-control studies (Torun et al., 1995; Mezzetti et al., 1998; Favero et al., 1998; and Mannisto et al., 1999), found an association between vitamin E and breast cancer risk, and these studies are flawed as discussed under lV.C.2.b. and b.i. above.

FDA explained earlier in section IV.B.2. the difficulties in interpreting the results of observational studies of vitamin E and cancer. After reviewing the available data, including the limitations associated with observational data on vitamin E, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin E and a reduced risk of breast cancer. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin E and reduced risk of breast cancer.

3. Cervical Cancer

a. Vitamin C

FDA’s review of the available scientific evidence identified one intervention trial (Mackerras et al., 1999), one prospective nestkd case control study (Wideroff et al., 1998), eight retrospective case control studies (Ho et al., 1998; Ramaswamy et al., 1996; Basu et al., 1991; Ziegler et al., 1990; Veirault etal., 1989; Brock et al., 1988;

VanEenwyk et al., 199 1; and Herrero et al., 199 1) and one cross-sectional study (Giuliano et al., 1997) that evaluated a possible relationship between vitamin C and cervical cancer risk.

In a 2-year, randomized, double-blind, placebo-controlled intervention trial, Mackerras et al. (1999) evaluated the effect of daily intakes of 500 mg vitamin C and beta-carotene, on the progression of cervical intraepithelial neoplasia (CIN) lesions. Mackerras et al. (1999) randomized 141 women diagnosed with CIN into a 2x2 factorial design with daily intakes of 500 mg vitamin C or placebo and beta-carotene or placebo (i.e., there were four groups: one group received only placebos, one received vitamin C and the placebo for beta-carotene, one received beta-carotene and the placebo for vitamin C, and one received both supplements). The investigators found no effect of vitamin C supplements on the rate of progression of CIN lesions.

CIN is a pre-cancerous stage in the process leading to invasive cervical cancer. It is well established that most of squamous cell cancers of the cervix progress through a series of well-defined pre-invasive CIN lesions (Rock et al., 2000). In the pre-invasive stages, the squamous cell dysplasia is confined within the epithelial layer of the cervix (i.e., intraepithelial neoplasia, CIN, or squamous intraepithelial lesions, CSIL). *Id.* When the dysplastic lesion has progressed through the entire thickness of the cervical epithelium, it is considered as carcinoma in *situ. Id.* Involvement of the epithelial basement membrane is the threshold distinguishing carcinoma *in situ* from invasive cervical cancer. *Id.* Progression of CIN through the pre-invasive stages is usually a protracted process. During the pre-invasive stages the disease is easily detected by Pap smear screening and can be successfully treated. The rate of CIN lesion progression is directly related to the risk of the lesion progressing to invasive cervical cancer. *Id.* The risk of developing invasive cervical cancer is directly related to the rate of progression of existing CIN lesions. Therefore, the finding by Mackerras et al. (1999) that vitamin C supplementation has no effect on the rate of CIN lesion progression is evidence that vitamin C supplementation does not reduce the risk of cervical cancer.

Wideroff et al. (1998), in a prospective nested case-control study, found no association between vitamin C intake and development of CIN. Three retrospective case-control studies observed a statistically significant association between dietary intakes of vitamin C and decreased risk of cervical cancer (Verrault et al.', 1989; Herrero et al., 1991; and VanEenwyk et al., 1991). However, Verrault et al. (1989) found that although dietary vitamin C intake was associated with reduced cervical cancer risk, regular use of vitamin C-containing dietary supplements was not. In addition, the results from VanEenwyk et al. (199 1) may be confounded by selection bias because the study had very low response rates (50-60 percent). Further, the relevance 'of the results from Herrero et al. (1991) are in question because of differences between the U.S. population and the population sampled by Herrero et al. (1991) (in Mexico and South America) in both nutritional status and cervical cancer etiology. Two retrospective case-control studies found no statistically significant association between dietary intakes of vitamin C and cervical cancer risk (Brock et al., 1988 and Ziegler et al., 1990). Two of the three

retrospective case control studies that compared blood levels of vitamin C in cases and controls showed an inverse association between blood vitamin C levels and cervical cancer risk. (Ramaswamy et al., 1996 and Ho et al., 1998) and the remaining study found no association (Basu et al., 1991). However, the results from case-control studies which use vitamin C blood levels as a surrogate for dietary intakes are difficult to interpret since it is not possible to tell whether blood levels are low because of low dietary intakes or whether low blood levels are a result of the disease itself. Consequently, the agency gave these studies very little weight in its analysis. Guiliano et al. (1997), in a cross-sectional study in 123 non-smoking, low-income Hispanic women in the US., found no statistically significant association between plasma vitamin C levels and grade of cervical dysplasia.

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin C and reduced risk of cervical cancer. Recent evidence from an intervention trial shows no protective effect of vitamin C supplements against progression of cervical intraepithelial neoplastic (CIN) lesions (Mackerras et al., 1999). Similarly, a prospective nested case-control study found no association between vitamin C intake and development of CIN (Wideroff et al., 1998). The remainder of the available evidence consisted of retrospective case-control and cross-sectional studies. Five of the eight retrospective case-control studies (Verrault et al., 1989; Herrero et al., 1991; VanEenwyk et al., 1991; Ramaswamy et al., 1996 and Ho et al., 1998) found an association between vitamin C and cervical cancer risk. The results from two of these studies (VanEenwyk et al. (1991) and Herrero et al (1991)) are not reliable because of design limitations as discussed above under IV.C.3.a. Verrault et al. (1989) found no association with vitamin C-containing dietary supplements. Further, the three case-control studies that found an association (VanEenwyk et al., 1991; Herrero et al., 1991; and Verrault et al., 1989) with dietary vitamin C intake, could not isolate the effect of vitamin C from other substances in the diet as being responsible for the association. The remaining case-control studies (Basu et al., 1991; Brock et al., 1988 and Ziegler et al., 1990) found no association between vitamin C and cervical cancer risk. The cross-sectional study (Giuliano et al. (1997) found no statistically significant association between plasma vitamin C levels and grade of cervical dysplasia. The well-designed vitamin C dietary supplement intervention tial by Mackerras et al. (1999), that demonstrates no effect of vitamin C supplements on cervical intraepithelial neoplasia progression, provides clear and compelling evidence that there is no relationship between vitamin C and reduced risk of cervical cancer. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C and reduced risk of cervical cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of cervical cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency considered the results of the most persuasive type of evidence available, i.e., a randomized, double-blinded, placebo-controlled clinical intervention trial, that found no effect of vitamin C supplementation on reducing cervical cancer risk. The intervention trial (Mackerras et al., 1999) results provide clear and compelling evidence against an association of vitamin C dietary supplements and reduction of cervical cancer risk, based on CIN dysplasia progression. Of the available observational evidence, the results of the prospective study (Wideroff et al., 1998) were consistent with the results of the intervention trial in finding no association of vitamin C and pre-invasive cervical neoplasia risk. Results from the retrospective case-control studies were mixed and, as noted above, some of the case-control studies that suggested an effect had serious limitations that adversely affected the reliability of their results.

The agency considers results from well-designed, large, randomized, double-blinded, placebo-controlled clinical intervention trials to be the "gold standard" of scientific evidence to establish a relationship of a nutrient and reduced disease risk. Results from such a study (Mackerras et al., 1999) show no protective effect of vitamin C supplementation and cervical cancer risk. Therefore, based on the totality of the scientific evidence, particularly the compelling evidence from a vitamin C dietary supplement intervention trial, the agency concludes that the scientific evidence against a relationship between vitamin C and reduced risk of cervical cancer outweighs the scientific evidence for such a relationship.

b. Vitamin E

FDA's review of the available scientific evidence identified no intervention trials that evaluated a possible relationship between vitamin E and cervical cancer risk. Without any relevant intervention trials, the agency evaluated evidence from observational studies to determine whether there is a relationship between vitamin E and cervical cancer risk. FDA identified two prospective nested case-control studies that evaluated the relationship (Wideroff et al., 1998 and Knekt et al., 1988), four retrospective case-control studies (Potischman et al., 1991; Verrault et al., 1989; and Cuzick et al., 1990; Ho et al., 1998), and one cross-sectional study (Giuliano et al., 1997).

Both of the prospective nested case-control studies reported no association between vitamin E and cervical cancer risk (Wideroff et al., 1998 and Knekt et al., 1988). Knekt et al. (1988) analyzed data from a cohort of approximately 15,000 Finnish women and found no association between serum vitamin E and cervical cancer risk. Wideroff et al. (1998) analyzed data from a cohort of over 17,000 Portland, Oregon area women and found no association of dietary vitamin E intake and risk of CIN.

Both of the retrospective case-control studies that evaluated serum levels of vitamin E reported an association between serum levels of vitamin E and cervical cancer risk (Cuzick et al. 1990 and Ho et al., 1998). However, in retrospective studies it is not

possible to determine whether lower serum levels of vitamin E are due to lower intakes or to effects of the disease. The two retrospective case-control studies that evaluated dietary vitamin E intake reported either an association of dietary vitamin E intake and cervical cancer risk (Verrault et al., 1989) or no association (Potischman et al., 1991). However, as previously noted in section IV.B.2., it is difficult to accurately estimate vitamin E intakes. Thus, in the available observational case-control studies that evaluated a possible relationship between vitamin E and cervical cancer, it was not possible to attribute any effects to vitamin *Eper* se, in those studies that suggested such effects, or to accurately estimate vitamin E intakes.

In a cross-sectional study, Giuliano et al. (1997) found an inverse association between grade of cervical intraepithelial neoplasia (CIN) lesion and plasma vitamin E in non-smoking, low-income Hispanic women in Tucson, Arizona. However, this finding depended upon relatively few cases of higher-grade lesions (only 12 had Grade II or Grade III lesions). The authors noted that due to the low numbers of women in the higher CIN-grade categories and the lack of histological confirmation for all subjects, conclusions about the relationship between vitamin E status and CIN cannot be drawn. Additional factors urging caution in interpreting these results include the possibility that the nutritional and health status, and thus predominant disease risk factors, of the study population do not reflect that of the general population.

i. Consideration of Significant Scientific Agreement

There were no relevant intervention trials to evaluate a possible relationship between vitamin E and reduced cervical cancer risk. The evidence from the prospective nested case-control studies (Wideroff et al., 1998 and Knekt et al., 1988) showed no statistically significant association between vitamin E and cervical cancer risk. None of the available studies was able to accurately estimate vitamin E intakes, or to isolate the effects of vitamin E from other components in the diet, where the data suggested that vitamin E was responsible for a protective effect. Moreover, the results among the available observational studies were mixed and inconsistent. Therefore, there is not a body of consistent, relevant, scientific evidence upon which a relationship between vitamin E and reduced risk of cervical cancer can be causally inferred. Thus, based on its review, FDA concludes that the totality of the available scientific evidence does not support a relationship between vitamin E and reduced risk of cervical cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of cervical cancer.

ii. Weight of the Evidence

The available evidence consisted of only two prospective nested case-control studies, four retrospective case-control studies, and one cross-sectional study. One of the two prospective nested case-control and two of the four retrospective case-control studies measured serum vitamin E levels and the other remaining studies measured dietary

vitamin E intake. The two prospective nested case-control studies found no statistically significant association between vitamin E and cervical pre-invasive neoplasia or invasive cancer risk (Wideroff et al., 1998 and Knekt et al., 1988). Further, although two case-control studies that measured serum vitamin E levels found a statistically significant association between vitamin E and cervical cancer (Cuzick et al., 1990; and Ho et al., 1998), their usefulness is limited because of the limitations imposed by serum vitamin E measurement in these type of studies and the inability to make inferences based on such measurements. The results from the one prospective cohort study (Wideroff, et al., 1998) and the two retrospective case-control studies (Verrault et al., 1989; and Potischman et al., 1991) that measured dietary intakes of vitamin E were mixed. As stated earlier, it is difficult to estimate vitamin E intakes in observational studies, and therefore, the data from these three studies that estimated vitamin E intakes are questionable at best.

In summary, the agency finds the available evidence to be limited and of low persuasiveness. The agency finds that there is an insufficient body of sound, relevant scientific evidence to support even a qualified claim about a relationship between supplemental vitamin E and reduced risk of cervical cancer in the general population. In order to make suggestions about any benefit of ingesting a substance to reduce the risk of cancer, without being false or misleading, there must be a credible scientific basis to do so. Put another way, a certain threshold level of scientific evidence supporting the purported substance-disease relationship must be met to make a claim about such a relationship, even with a disclaimer that the available evidence is inconclusive or suggestive. Below this threshold, the agency would deem any qualified claim about such a relationship to be inherently misleading because there would be an insufficient scientific basis for the claim.

Thus, the agency concludes that the available observational data do not provide a sufficient body of sound, relevant scientific evidence to support the use of a qualified claim for a relationship between vitamin E and cervical cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin E and a reduced risk of cervical cancer.

4. Colorectal Cancer

a. Vitamin C

FDA's review of the available scientific evidence identified six intervention trials (Greenberg et al., 1994; Roncucciet al, 1993; Hofstad et al., 1998; Paganelli et al.; 1992; McKeown-Eyssen et al., 1988; and DeCosse et al., 1989), four prospective cohort studies (Eichholzer et al., 1996; Bostick, et al, 1993; Enstrom et al., 1992; and Shibata et al., 1992), and eight retrospective case control studies (Ferraroni et al., 1994; Whelan et al., 1999; Enger et al., 1996; LaVecchia et al., i997; Benito et al., 1991; West et al., 1989; LaVecchia et al., 1988; and Freudenheim et'al., 1990) that investigated a possible relationship between vitamin C and reduced. colorectal cancer risk.

Five of the randomized intervention trials used the incidence of recurrent colorectal adenomatous polyps, a precursor of malignant cancer, as a surrogate marker of colorectal cancer risk (McKeown-Eyssen et al., 1988; DeCosse et al., 1989; Roncucci et al., 1993; Greenberg et al., 1994; Hofstad et al., 1998). Development of colorectal cancer is a multi-step process beginning with adenomatous polyps. Most colorectal adenomatous polyps remain as small non-malignant polyps, but a small proportion grow into larger, more dysplastic polyps, which in turn evolve into malignant adenocarcinomas. Because all colorectal cancers are believed to develop from adenomatous polyps, polyp appearance (i.e., incidence) is considered a surrogate for a cancer endpoint (Einspahr et al., 1997). Furthermore, it has been established that screening for and removal of adenomatous polyps prevents the development of colorectal cancer (Winawer et al., 1993); that is, colorectal cancer does not develop in the absence of adenomatous polyps. Thus, the link between adenomatous polyps and subsequent colorectal cancer risk in humans is established.

The standard colorectal polyp prevention trial protocol begins with colonoscopy screening of prospective subjects. All detected polyps are removed, and cancer-free subjects in whom at least one initial adenomatous polyp was found are enrolled in the study. The first follow up colonoscopy examination is scheduled within one year of the initial screening examination, and any polyps detected within one year are considered as polyps missed in the initial examination rather than new polyps. A second follow up colonoscopy examination is scheduled several years later to determine the rate of polyp recurrence. Because invasive colorectal cancer begins as an adenomatous polyp, a treatment that reduces the reappearance of adenomatous polyps is considered as reducing the risk of developing invasive cancer (Einspahr et al., 1997). The expected reappearance rate of adenomatous polyps in patients having had a previous adenomatous polyp is approximately 10 percent per year (Schatzkin et al., 1994). Therefore, use of the recurrence of adenomatous polyps, in subjects who had an initial polyp detected and removed, as a clinical trial endpoint provides much greater chance of detecting treatment effects on cancer risk than would a study of the actual cancer endpoint (Schatzkin et al., 1994). The incidence of colorectal adenomatous polyp recurrence correlates with dietary factors known to influence colorectal cancer risk, e.g., total fat, fruit, vegetable, and cereal grain consumption (Platz et al., 1997 and Giovannucci et al., 1992).

Among the five colorectal adenomatous polyp prevention intervention trials, two trials reported no statistically significant protective effect of vitamin C supplements on reducing colon cancer risk (McKeown-Eyssen et al., 1988 and Greenberg et al., 1994). The Greenberg trial (Greenberg et al., 1994) was a randomized, placebo-controlled 2x2 factorial design with a beta-carotene supplement and a combined vitamins E and C supplement as treatments. They reported no treatment effects on recurrent polyp incidence after 4 years of supplementation. The Greenberg study was the largest of the vitamin C supplement polyp prevention trials; 864 subjects were enrolled and 751 subjects underwent two planned follow up colonoscopy examinations (at one year and four years). Therefore, it is the study with the most statistical power to detect an effect of the vitamin supplements. The results of this trial show that vitamin supplementation for

four years with vitamins C and E did not affect the rate of adenomatous polyp recurrence, a surrogate measure of colorectal cancer risk, in subjects who had adenomatous polyps removed before entering the study. Neither was the antioxidant vitamin supplementation effective for polyp prevention in any subgroup of subjects or in any subtype of polyp defined by size or location

The polyp prevention trial reported in McKeown-Eyssen et al. (1988) used, as the intervention, a vitamin supplement combination consisting of vitamins E and C. This intervention trial included 185 subjects with adenomatous polyps at time of initial screening, 137 of whom underwent the planned 2-year follow up colonoscopy examination. The results of this trial show no statistically significant effect of the vitamin supplement on incidence of colorectal adenomatous polyp recurrence. Thus, this study is not supportive of a relationship between vitamin C supplementation and reduced risk of colorectal cancer.

Two polyp prevention intervention trials that reported a protective effect of antioxidant vitamin supplements had design limitations that preclude reliance on their results (Roncucci et al., 1993 and Hofstad et al., 1998). The Roncucci et al. (1993) trial was an intervention trial that randomized 255 subjects into one of three treatment groups, 1) vitamin supplement of vitamins A, E, and C, 2) lactulose, or 3) no treatment, Unlike the other polyp prevention trials, the Roncucci et al. (1993) trial was not placebo controlled. The authors reported that the incidence of polyp recurrence, for subjects reexamined between 12 and 65 months after entry into the trial, was reduced in the vitamin supplement group. However, the Roncucci et al. (1993) trial was compromised by a very low follow-up rate; approximately 80 percent of the subjects dropped-out before 24 months. The high dropout rate in this study makes the results difficult to interpret and possibly introduces bias. Moreover, this study was not placebo-controlled which also introduces bias. This study protocol did not have a means of determining compliance with the vitamin supplement-dosing regimen, other than asking patients if they had adhered to the treatment schedule. In summary, because of the high attrition rate and lack of placebo controls, the results cannot be relied upon.

The polyp prevention tial reported by Hofstad et al. (1998) included as the active treatment a vitamin-mineral supplement combination consisting of calcium, selenium, beta-carotene, and vitamins E and C. This three-year, placebo-controlled intervention trial included only 93 subjects with adenomatous polyps at time of initial screening. Colorectal cancer patients and patients who had sections of their colons surgically removed were also included in the study. Both of these conditions could influence subsequent recurrent polyp development and thus bias the study results. Hofstad et al. (1998) found that the combination vitamin-mineral supplement was protective against recurrent adenomatous polyps in study subjects with a single initial polyp, but was not protective for study subjects with multiple initial polyps. One-half of the study subjects included in the recurrent polyp analysis had multiple initial polyps. Because the supplement was not protective against recurrent polyps in one-half of the subjects, i.e., in those who had multiple initial adenomatous polyps, the applicability of the results are

limited. Further, the study protocol allowed subjects to continue consuming self-selected dietary supplements in addition to the study-provided supplement, which confounded the results of this trial. Due to the limitation in the design of the study and the limited applicability of the results, the agency is using caution in interpreting the conclusions of this study with respect to the proposed claim.

The fifth vitamin C colorectal polyp prevention intervention trial, by DeCosse et al. (1989), studied patients with familial polyposis who have a hereditary predisposition to developing both a profusion of polyps and colorectal cancer. All subjects had undergone complete surgical removal of the colon and a portion of the rectum as a cancer preventive procedure prior to the study. Because the familial polyposis patients in this study did not have intact colons and because the etiology of colorectal cancer in these patients is different from that of the general population, the true effect of vitamin C or of vitamin E supplementation on colorectal polyps cannot be determined. Nevertheless, no effect of vitamin C and E supplementation on polyp recurrence was detected.

The sixth vitamin C intervention trial examined effects of antioxidant vitamin intervention on subsequent *in vitro* epithelial cell proliferation rates in tissues obtained from rectal mucosal biopsies (Paganelli et al., 1992). However, the agency did not find this study to be relevant to its evaluation because of the uncertainties involved in the *in vitro* measurement of mucosal proliferation and the uncertainties about the relationship of altered mucosal cell proliferation rates and risk of colorectal cancer.

Among the five polyp prevention intervention trials, the Greenberg trial (Greenberg et al., 1994) is the most persuasive in terms of study size, duration of intervention, and completeness of follow-up. All five of the polyp prevention trials used supplements with vitamin C in combination with other nutrients in their treatments. Consequently, the two trials that reported a protective effect (Roncucci et al., 1993 and Hofstad et al., 1998) were not able to distinguish an effect of vitamin C from potential effects of the other components of the test supplements. Considered overall, the results from these adenomatous polyp prevention trials do not support a protective effect of vitamin C against the risk of colorectal cancer.

Three prospective cohort studies found colon cancer risk not to be statistically significantly associated with vitamin C (Eichholzer et al., 1996; Enstrom et al., 1992; and Bostick et al., 1993). Although Bostick et al. (1993) found a statistically significant inverse association between vitamin C supplement use and colorectal cancer risk by comparing the lowest to the highest quintile of vitamin C supplement use, after adjusting for other dietary factors in a multivariate analysis of the same data they found no statistically significant association of dietary vitamin C intake and colorectal cancer risk. This suggests that the original univariate association may have been due to dietary factors other than vitamin C. Another prospective study reported a statistically significant inverse association between both dietary vitamin C intake and vitamin C supplement use and colorectal cancer risk in women (Shibata et al., 1992). However, Shibata et al. (1992) reported no association of dietary vitamin C intake or vitamin C supplement use

and colorectal cancer risk in men (Shibata et al., 1992). Four retrospective case-control studies of colorectal cancer or colorectal polyp risk reported no statistically significant association between dietary vitamin C intake and colorectal cancer risk (West et al., 1989; Benito et al., 1991; Whelan et al., 1999; and Enger et al., 1996), while four others reported a statistically significant inverse association with dietary vitamin C intake (Freudenheim et al., 1990; Ferraroni et al., 1994; and LaVecchia et al., 1988 and 1997).

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence establishes a relationship between vitamin C and reduced risk of colorectal cancer. The largest and most persuasive of the polyp prevention intervention trials, Greenberg et al. (1994) showed no statistically significant effect of vitamin C supplementation on reducing colorectal cancer risk. The smaller polyp prevention intervention trial by McKeown-Eyssen et al. (1988) also showed no statistically significant effect. Limitations in the design and conduct of the trials by Roncucci et al. (1993) and Hofstad et al. (1998) preclude their results from being considered as sound, relevant scientific evidence. Also, the Roncucci et al. (1993) and Hofstad et al. (1998) trials would not have been able to distinguish an effect of vitamin C from potential effects of the other components of the test supplement because they used supplements with vitamin C in combination with other nutrients in their treatments. The DeCosse tial (DeCosse et al., 1989) is not relevant to this evaluation because their study subjects were familial polyposis patients with complete colectomies. The Paganelli tial (Paganelli et al., 1992) is not relevant to this evaluation because of uncertainties about the relationship between altered mucosal cell proliferation rates and cancer risk.

Three prospective cohort studies reported no statistically significant association between vitamin C and colorectal cancer risk (Eichholzer et al., 1996; Enstrom et al., 1992; and Bostick et al., 1993). Another prospective study reported a statistically significant inverse association between both dietary vitamin C and the use of vitamin C supplements and colorectal cancer risk in women, but reported no statistically significant association in men (Shibata et al., 1992). Among the retrospective case-control observational studies, four reported no statistically significant association between dietary vitamin C intake and colorectal cancer or colorectal polyp risk (West et al,, 1989; Benito et al., 1991; Whelan et al., 1999; and Enger et al., 1996), while four others reported a statistically significant inverse association with dietary vitamin C intake (Freudenheim et al., 1990; Ferraroni et al., 1994; and LaVecchia et al., 1988 and 1997).

The well-designed vitamin C dietary supplement intervention trial by Greenberg et al. (1994), that demonstrates no effect of vitamin C supplementation on colorectal adenomatous polyp recurrence, provides clear and compelling evidence that there is no relationship between vitamin C and reduced risk of colorectal cancer. Further, the results of Greenberg et al. (1994) are supported by the results of a smaller polyp prevention intervention trial (McKeown-Eyssen et al., 1988) and a body of prospective observational study evidence. Two polyp prevention intervention trials that found associations between

vitamin C and colorectal cancer risk (Roncucci et al., 1993; and Hofstad et al., 1998) had major limitations that limit the relevance and reliability of their results. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C and reduced risk of colorectal cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of colorectal cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency considered the results of the most persuasive type of evidence available, i.e., a well-designed, randomized, double-blinded, placebo-controlled clinical intervention trial, that found no protective effect of antioxidant vitamin supplements (i.e., vitamin C and vitamin E) against colorectal cancer risk. Results from the Greenberg et al. (1994) vitamin C intervention trial, which is the largest polyp prevention trial, in terms of subjects completing the study and in duration of intervention, and thus is the study with the most statistical power to detect any differences between the vitamin supplemented and placebo groups, provides clear and compelling evidence against a relationship of vitamin C dietary supplements and reduction of colorectal cancer risk. A smaller polyp prevention intervention trial (McKeown-Eyssen et al., 1988) also found no statistically significant effect of antioxidant vitamin supplementation on adenomatous polyp recurrence. Two intervention trials that reported a protective effect (Roncucci et al., 1993; and Hofstad et al., 1998) had design limitations which produced results that are unreliable. Thus, FDA placed less weight on these two studies. The agency did not include the remaining two intervention trials (DeCosse et al., 1989 and Paganelli et al., 1992) in its consideration of weight of the evidence because of design limitations that raised questions about the relevancy of these results to the relationship between vitamin C and reduced risk of colorectal cancer in the general population. The majority of the prospective observational studies reported no statistically significant association between vitamin C and colorectal cancer risk (Eichholzer et al., 1996, Bostick et al., 1993; and Enstrom et al., 1992) although one reported a statistically significant association in women but not in men (Shibata et al., 1992).

The agency considers results from large, well-designed, randomized, double-blinded, placebo-controlled clinical intervention trials to be the "gold standard" of scientific evidence to establish a relationship of a nutrient and reduced disease risk. Results from such a study (Greenberg et al., 1994) show no protective effect of vitamin C supplementation on colorectal cancer risk. Therefore, based on the totality of the available scientific evidence, particularly the compelling evidence from a vitamin C dietary supplement intervention trial by Greenberg et al. (1994), the agency concludes that the scientific evidence against a relationship between vitamin C and colorectal cancer risk outweighs the scientific evidence' for such a 'relationship. Thus, the agency is not providing for the use of a qualified claim about the use of vitamin C and a reduced risk of colorectal cancer.

b. Vitamin E

FDA's review of the available evidence identified six intervention trials (Greenberg et al., 1994; Roncucci et al., 1993; Hofstad et al., 1998; Paganelli et al., 1992; McKeown-Eyssen et al., 1988; and DeCosse et al.", 1989) that investigated a possible relationship between vitamin E and colorectal cancer risk. The agency also identified three post-hoc analyses of colorectal cancer risk data from the ATBC Lung Cancer Prevention Study (ATBC Study Group; 1994; Malila et al., 1999; and Albanes et al., 2000). In addition, the agency identified eight relevant prospective cohort studies (Eichholzer et al., 1996, Shibata et al., 1992; Comstock et al., 1991; Schober et al., 1987; Wald et al., 1987; Stahelin et al., 1991; Knekt et al., 1988; and Bostick et al., 1993) and six relevant retrospective case-control studies (Benito et al., 1991; Ferraroni et al., 1994; Enger et al., 1996; Freudenheim et al., 1990; LaVecchia et al., 1997; and Whelan et al., 1999).

All five of the polyp prevention trials discussed above in the vitamin C section (Greenberg et al., 1994; Roncucci et al., 1993; Hofstad et al., 1998; McKeown-Eyssen et al., 1988; and DeCosse et al., 1989), included both vitamins C and E in their dietary supplement treatments. Accordingly, the agency's discussion and conclusions about these studies provided in the previous section on vitamin C apply to this section on vitamin E. To reiterate,. the most persuasive intervention trial, Greenberg et al. (1994), found no protective effect of a vitamin E and C dietary supplement on colorectal cancer risk, as assessed by adenomatous polyp recurrence, a surrogate measure of colorectal cancer risk. McKeown-Eyssen et al. (1988) also found no statistically significant effect of a vitamin E and C supplement on the incidence of colorectal adenomatous polyp recurrence, as discussed above. The two trials that reported a protective effect of a dietary supplement intervention of antioxidant vitamins had major limitations which made their results unreliable (Roncucci et al., 1993 and Hofstad et al., 1998). Also, nutrients other than vitamins E or C were included in the suppiements used by Roncucci et al. (1993) and Hofstad et al. (1998), raising questions as to what nutrients or nutrient combinations would have been responsible for the reported protective effect. DeCosse et al. (1989) studied familial polyposis'patients who have a hereditary strong predisposition for colorectal cancer, and had their colons surgically removed to prevent colorectal cancer. They found that vitamin C and E supplements had no effect on polyp recurrence in this unique population. Because the familial polyposis patients in this study did not have colons and because the etiology of colorectal cancer in these patients is different from that of the general population, the relevance of these results to colorectal cancer risk on the general population cannot be determined.

One randomized antioxidant vitamin intervention trial examined the effects of vitamins A, C, and E supplementation on subsequent *in vitro* epithelial cell proliferation rates on tissues from rectal mucosal biopsies (Paganelli et al., 1992). The agency did not find this trial to be relevant to its evaluation because of the uncertainties involved in the *in vitro* measurement of mucosal proliferation and the uncertainties about the relationship of altered mucosal cell proliferation rates and risk of colorectal cancer.

In addition to the results of the polyp prevention trials, the ATBC lung cancer prevention trial reported colorectal cancer incidence (ATBC Study Group, 1994). The incidence of colorectal cancers among male smokers receiving the vitamin E supplement was somewhat lower than that among the subjects who did not receive vitamin E (Albanes et al., 2000). However, this trial was designed as a lung cancer prevention trial. For this reason, the results with respect to cancer other than lung cancer cannot be relied on to support any relationship of vitamin E supplementation other than with lung cancer risk. With this caution in mind, FDA notes that the observation in the ATBC lung cancer prevention trial of a higher cancer incidence at two sites other than lung (i.e., bladder and stomach) suggests that there may be potential safety concerns with vitamin E supplementation. The results from the ATBC lung cancer prevention trial raise concerns about the safety of vitamin E supplementation and the ability of vitamin E observational studies to predict benefit. These results underscore the critical need for more clinical research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real, and that safe conditions of use for vitamin E supplementation can be ascertained.

An adjunct follow-up study of the ATBC trial evaluated reported cases of adenomatous polyps in the ATBC trial subjects during the intervention period (Malila et al., 1999). Malila et al. (1999) found a statistically significant greater prevalence of adenomatous polyps among the ATBC subjects who took vitamin E supplements relative to those subjects who did not. Because the ATBC trial protocol had no systematic colonoscopy screening either at enrollment or following the intervention period, the relevance of this result to colorectal cancer risk is difficult to interpret. However, this result does raise questions about the safety of vitamin E supplementation and underscores the critical need for more research on vitamin E and cancer risk.

Seven prospective cohort studies reported no association between vitamin E and colorectal cancer risk (Eichholzer et al., 1996, 'Shibata et al., 1992; Comstock et al., 1991; Schober et al., 1987; Wald et al., 1987; Knekt et al., 1988; and Stahelin et al., 1991). One other prospective study reported an association between vitamin E supplement use and risk of colorectal cancer (Bostick et al., 1993). Among the retrospective case-control studies of colorectal cancer or polyp risk, four reported no association of vitamin E intake and colorectal cancer risk (Benito et al., 1991; Ferraroni et al., 1994; Enger et al., 1996; and Freudenheim et al., 1990), while two reported an inverse association with vitamin E intake (LaVecchia et al., 1997; and Whelan et al., 1999).

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin E and reduced risk of colorectal cancer. The largest and most persuasive of the polyp prevention intervention trials, Greenberg et al. (1994) showed no statistically significant effect of vitamin E supplements on colon cancer risk. The polyp prevention intervention trial by McKeown-Eyssen et al. (1988) also showed no statistically significant effect of vitamin E-containing supplements. Limitations in the

design and conduct of the trials by Roncucci et al. (1993) and Hofstad et al. (1998) preclude their results from being considered as sound, relevant scientific evidence. Also, the Roncucci et al. (1993) and Hofstad et al. (1998) trials would not have been able to distinguish an effect of vitamin E from potential effects of the other components of the test supplement because they used supplements with vitamin E in combination with other nutrients in their treatments. The DeCosse trial (DeCosse et al., 1989) with familial polyposis patients who had complete colectomies is not relevant to colorectal cancer risk in the general population. The relationship between vitamin E and colorectal cancer risk cannot be determined in the Paganelli trial (Paganelli et al., 1992) because of uncertainties about the relationship between altered mucosal cell proliferation rates and cancer risk.

Colorectal cancer incidence among ATBC intervention trial subjects who took vitamin E supplements was not statistically different from that of those subjects who did not (Albanes et al., 2000), and the colorectal adenomatous polyp prevalence was actually higher among trial subjects taking vitamin E supplements than among those subjects who did not (Malila et al., 1999). The agency is not including these results in its consideration of whether there is a relationship between vitamin E and colorectal cancer risk because the ATBC trial was designed as a lung cancer prevention trial and the results cannot be use to support any conclusions about cancer relationships other than those related to effects of vitamin E supplements on lung cancer incidence. Moreover, the results from the ATBC trial do raise safety concerns about vitamin E supplementation and show that more research is needed to ascertain conditions of safe use and whether such use is associated with benefit or risk for certain cancers.

There is a consistent body of seven prospective cohort studies that reported no association between vitamin E and colorectal cancer risk (Eichholzer et al., 1996, Shibata et al., 1992; Comstock et al., 1991; Schober et al., 1987; Wald et al., 1987; Knekt et al., 1988; and Stahelin et al., 1991). One other prospective study reported an association (Bostick et al., 1993). Among the retrospective case-control studies of colorectal cancer or polyp risk, four reported no effect of vitamin E intake (Benito et al., 1991; Ferraroni et al., 1994; Enger et al., 1996; and Freudenheim et al., 1990), while two reported an inverse association with vitamin E intake (LaVecchia et al., 1997; and Whelan et al., 1999).

The large, well-designed polyp prevention intervention trial with a vitamin E-containing supplement (Greenberg et al., 1994) that demonstrates no effect of vitamin E supplements on colorectal adenomatous polyp recurrence 'provides clear and compelling evidence that there is no relationship between vitamin E and reduced colorectal cancer risk. The results of the Greenberg et al. (1994) trial are consistent with the results of an earlier and smaller polyp prevention trial (McKeown-Eyssen et al., 1988). Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E and reduced risk of colorectal cancer. Accordingly, the agency concludes that there is not significant scientific agreement

among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of colorectal cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency considered the results of the most persuasive type of evidence available, i.e., a well-designed, randomized, double-blinded, placebo-controlled clinical intervention trial, that found no protective effect of antioxidant vitamin supplements (i.e., vitamin C and vitamin E) against colorectal cancer risk. Results from the Greenberg et al. (1994) vitamin E intervention trial, which is the largest polyp prevention trial in terms of subjects completing the study and in duration of intervention, and thus is the study with the most statistical power to detect any differences between the vitamin supplemented and placebo groups, provides clear and compelling evidence against an a relationship of vitamin E dietary supplements and reduction of colorectal cancer risk. A smaller polyp prevention intervention trial (McKeown-Eyssen et al., 1988) also found no statistically significant effect of antioxidant vitamin supplementation and incidence of adenomatous polyp recurrence. Limitations in the design and conduct of the trials by Roncucci et al. (1993) and Hofstad et al. (1998) preclude their results from being considered as sound relevant scientific evidence. The agency did not include two intervention trials (DeCosse et al., 1989; and Paganelli et al., 1992) in its consideration of weight of the evidence because of design limitations that raised questions about the relevancy of these results to the relationship between vitamin E and reduced risk of colorectal cancer in the general population.

Post-hoc analyses of data from the ATBC lung cancer prevention trial suggest no effect of vitamin E supplements on colorectal cancer incidence (Albanes et al., 2000), but an effect on increased colorectal adenomatous polyp prevalence (Malila et al., 1999). The ATBC trial was not designed to investigate effects of vitamin E on cancers at sites other than the lung. For this reason, the cancer data from this tial cannot be relied upon to support any relationship of vitamin E intake other than with lung cancer risk. However, in consideration of the conflicting results reported on colorectal adenomatous polyp prevalence and colorectal cancer incidence (Malila et al., 1999; and Albanes et al., 2000), in addition to the reported greater incidence of some cancers (i.e., bladder and stomach) (ATBC Study Group, 1994), the ATBC post-hoc analyses 'underscore the critical need for more research to ensure both that any suggestion of benefit or increased risk from vitamin E supplementation is real and that safe conditions of use from vitamin E supplementation can be ascertained.

Most of the prospective observational studies reported no statistically significant association between vitamin E and colorectal cancer risk (Eichholzer et al., 1996, Shibata et al., 1992; Comstock et al., 1991; Schober et al., 1987; Wald et al., 1987; Knekt et al., 1988; and Stahelin et al., 1991).

The agency considers results from large, well-designed, randomized, double-blinded, placebo-controlled clinical intervention trials to be the "gold standard" of scientific

Health Survey cohort found no statistically significant association of plasma vitamin C and lung cancer risk (Cornstock et al., 1997).[13]

Five prospective cohort studies reported associations between vitamin C intake and lung cancer risk (Knekt et al., 1991; Bandera et al., 1997; Ocke et al., 1997; Yong et al., 1997; and Voorrips et al., 2000). Knekt et al. (1991) found a statistically significant inverse association of vitamin C intake and lung cancer incidence in a 20-year follow up of cohort of Finnish men. Ocke et al. (1997) also found a statistically significant inverse association of vitamin C intake and lung cancer incidence in 20-year cohort follow-up data; however, the investigators characterized the results as a weak association. Bandera et al. (1997) found a statistically significant inverse association of vitamin C intake and lung cancer incidence among men, but not among women, in 7-year follow up data from a cohort of New York residents. Two cohort studies (Yong et al., 1997 and Voorrips et al., 2000) reported a statistically significant association between dietary vitamin C intake and reduced lung cancer risk, but found no statistically significant association with the use of vitamin C supplements. The results from Yong et al. (1997) and Voorrips et al. (2000) suggest that factors other than vitamin C in the diet are responsible for the observed association of dietary vitamin C with cancer risk, and therefore, are not supportive of a relationship between supplemental vitamin C and reduced risk of lung cancer. In the less persuasive retrospective case-control studies, one study reported no statistically significant association between serum vitamin C and reduced risk of lung cancer (LeGardeur et al., 1990) and two retrospective case control studies (Fontham et al., 1988; and LeMarchand et al., 1989) reported a statistically significant association between dietary vitamin C and lung cancer risk.

i. Consideration of Significant Scientific Agreement

Without relevant intervention trials to evaluate a possible relationship between vitamin C and reduced lung cancer risk, the agency considered whether the data from the observational studies are sufficient to establish such a relationship. The evidence from six prospective observational studies show no statistically significant association between vitamin C and lung cancer risk (Enstrom et al., 1992; Chow et al., 1992; Stahelin et al., 1991; Eichholzer et al., 1996; Shibata et al., 1992; and Comstock et al., 1997). Two prospective observational studies that analyzed vitamin C intake from both diet and supplements, found a statistically significant association of lung cancer risk with dietary vitamin C intake, but not with vitamin C supplement use (Yong et al., 1997; and Voorrips et al., 2000) suggesting that other factors correlated with dietary patterns giving high dietary vitamin C intake are likely responsible for the reduced risk of lung cancer. Three prospective cohort studies (Knekt et al., 1991; Bandera et al., 1997; Ocke et al., 1997) reported a statistically significant association between vitamin C intake and lung cancer

[13] Nested case-control studies were counted among the prospective cohort studies when the agency could ascertain that the exposure variable (i.e., blood samples or dietary questionnaire) was measured at the beginning of the follow up period and prior to disease diagnosis.

b. Vitamin E

FDA's review of the available evidence identified one intervention trial (ATBC Study Group, 1994) that evaluated a possible relationship between vitamin E and lung cancer risk. The agency also identified ten relevant prospective cohort studies (Bandera et al., 1997; Stahelin et al., 1991; Eichholzer et al., 1996; Ocke et al., 1997; Yong et al., 1997; Shibata et al., 1992; Wald et al., 1987; Gey et al., 1987; Knekt et al., 1991; and Voorrips et al., 2000), four relevant prospective nested case-control studies (Cornstock et al., 1991 and 1997; Knekt et al., 1993; and Woodson et al., 1999) and two relevant retrospective case-control studies (Harris et al., 1991 and LeGardeur et al., 1990).

The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study was an 8-year intervention trial that tested, in a 2x2 factorial design, the effect of 20 milligrams per day of supplemental beta-carotene and 50 milligrams per day of supplemental vitamin E on lung cancer (ATBC Study Group, 1994). The ATBC Cancer Prevention Study subject population was male cigarette smokers, who are a well-defined population at high risk for lung cancer. Among the 29,133 male Finnish smokers enrolled, 876 new cases of lung cancer were detected during the trial period. The lung cancer incidence among the subjects taking a daily vitamin E supplement was 5 1.3 cases per 10,000 person-year compared to 52.4 cases per 10,000 person-year among those who did not. This difference is not statistically significant and clearly demonstrates that there is no effect of supplemental vitamin E on lung cancer incidence in male smokers.

Five prospective cohort studies reported finding no statistically significant association between lung cancer risk and either dietary vitamin E intake (Ocke et al., 1997; Bandera, et al., 1997; and Voonips et al. 2000) or vitamin E supplement use (Shibata et al., 1992; Yong et al., 1997; and Voorrips et al. 2000). Three other prospective cohort studies (Eichholzer et al., 1996; Wald et al., 1987; and Gey et al., 1987) and one prospective nested case-control study (Cornstock et al., 1997) found no statistically significant association between plasma or serum vitamin E levels and lung cancer risk. While Eichholzer et al. (1996) found that low plasma vitamin E level was not statistically significantly associated with lung cancer risk, they did find that simultaneously low levels of both vitamins C and E were statistically significantly associated with increased lung cancer mortality. Two prospective cohort studies (Knekt et al., 1991; and Yong et al., 1997) and three prospective nested case-control studies (Knekt et al., 1993; Woodson et al., 1999; and Comstock et al., 1991) reported statistically significant inverse associations of plasma or serum vitamin E levels with lung cancer risk. The initial evaluation of data from a Washington County, Maryland cohort reported by Comstock et al. (1991) included 99 lung cancer cases and found base-line plasma vitamin E levels to be inversely associated with lung cancer risk. A subsequent evaluation six years later (Cornstock et al., 1997) -- at which time there were 258 recorded lung cancer cases within the cohort -- found no statistically significant association with regard to vitamin E and lung cancer. The two retrospective case-control studies found a statistically significant association of serum vitamin E levels and lung cancer risk (Harris et al,, 1991 and LeGardeur et al., 1990).

Study Group, 1994 data do not present the same difficulties because of improved study design of an intervention trial that can overcome the limitations associated with observational data.

The agency considers results from large, randomized, double-blinded, placebo-controlled clinical intervention trials to be the "gold standard" of scientific evidence to establish a relationship of a nutrient and reduced disease risk. Results from such a study (ATBC Study Group, 1994) show no protective effect of vitamin E supplementation on lung cancer risk. Therefore, based on the totality of the scientific evidence, particularly the compelling evidence from a vitamin E dietary supplement intervention trial, the agency concludes that the scientific evidence against a relationship between vitamin E and reduced risk of lung cancer outweighs the scientific evidence for such a relationship.

6. Oral, Pharyngeal, and Esophageal Cancer

a. Vitamin C

FDA's review of the available evidence identified several reports from an intervention trial conducted in Linxian, China on effects of dietary vitamin/mineral supplementation on esophageal dysplasia and cancer (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994), as well as two prospective cohort studies (Zheng et al., 1995 and Enstrom et al., 1992) and five retrospective case control studies (Barone et al., 1992; DeStefani et al., 1999; McLaughlin et al., 1988; Gridley et al., 1992; and Negri et al., 2000) that investigated a possible relationship of vitamin C and risk of cancers of the upper digestive tract, including oral, pharyngeal, or esophageal cancer.

The Linxian, China intervention trial consisted of two stages, the Dysplasia Trial (Li et al., 1993; Dawsey et al., 1994) and the General Population Trial (Blot et al., 1993; and Wang et al., 1994). In the Dysplasia Trial, residents of rural Linxian County in north-central China were screened by endoscopic esophageal cytology. A total of 3,318 subjects diagnosed with esophageal dysplasia and with no history of cancer were randomized into either an active treatment group or placebo group. The active treatment consisted of a multivitamin/multimineral supplement containing vitamins C and E (Centrum, Lederle Laboratories, Inc.) plus a beta-carotene capsule. After 2.5 years and 6 years, gastric endoscopic surveys of a random sample of trial subjects found there were no statistically significant effects of the dietary supplement intervention on risk of either esophageal dysplasia (a precursor of esophageal cancer) or esophageal cancer (Dawsey et al., 1994). Neither was there any beneficial effect of the dietary supplement treatment on esophageal/gastric cancer mortality (Li et al., 1993). The active treatment in this intervention trial was a multivitamin-mineral dietary supplement consisting of 26 nutrients. These data show that long-term supplementation with a dietary supplement product containing vitamins C and E had no effect on reducing esophageal cancer risk in this Chinese population with a high esophageal cancer risk (i.e., individuals with existing precancerous esophageal dysplasia).

The General Population Trial was a randomized, placebo-controlled intervention trial with approximately 30,000 healthy adults in Linxian, China. The trial consisted of four intervention factors (i.e., nutrient combinations). One of the nutrient combinations consisted of vitamin C plus molybdenum. Following five years of dietary supplement intervention, there was no statistically significant effect of the vitamin C-containing supplement on total cancer mortality nor specifically on esophageal cancer mortality (Blot et al., 1993). Also, at the end of the five year intervention, an esophageal/gastric endoscopy survey on a random sample of 391 subjects was performed to diagnose precancerous dysplasia and early invasive cancer of the esophagus. There were no significant reductions in the prevalence of gastric and esophageal dysplasia or cancer seen with any of the four dietary supplements, including the vitamin C and molybdenum combination (Wang et al., 1994). In any case, the relevance of any anti-cancer protective effect of vitamin C supplementation, if such a protective effect had been found, in the Linxian, China population to the general U.S. population would be questionable due to persistently low intake of multiple nutrients and one of the world's highest rates of esophageal cancer (Li et al., 1993). However, the demonstration of no protective effect for antioxidant vitamin supplementation in a sensitive population (i.e., high cancer risk and vitamin deficient diets) is strong evidence that there is no relationship between vitamin C and esophageal cancer risk.

Both of the two prospective cohort studies found no statistically significant protective effect of vitamin C and upper digestive tract cancer (Zheng et al., 1995; and Enstrom et al., 1992). Zheng et al. (1995) analyzed 7 years of follow-up data from the Iowa Women's Health Study cohort and found no statistically significant association of upper digestive tract (oral, pharyngeal, esophageal) cancer risk with either dietary vitamin C intake or with vitamin C supplement use. Enstrom et al. (1992) analyzed approximately 10 years of follow-up data from the NHANES-I cohort. They found that although the combined stomach and esophageal cancer mortality among males consuming at least 50 mg per day of vitamin C appeared to be substantially lower than the mortality for males consuming less than 50 mg per day of vitamin C, there were very few upper digestive tract cancers in the cohort data. No similar trend for esophagus or stomach cancers was observed among females. As such, Enstrom et al. (1992) concluded that, due to the few esophageal cancer cases and the resulting large confidence intervals around the mortality ratios, these data do not show a statistically significant beneficial association of vitamin C and esophageal cancer.

The results of the five relevant retrospective case-control studies (McLaughlin et al., 1988; Barone et al., 1992; Gridley et al., 1992; DeStefani et al., 1999; and Negri et al., 2000) were mixed. Three case-control studies (McLaughlin et al., 1988; DeStefani et al., 1999; and Negri et al., 2000) reported finding statistically significant inverse associations between dietary vitamin C intake and risk of cancers of the upper digestive tract. Barone et al. (1992) reported finding no statistically significant association of vitamin C supplement use with risk of oral cancer, but did find an inverse association with risk of esophageal cancer among current smokers and not among either non-smokers or ex-smokers. Gridley et al. (1992) initially found a statistically significant decreased risk

of oral cancer associated with dietary supplement use, specifically with individual vitamin C and E supplement use. However, when the analyses were adjusted for use of other supplements, vitamin C was not significantly associated with reduced risk.

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin C and reduced risk of oral, pharyngeal, or esophageal cancer. Evidence from the well-designed, well-conducted, large Linxian intervention trials show no protective effect of vitamin C-containing dietary supplements against esophageal cancer in a malnourished Chinese population (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al. 1994). These trials 'were conducted in this antioxidant-vitamin deficient, high esophageal-cancer incidence population because it was expected that they would be most likely to show a cancer protective effect should there be a relationship of antioxidant vitamins and reduced risk of esophageal cancer. As such, a lack of protective effect of antioxidant vitamin supplementation on esophageal cancer risk in the sensitive Linxian, China population is strong evidence that there is no such relationship. Consistent with the Linxian intervention tial results, the prospective cohort studies did not find statistically significant associations between vitamin C intake and reduced risk of cancers of the upper digestive tract (Enstrom et al., 1992; and Zheng et al., 1995). Among the retrospective case-control studies, three studies (McLaughlin et al., 1988; DeStefani et al., 1999; and Negri et al., 2000) found a statistically significant inverse association of dietary vitamin C intake and upper digestive tract cancer risk. However, these studies all calculated vitamin C intake from food intake and could not isolate the effect of vitamin C from other substances in the diet as being responsible for the association. By contrast, two other case-control studies found mixed results (Barone et al., 1992; and Gridley et al., 1992).

The available evidence from large, well-designed and conducted randomized clinical intervention trials of vitamin C-containing dietary supplements (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994) that demonstrated no effect of vitamin C-containing dietary supplements on esophageal cancer risk in a high esophageal cancer-risk, antioxidant vitamin-deficient population provide strong evidence that there is no relationship between vitamin C and reduced upper digestive tract cancers. Available evidence from prospective cohort studies did not show statistically significant associations of vitamin C and reduced risk of oral, pharyngeal, or esophageal cancer. There is no strong, relevant, consistent body of observational evidence from which to support a causal relationship between vitamin C and risk of oral, pharyngeal, or esophageal cancer. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C and reduced risk of oral, pharyngeal, or esophageal cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of oral, pharyngeal, or esophageal cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency considered the results from the most persuasive type of evidence available, i.e., randomized, double-blinded, placebo-controlled clinical intervention trials. The Linxian, China intervention trials (Li et al,, 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., '1994) provide strong evidence that there is not a relationship between vitamin C-containing dietary supplements and development of esophageal cancer. The findings of no antioxidant vitamin protective effect in these trials is strong evidence that there is no relationship. The results of the relevant prospective cohort studies were consistent with the intervention trials in finding no statistically significant association between vitamin C and oral, pharyngeal, or esophageal cancer risk (Zheng et al., 1995; and Enstrom et al., 1992). Results from the retrospective case-control studies were mixed. Therefore, based on the totality of the scientific evidence, the agency concludes that the scientific evidence against a relationship between vitamin C and reduced risk of oral, pharyngeal, and esophageal cancers outweighs the scientific evidence for such a relationship.

b. Vitamin E

FDA's review of the available evidence identified several reports from an intervention trial conducted in Linxian, China on effects of dietary vitamin/mineral supplementation on esophageal dysplasia and cancer (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994). FDA also identified several reports of intervention trials on effects of vitamin E supplementation on progression of precancerous oral and esophageal lesions (Liede et al., 1998; Zaridze et al., 1993; and Kaugars et al., 1994). FDA identified one prospective cohort study (Zheng et al., 1995), four prospective nested case-control studies (Zheng et al., 1993; Nomura et al., 1997; and Knekt et al., 1988 and 1991) and five retrospective case-control studies (DeStefani et al., 1999; Barone et al., 1992; Gridley et al., 1992; Drozdz et al., 1989; and Negri et al., 2000) that evaluated a possible relationship between vitamin-E and reduced risk of oral, pharyngeal, and esophageal cancers.

As discussed previously under evidence for a relationship of vitamin C and upper digestive tract cancer risk, the Dysplasia Trial stage of the Linxian, China cancer prevention trial (Li et al., 1993; and Dawsey et al., 1994) found no statistically significant effects of 6-years of intervention with a daily vitamin E-containing m&vitamin-mineral dietary supplement on reducing esophageal cancer risk or mortality in a high risk population. The General Population Trial was a randomized, placebo-controlled intervention trial with approximately 30,000 healthy adults in Linxian, China. The trial consisted of four intervention factors (i.e., nutrient combinations). One of the nutrient combinations consisted of beta-carotene, vitamin E and selenium. Following five years of supplementation, there were no statistically significant effects of the vitamin E-containing dietary supplement on either esophageal cancer mortality (Blot et al., 1993) or prevalence of esophageal cancer or dysplasia among a random subset of

the study population who participated in an end-of-study endoscopic survey (Wang et al., 1994).

Leukoplakia lesions of the oral cavity and chronic gastritis of the esophagus often result from tobacco or alcohol exposure and may precede development of invasive cancer. These lesions are predisposed to dysplasia and subsequent progression to invasive cancer, In an adjunct study to the ATBC lung cancer prevention trial, Liede et al. (1998) conducted oral examinations of a random sample of 409 men at the end of the 5 - 7 'year intervention period. The purpose for the Liede et al. (1998) study was to evaluate whether the vitamin E and beta-carotene antioxidant supplementation had an effect on preventing oral mucosal changes associated with smoking, some of which are precancerous and predisposed to progressing to malignant cancer. Liede et al. (1998) found no statistically significant effect of vitamin E supplementation on the prevalence of oral mucosal lesions among the male smokers of the ATBC intervention trial. Zaridze et al. (1993) conducted a 2x2 factorial design intervention trial among Uzbekistan men recently diagnosed with either oral leukoplakia or chronic esophagitis. Tobacco use (chewing and smoking) among men in Uzbekistan is high. The two treatments were a riboflavin supplement and a combination supplement of retinol, beta-carotene and vitamin E. The results of this intervention showed no statistically significant effect of the vitamin E-containing dietary supplement on progression or regression of either oral leukoplakia (after 6 months) or chronic esophagitis (after 20 months). Neither did these results show a statistically significant-association of post-intervention serum vitamin E levels and prevalence of oral leukoplakia or chronic esophagitis (Zaridze et al., 1993). Kaugars et al. (1994) conducted an uncontrolled clinical trial in which patients with diagnosed oral leukoplakia received a vitamin E-containing antioxidant dietary supplement for 9-months. The antioxidant supplementation significantly increased serum and tissue vitamin E levels, but these changes did not correlate with clinical improvement of the oral lesions.

The evidence from the Linxian cancer prevention trials consistently demonstrate a lack of a vitamin E effect on upper digestive tract cancer risk (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994). The relevance of any anti-cancer protective effect of vitamin supplementation, if such protection was found, in the Linxian, China population to the general U.S. population would be questionable due to persistently low intake of multiple nutrients and one of the world's highest rates of esophageal cancer (Li et al., 1993). However, the demonstration of no protective effect for antioxidant vitamin supplementation in a sensitive population (i.e., high cancer risk and vitamin deficient diets) is strong evidence that there is no relationship between vitamin E and esophageal cancer risk. Further, evidence from precancerous oral or esophageal lesion intervention trial data (Liede et al., 1998; Zaridze et al., 1993; and Kaugars et al., 1994) show no effects of vitamin E supplementation on prevalence or progression of such lesions, and therefore do not support a relationship between vitamin E and upper digestive tract cancer risk. The results of all the intervention trials reviewed are consistent in concluding that vitamin E-containing supplements do not have a protective effect on upper digestive tract cancer risk.

Zheng et al. (1995) analyzed 7-years of follow-up- diet-and cancer incidence data from the Iowa Women's Health Study cohort. While they concluded that higher intakes of antioxidant vitamins may be related to'lower risk of upper digestive tract cancers, their results showed no statistically significant association of upper digestive'tract 'cancer risk with dietary vitamin E intake. Among the prospective nested case-control studies, two studies reported no statistically significant association between pre-diagnostic 'serum vitamin E levels and upper digestive tract cancer risk (Knekt et al., 1991; and Nomura et al., 1997). Conversely, two other nested case-control studies reported statistically significant inverse associations of serum vitamin E and upper digestive tract cancer risk (Knekt et al., 1988; and Zheng et al., 1993). Zheng et al. (1993) reported that their analysis of data from the Washington County, Maryland Health Survey cohort found no statistically significant associations of serum total vitamin E, or of serum alpha-tocopherol, and oral/pharyngeal cancer risk. However, they did find a statistically significant increased oral/pharyngeal cancer risk associated with serum gamma-tocopherol. Nomura et al. (1997) reported results of upper digestive tract cancer risk analyses from a cohort of Japanese-American men in Hawaii. They also found no statistically significant associations of serum total vitamin E, or of alpha-tocopherol, and cancer risk. However, Nomura et al. (1997) found a statistically significant association of decreased upper digestive tract cancer risk with serum gamma-tocopherol. Gamma-tocopherol is a minor component of serum total vitamin E and has only a fraction of the antioxidant activity of alpha-tocopherol, the predominant component of serum vitamin E. The relevance of serum gamma-tocopherol to dietary vitamin E intake is questionable. Further, the two studies reporting analyses of serum gamma-tocopherol and oral cancer risk had contradictory results. The difficulties in interpreting the results of observational studies of vitamin E and cancer, as FDA explained earlier in section IV.B.2., warrants further caution in relying on the outcomes from the observational data on vitamin E and a reduced risk of oral, pharyngeal, and esophageal cancer.

Available results from retrospective case-control studies generally found mixed results regarding associations of vitamin E and upper digestive tract cancer risk. One small case-control study in Poland (Drozdz et al., 1989) reported finding no statistically significant association of serum vitamin E and larynx cancer risk. Barone et al. (1992 j found a statistically significant inverse association of vitamin E supplement use with risk of cancer of the oral cavity, but no association with risk of esophageal cancer. However, when Barone et al. (1992) stratified their analyses by smoking status, there were no oral cancer protective effects of vitamin E supplement use for current smokers, ex-smokers or non-smokers. A retrospective case-control study conducted in Uruguay (DeStefani et al., 1999) reported finding a statistically significant inverse association of dietary vitamin E intake and upper digestive tract cancer risk. The mean dietary vitamin E intake for the study population was reported (with no units of measure associated with the data) as 3.6 (cancer cases) and 4.0 (controls). Assuming DeStefani et al. (1999) to have reported these intake values as the usual units of reporting vitamin E intake (mg of alpha-tocopherol equivalents per day), the nutritional status of the Uruguayan subjects with respect to vitamin E is deficient by U.S. standards (the DRI for U.S. adult population is 15 mg/day) and the reported study results that suggest an association

therefore could not be extrapolated to the general U.S. population. Gridley et al. (1992) found a statistically significant inverse association of oral cancer risk with dietary supplement use and specifically with individual vitamin E supplement use. Negri et al. (2000) found a statistic&y significant inverse relationship between oral and pharyngeal cancer risk and dietary vitamin E intake.

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin E and reduced risk of oral, pharyngeal, or esophageal cancer. Evidence from the Linxian, China intervention trials (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994) and from adjunct data to the ATBC intervention trial (Liede et al., 1998) show no protective effect of vitamin E supplementation for esophageal and oral cancer risk. The Linxian trials were conducted in an antioxidant-vitamin deficient, high esophageal-cancer incidence population because it was expected that they would be most likely to show a cancer protective effect should there be a relationship of antioxidant vitamins and reduced risk of esophageal cancer. As such, a lack of protective effect of antioxidant vitamin supplementation on esophageal cancer risk in the sensitive Linxian, China population is strong evidence that there is no relationship. In two other clinical trials, vitamin E supplementation had no effect on clinical improvement of oral leukoplakia (Zaridze et al., 1993; and Kaugars et al., 1994).

FDA explained earlier in section IV.B.2., the difficulties in interpreting the results of observational studies of vitamin E and cancer. Those difficulties apply to this evaluation of the vitamin E observational data for oral, pharyngeal and esophageal cancer risk. The results from four prospective studies show no statistically significant association between vitamin E intake (as estimated from dietary intake, serum total vitamin E or serum alpha-tocopherol) and reduced risk of cancers of the upper digestive tract (Knekt et al., 1991; Zheng et al., 1993; Zheng et al., 1995; and Nomura et al., 1997). The results of Zheng et al. (1993) and Nomura et al. (1997), with respect to an association of upper digestive tract cancer and serum gamma-tocopherol, are contradictory. Although three retrospective case-control studies found a statistically significant association between vitamin E and oral, pharyngeal, and esophageal cancer risk (Gridley et al., 1992; DeStefani et al., 1999; and Negri et al., 2000), it appears that the findings from one of these (DeStefani et al. (1999) cannot be extrapolated to the general U.S. population. Two others found no statistically significant association (Drozdz et al., 1989; and Barone et al., 1992).

The available evidence from large, well-designed and conducted randomized clinical intervention trials of vitamin E-containing dietary supplements (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994) that demonstrated no effect of vitamin E-containing dietary supplements on esophageal cancer risk in a high esophageal cancer-risk, antioxidant vitamin-deficient population provides strong evidence that there is no relationship between vitamin E and reduced upper digestive tract cancers. The evidence from the intervention trials that focused on precancerous oral or esophageal

lesions (Liede et al., 1998; Zaridze et al., 1993; and Kaugars et al., 1994) do not support a relationship of vitamin E supplementation and reduced risk of oral, pharyngeal, and esophageal cancer. Two prospective cohort studies reported an association of serum vitamin E and upper digest tract cancer risk (Knekt et al., 1988; and Zheng et al., 1993). FDA explained earlier in section lV.B.2. the limitations in interpreting the results of observational studies of vitamin E and cancer particularly with respect to serum vitamin E data. Three other prospective cohort studies did not show statistically significant associations of vitamin E and reduced risk of oral, pharyngeal, or esophageal cancer. There is no strong, relevant, consistent body of observational evidence from which to infer a causal relationship between vitamin E and oral, pharyngeal and esophageal cancer risk. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E and reduced risk of oral, pharyngeal, and esophageal cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of oral, pharyngeal, or esophageal cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency considered the results from the most persuasive type of evidence available, i.e., randomized, double-blinded, placebo-controlled clinical intervention trials. The Linxian, China intervention trials (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et 'al.; 1994) provide strong evidence that there is not a relationship between vitamin E-containing dietary supplements and development of esophageal cancer. Other clinical intervention trials (Liede, et al., 1998; Zaridze et al., 1993; and Kaugars et al., 1994) consistently found no effect of vitamin E-containing dietary supplements on the prevalence or progression of precancerous lesions of the oral cavity or esophagus. The agency noted that four out of five prospective studies (cohort and nested case-control) found no significant association of alpha-tocopherol vitamin E intake and oral, pharyngeal or esophageal cancer risk (Zheng et al., 1993; Zheng et al., 1995; Nomura et al., 1997; and Knekt et al., 1991). Results from the retrospective case-control studies were mixed. FDA explained the difficulties in interpreting the results of observational studies of vitamin E and cancer earlier in section IV.B.2. Therefore, based on the totality of the scientific evidence; the agency concludes that the scientific evidence against a relationship between vitamin E and reduced risk of oral, pharyngeal, and esophageal cancers outweighs the scientific evidencefor such 'a relationship.

7. Pancreatic Cancer

a. Vitamin C

FDA's review of the available scientific evidence found no intervention trials that evaluated a possible relationship between vitamin C and reduced pancreatic cancer risk. However, the agency identified three relevant prospective cohort studies (Shibata et al.,

1994; Eichholzer et al., 1996; and Enstrom et al., 1992) and two relevant retrospective case control studies (Zatonski et al., 1991 and Farrow et al., 1990).

Two of the prospective cohort studies found no statistically significant association between dietary or supplemental vitamin C and pancreatic cancer risk (Enstrom et al., 1992 and Shibata et al., 1994), whereas a third prospective cohort study (Eichholzer et al., 1996) reported a statistically significant inverse association between plasma vitamin C and reduced risk of pancreatic cancer. A ten-year follow up of the NHANES-I cohort found no statistically significant association of total vitamin C intake and pancreatic cancer incidence (Enstrom et al., 1992) in both regular users of vitamin C supplements and non-users. Simiiarly, a nine-year follow up of a California retirement community cohort found no statistically significant association of dietary vitamin C intake and pancreatic cancer risk among elderly men (Shibata et al., 1994). Conversely, Eichholzer et al. (1996), in a 17-year prospective study in a cohort of 2,974 males, found lower mean pre-study baseline plasma vitamin C levels among subjects who died of pancreatic cancer than among survivors. Several factors urge caution in the interpretation of the results of this study, e.g., there were too few pancreatic cancer-related deaths for the investigators to perform a statistical risk analysis of pancreatic cancer risk. In addition, this study relied upon a single pre-study determination of plasma vitamin C as a surrogate for long-term dietary vitamin C intake. Single measures of plasma levels of vitamin C are influenced by day-to-day variations in intake and thus are not necessarily reflective of long-term nutritional status.

One of two retrospective case-control studies found no statistically significant association between vitamin C and pancreatic cancer risk (Farrow et al., 1990). Conversely, the other case-control study found a statistically significant association between vitamin C intake and pancreatic cancer (Zatonski et al., 1991). In Zatonski et al. (1991) vitamin C intake estimates were computed from a food frequency questionnaire interview with the study subjects. However, while the study investigators interviewed 100 percent of the control subjects, surrogate interviews (such as with a spouse) were used in 71 percent of the cancer cases. This substantial use of proxy interviews for the cases introduces bias and limits the credibility of these results.

i. Consideration of Significant Scientific Agreement

Without relevant intervention trials to evaluate whether there is a relationship between vitamin C and reduced pancreatic cancer risk, the agency considered whether the data from the observational studies are sufficient to establish such a relationship. Of the available observational evidence, two of three prospective observational studies show no statistically significant association between vitamin C intake and pancreatic cancer risk (Enstrom et al., 1992 and Shibata et al., 1994). The third prospective cohort study (Eichholzer et al., 1996) had neither vitamin intake data nor an adequate number of pancreatic cancer cases for a risk analysis, both of which limit confidence in the reported association of low pre-diagnosis plasma vitamin C with pancreatic cancer risk. Although one retrospective case-control study (Zatonski et al., 1991) found an association between

available evidence is inconclusive or suggestive. Below this threshold, the agency would deem any qualified claim about such a relationship to be inherently misleading because there would be an insufficient scientific basis for the claim.

Thus, the agency concludes that the available observational data do not provide a sufficient body of sound, relevant scientific evidence to support the use of a qualified claim for a relationship between vitamin C and pancreatic cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin C and a reduced risk of pancreatic cancer.

b. Vitamin E

FDA's review of the available scientific evidence identified one post-hoc analysis of the ATBC intervention trial data (Rautalahti et al., 1999), one prospective cohort study (Eichholzer et al., 1996), and one prospective nested case control study (Burney et al., 1989; also reported by Comstock et al., 1991) that evaluated a possible relationship between vitamin E and risk of pancreatic cancer.

Rautalahti et al. (1999) conducted a post-hoc analysis of pancreatic cancer data from the ATBC intervention trial of male Finnish smokers and found that vitamin E supplements had no effect on pancreatic cancer incidence. However, as noted previously, the ATBC trial was designed to evaluate the effect of vitamin E on lung cancer. Because the enrollment protocols were not designed to evaluate and control for risks associated with other cancers, the results with respect to pancreatic cancer risk in male smokers must be interpreted with caution. With this caution in mind, FDA notes that the observation of a higher cancer incidence at two sites other than the lung (i.e., bladder and stomach), despite observation of a lower cancer incidence at two sites (i.e., prostate and colorectal), suggests that there may be potential safety concerns from supplemental vitamin E. These post-hoc findings, while useful in generating hypotheses, underscore the critical need for more research to ensure both that any suggestion of benefit or increased risk from supplemental vitamin E is real, and that safe conditions of use from such supplementation can be ascertained.

One prospective cohort study (Eichholzer et al., 1996) reported no association between plasma vitamin E and pancreatic cancer. As noted in the vitamin C section, the Eichholzer et al. (1996) study included too few pancreatic cancer-related deaths for the investigators to conduct a statistical risk analysis. Similarly, one prospective nested case-control study reported that serum vitamin E was not significantly associated with pancreatic cancer risk (Burney et al., 1989; also reported by Comstock et al., 1991).

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin E and reduced risk of pancreatic cancer. Because the ATBC trial was designed as a lung cancer prevention trial, post-hoc analyses of data for

other cancers (e.g., Rautalahti et al., 1999) cannot be relied upon to support any anti-cancer effects of vitamin E supplementation other than what may occur for lung cancer. The agency does, however, note that risk analyses conducted by Rautalahti et al. (1999) with pancreatic cancer incidence in the ATBC trial subjects had no suggestion of any effect of vitamin E supplementation on pancreatic cancer risk. The ATBC trial results do raise safety concerns about vitamin E supplementation and show that more research is needed to ascertain conditions of safe use from vitamin E supplementation and whether such use is associated with benefit or risk for certain cancers. Evidence from the two available prospective observational studies (Eichholzer et al., 1996 and Burney et al., 1989) show no association of vitamin E and pancreatic cancer risk. There is no relevant, consistent body of observational data to support a causal relationship between vitamin E and reduced risk of pancreatic cancer. Therefore, based on its review, FDA concludes that the totality of the available scientific evidence does not support a relationship between vitamin E and reduced risk of pancreatic cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of pancreatic cancer.

ii. Weight of the Evidence

The agency noted that the available evidence consisted of only one post-hoc analysis of ATBC intervention trial data (Rautalahti et al.; 1999) and two prospective observational studies (Eichholzer et al., 1996 and Burney et al., 1989). None of the available evidence found that pancreatic cancer risk was associated with vitamin E.

The available evidence is limited and of low persuasiveness. Given the concerns previously noted that arise from the ATBC lung cancer prevention trial (about the safety of vitamin E supplementation and the ability of vitamin E observational studies to predict benefit), the post-hoc nature of the ATBC pancreatic cancer risk analysis, and the difficulties in interpreting the results of observational studies of vitamin E and cancer, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin E and reduced pancreatic cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin E and a reduced risk of pancreatic cancer.

8. Prostate Cancer

a. Vitamin C

FDA's review of the available scientific evidence did not identify any intervention trials that evaluated a possible relationship between vitamin C and prostate cancer risk. However, the agency identified five prospective cohort studies (Daviglus et al., 1996; Stahelin et al., 1991; Eichholzer et al., 1996 and 1999; Shibata et al., 1992; and Enstrom et al., 1992) and six retrospective case-control studies (Kolonel et al., 1988; Ohno et al.,

1988; Deneo-Pellegrini et al., 1999; Kristal et al., 1999; Bravo et al., 1991; and West et al., 1991) that evaluated this relationship.

None of the prospective cohort studies reported a statistically significant association between vitamin C and prostate cancer risk (Daviglus et-al., 1996; Stahelin et al., 1991; Eichholzer et al., 1996 and 1999; Enstrom et al., 1992; and Shibata et al., 1992). A 3 l-year follow-up of a Western Electric Company employee cohort found no statistically significant association between dietary vitamin C intake and prostate cancer risk (Daviglus et al., 1996). A ten-year follow-up of the NHANES-I cohort found no statistically significant association of dietary vitamin C intake and prostate cancer incidence (Enstrom et al., 1992). An eight-year follow up of a California retirement community cohort found no statistically significant association of dietary vitamin C intake, nor of vitamin C dietary supplement use, and prostate cancer incidence among elderly men (Shibata et al., 1992). Finally, risk analyses on 12 years of follow-up data (Stahelin et al., 1991) and on 17 years of follow-up data (Eichholzer et al., 1996 and 1999) from a Basel, Switzerland male cohort found no statistically significant association of plasma vitamin C levels and prostate cancer risk.

Five retrospective case-control studies (Kolonel et al., 1988; Ohno et al., 1988; Bravo et al., 1991; West et al., 1991; and Kristal et al., 1999) found no statistically significant association between vitamin C intake and prostate cancer risk. One of these studies (Kristal et al., 1999) reported finding an "ordered dose-response trend" for vitamin C supplement use and prostate cancer risk. However, this study found no statistically significant association of vitamin C and reduced prostate cancer risk. One retrospective case-control study in Montevideo, Uruguay reported an association between vitamin C and prostate cancer risk (Deneo-Pellegrini et al., 1999).

i. Consideration of Significant Scientific Agreement

Without relevant intervention trials to evaluate whether there is a relationship between vitamin C intake and reduced prostate cancer risk, the agency considered whether the data from the observational studies are sufficient to establish such a relationship. The results from all five prospective cohort studies were consistent in finding no statistically significant association between vitamin C and prostate cancer risk. Three of these prospective cohort studies used dietary data (Enstrom et al., 1992; Daviglus et al., 1996; and Shibata et al., 1992) and two used plasma vitamin C data (Stahelin et al., 1991 and Eichholzer et al., 1996 and 1999). Among the retrospective case-control studies, five found no statistically significant association of dietary vitamin C intake (Kolonel et al., 1988; Ohno et el., 1988; Bravo et al., 1991; and West et al., 1991), or vitamin C supplement use (Kristal et al., 1999) and prostate cancer risk. In contrast, one retrospective case-control study (Deneo-Pellegrini et al., 1999) found a statistically significant association of dietary vitamin C intake and prostate cancer risk. The lone finding of an association in a retrospective case-control study (Deneo-Pellegrini et al., 1999) provides insufficient scientific evidence to support a relationship between vitamin C and reduced prostate cancer risk. A single non-replicated result from an

observational study does not provide a sufficient body of scientific evidence to permit a determination of whether a change in the dietary intake of the substance will result in a change in a disease endpoint. (See memorandum to the file in Docket 91N-0101- "Replication of research findings" April 30, 2001.) Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C and reduced risk of prostate cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of prostate cancer.

ii. Weight of the Evidence

The agency noted that the available evidence consisted of eleven observational studies, five prospective and six retrospective, of which only one retrospective case-control study (Deneo-Pellegrini et al., 1999) found a statistically significant association between vitamin C and prostate cancer risk. The available evidence for a relationship between vitamin C and prostate cancer is very limited and of relatively low persuasiveness. In this case, the single finding of a suggested protective effect of vitamin C from a retrospective observational study (Deneo-Pellegrini et al., 1999) is both unconfirmed and inconsistent with the results of the ten other available observational studies.

After reviewing the available data, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin C and a reduced risk of prostate cancer. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin C and a reduced risk of prostate cancer.

b. Vitamin E

FDA's review of the available scientific evidence identified three post-hoc analyses of data from a vitamin E intervention trial (ATBC Study Group, 1994; Heinonen et al., 1998; and Hartman et al., 1998), four prospective cohort studies (Eichholzer et al., 1996 and 1999; Shibata et al., 1992; Chan et al., 1999; and Comstock et al., 1991), two prospective nested case-control studies (Nomura et al., 1997 and Gann et al., 1999) and three retrospective case-control studies (Deneo-Pellegrini et al., 1999; Kristal et al., 1999; and Tzonou 1999) that 'evaluated a possible relationship between vitamin E and prostate cancer.

Although the ATBC lung cancer intervention trial was designed to evaluate the effect of vitamin E supplements on risk of lung cancer, it also recorded data on cancer incidence at other sites. The ATBC Study Group-(1994) reported a lower'mcidence of prostate cancer cases among participants receiving the vitamin E supplement than among those who did not (11.7 versus 17.8 cases per 10,000 person-years; the statistical significance of these numbers was not determined). A subsequent post-hoc analysis of the ATBC trial data found that vitamin E supplementation had a statistically significant protective effect on

both prostate cancer incidence and mortality (Heinonen et al., 1998). However, the results of the Heinonen et al. (1998) risk analysis are inconsistent with a separate post-hoc risk analysis of the ATBC trial data reported by Hartman et al. (1998). Hartman et al. (1998) found that while several different types of comparisons suggested a protective effect of vitamin E intake against prostate cancer risk, no statistically significant protective effects of vitamin E were found.

Several factors require caution in interpreting pancreatic cancer results from the ATBC trial. This trial was designed to evaluate the effect of vitamin E on lung cancer. Because the enrollment protocols were not designed to evaluate and control for risks associated with other cancers, the prostate cancer data must be interpreted with caution; e.g., there was no systematic prostate cancer screening in the ATBC trial protocol so the actual prostate cancer prevalence in the ATBC cohort is unknown and subject to potential bias. Further, the fact that the post-hoc prostate cancer risk analyses (Heinonen et al., 1998; and Hartman et al., 1998) are contradictory further confuse the prostate cancer results and preclude reliance on these results. With these cautions in mind, FDA notes that the ATBC trial observations of a supplemental vitamin E-associated higher cancer incidence at two sites other than the lung (i.e., bladder and stomach), suggests that there may be potential safety concerns from the use of supplemental vitamin E. The results from the ATBC lung cancer prevention trial raise concerns about the safety of vitamin E supplementation and the ability of observational studies to predict benefit. These results underscore the critical need for more clinical research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real, and that safe conditions of use for vitamin E supplementation can be ascertained.

None of the six prospective observational studies found a statistically significant association of vitamin E and prostate cancer risk (Comstock et al., 1999 1; Eichholzer et al., 1996 and 1999; Nomura et al., 1997; Gann et al., 1999; Shibata et al., 1992; and Chan et al., 1999). Comstock et al. (199 1) reported an analysis of 14-year follow up data from the Washington County Maryland Health Survey cohort, which found no statistically significant association between plasma vitamin E and prostate cancer risk. Similarly, an analysis of 17-year follow up data from a Base1 Switzerland cohort found no statistically significant association of plasma vitamin E and prostate cancer risk among non-smoking men. However, among' current smokers, low baseline plasma vitamin E was associated with increased prostate cancer risk (Eichholzer, et al., 1996 and 1999). An analysis of data from a 22-year follow up prospective nested case-control study in a cohort of Japanese-American men in Hawaii (Nomura et al., 1997) found no statistically significant association between serum vitamin E and prostate cancer risk. An analysis of prospective nested case-control 6-year follow up data from the Physicians' Health Study cohort (Gann et al., 1999) found no statistically significant association of serum vitamin E and prostate cancer risk. Consistent with the plasma vitamin E data, neither of the two prospective cohort studies with vitamin E intake data (Shibata et al. 1992; and Chan et al., 1999) found a statistically significant association of vitamin E and prostate cancer risk. Shibata et al. (1992) reported an analysis of 8-year follow up data from a California retirement community cohort, which found no statistically significant

association between either dietary vitamin E or vitamin E supplement use and prostate cancer risk. Similarly, an analysis of vitamin E supplement use data in the Health Professionals Study cohort found no statistically significant association of vitamin E dietary supplements and prostate cancer risk (Chan et al., 1999).

Among the three retrospective case-control studies, one (Kristal et al., 1999) found no statistically significant association of prostate cancer risk and vitamin E in a study that compared vitamin supplement use between prostate cancer cases and healthy controls in King County Washington. Conversely, two other retrospective case-control studies reported a statistically significant association of dietary vitamin E intake and prostate cancer risk (Deneo-Pellegrini, et al., 1999 and Tzonou et al., 1999). Deneo-Pellegrini et al. (1999), in a study conducted in Uruguay, found a statistically significant inverse association between prostate cancer risk from the lowest quartiles of dietary vitamin E intake (< 5 mg/day) to the highest quartile (< 7.9 mg/day). The daily intake of vitamin E at the highest quartile threshold is only one-half of the vitamin E Daily Recommended Intake @RI) for the adult U.S. population (15 mg/day). Generalizing these results to the U.S. population requires caution as the dietary vitamin E intake of the Uruguayan population appears deficient by U.S. dietary standards. Tzonou et al. (1999) reported results from a case-control study in Athens, Greece on prostate cancer and diet, in which they found a statistically significant inverse association of vitamin E from the diet and prostate cancer risk.

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin E and a reduced risk of prostate cancer. The available evidence includes post-hoc analyses of prostate cancer incidence data from the ATBC intervention trial (ATBC Study Group, 1994; Heinonen et al., 1998; and Hartman et al., 1998). One risk analysis of ATBC prostate cancer data found a statistically significant protective effect of vitamin E supplementation (Heinonen et al., 1998) while a separate analysis (Hartman et al., 1998) did not. The post-hoc results from the ATBC intervention trial, that suggest that vitamin E was associated (Heinonen et al., 1998) or was not associated (Hartman et al., 1998) with a protective effect on prostate cancer risk, cause confusion about the role of vitamin E dietary supplementation in modifying cancer risk. Further, the results from the ATBC intervention tial (ATBC Study Group, 1994) that suggest vitamin E supplementation was associated with both a reduced cancer incidence at some sites and increased cancer incidence at other sites, as discussed previously, cause additional confusion about the role for vitamin E dietary supplementation in modifying cancer risk. Such confusion can only be resolved by further clinical intervention research. Because the ATBC trial was designed as a lung cancer prevention trial, the results cannot be relied upon to support any effect of vitamin E supplements other than those on lung cancer incidence. However, the results from the ATBC trial do raise safety concerns about vitamin E supplementation and show that more research is needed to ascertain conditions of safe use and whether such use is associated with benefit or risk for certain cancers.

The results of the six prospective cohort studies were consistent in finding no associations of prostate cancer risk with either dietary vitamin E intake (Shibata et al., 1992 and Chan et al., 1999), or serum vitamin E level (Eichholzer et al., 1999; Comstock et al., 1991; Gann et al., 1999; and Nomura et al., 1997). One retrospective case-control study (Kristal et al., 1999) also found no significant association of prostate cancer and vitamin E supplement use. Two other retrospective case-control studies reported dietary vitamin E intake to be associated with prostate cancer risk (Deneo-Pellegrini, et al., 1999 and Tzonou et al., 1999). There is no strong, relevant, consistent body of evidence to support a casual relationship between vitamin E and reduced risk of prostate cancer. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E intake and a reduced risk of prostate cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of prostate cancer.

ii. Weight of the Evidence

The agency first considered the only available intervention trial evidence (ATBC Study Group, 1994; Heinonen et al., 1998; and Hartman et al., 1998). The results of Heinonen et al. (1998) and Hartman et al. (1998) for vitamin E and prostate cancer risk were mixed. Further, as noted previously, the ATBC Study Group (1994) results raise concerns about the safety of vitamin E supplementation with respect to cancer at other sites, and the difficulty in relying upon observational studies for prediction of the safety and efficacy of vitamin E supplementation on cancer risk. As such, the cancer data from this trial cannot be relied upon to support any relationship of vitamin E intake other than with lung cancer risk. These results underscore the critical need for more research to ensure both that any suggestion of benefit or increased risk from vitamin E supplementation is real and that safe conditions of use from vitamin E supplementation can be ascertained.

In evaluating the observational evidence, the agency noted that the results from all six of the prospective observational studies are consistent in finding no association between vitamin E and prostate cancer risk (Shibata et al., 1992; Comstock et al., 1991; Chan et al., 1999; Eichholzer et al., 1996 and 1999; Nomura et al., 1997; and Gann et al., 1999). The results from the less persuasive retrospective case-control studies were mixed. One retrospective case-control study found no statistically significant association (Kristal et al., 1999), while two other retrospective case-control studies reported statistically significant association between vitamin E and reduced prostate cancer risk (Deneo-Pellegrini et al., 1999 and Tzonou et al., 1999). The agency placed less weight on the results from Deneo-Pellegrini et al. (1999) because of the apparent vitamin E deficiency of the diets of the Uruguayan population studied. Moreover, these results of retrospective studies (Deneo-Pellegrini et al., 1999 and Tzonou et al., 1999) were inconsistent with the body of evidence from more persuasive, prospective cohort studies.

The post-hoc analyses of the large ATBC vitamin E intervention trial that suggest that vitamin E supplementation both might reduce incidence of prostate cancer and to the

contrary might have no effect on incidence of prostate cancer, in addition to both a decreased and increased incidence of some other cancers, causes confusion about the role of vitamin E dietary supplements in modifying cancer risk, such that no disclaimer could render a claim regarding the relationship of vitamin E and reduced risk of prostate cancer non-misleading. Further, FDA explained earlier in section IV.B.2. the difficulties in interpreting the results of observational studies of vitamin" E and cancer. After reviewing the available data, including the post-hoc results from the ATBC intervention trial and the limitations associated with the observational data on vitamin E, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin E and reduced prostate cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use if' vitamin E dietary supplements and reduced risk of prostate cancer.

9. Skin Cancer

a. Vitamin C

FDA's review of the available scientific evidence did not identify any intervention trials that evaluated a possible relationship between vitamin C and skin cancer risk. Without relevant data from intervention trials, the agency must evaluate results of observational studies to determine whether there is a relationship between vitamin C and skin cancer risk. The sole relevant observational study is a prospective cohort study (Hunter et al., 1992). In this analysis of four-year follow up data from the Nurses Health Study cohort, no statistically significant association was found for incident basal cell carcinoma with dietary intake of vitamin C, either with or without supplements, or with use of multivitamins or specific vitamin C supplements.

i. Consideration of Significant Scientific Agreement

In this case, the agency found no evidence for a relationship between vitamin C and skin cancer risk in a single prospective cohort study. Significant scientific agreement cannot be reached without a strong, relevant, and consistent body of evidence on which experts in the field may base a conclusion that a substance/disease relationship exists. In that the relevant data are limited to a sole prospective observational study finding no association between vitamin C an skin cancer risk (Hunter et al., 1992), the agency concludes that there is not a sufficient body of sound, relevant, and consistent scientific evidence to support a finding of significant scientific agreement. Therefore, based on its'review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C and a reduced risk of skin cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of skin cancer.

ii. Weight of the Evidence

The available evidence is limited and of low persuasiveness. In this case, the evidence consists of one non-replicated observational study suggesting no relationship between vitamin C and reduced skin cancer risk. The agency finds that there is an insufficient body of sound, relevant scientific evidence to support even a qualified claim about a relationship between supplemental vitamin C and reduced risk of skin cancer in the general population, In order to make suggestions about any benefit of ingesting a substance to reduce the risk of cancer, without being false or misleading, there must be a credible scientific basis to do so. Thus, a certain threshold level of scientific evidence supporting the purported substance-disease relationship is needed to make a claim about such a relationship, even with a disclaimer that the available evidence is inconclusive or suggestive. Below this threshold, the agency would deem any qualified claim about such a relationship to be inherently misleading because there'would be an insufficient scientific basis for the claim.

Thus, the agency concludes that the available observational data do not provide a sufficient body of sound, relevant scientific evidence to support the use of a qualified claim for a relationship between vitamin C and skin cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin C and a reduced risk of skin cancer.

b. Vitamin E

FDA's review of the available scientific evidence did not identify any intervention trials that evaluated a possible relationship between vitamin E and skin cancer risk. Without relevant data from intervention trials, the agency evaluated results of observational studies to determine whether there is a relationship between vitamin E and skin cancer risk. FDA identified &relevant prospect& cohort studies (Hunter et al., 1992; Wald et al., 1987; Comstock et al., 1991; Knekt et al., 1991; Breslow et al., 1995; and Karagas et al., 1997), and one retrospective case-control study (Stryker et al., 1990).

Hunter et al. (1992) conducted an analysis of four-year follow up data from over 73,000 women in the Nurses Health Study cohort involving 771 diagnosed incident cases of basal cell carcinoma. No statistically significant associations of basal cell carcinoma with dietary intake of vitamin E, either with or without supplements, or with use of multivitamins or specific vitamin E supplements were found. The rive other cohort studies (Wald et al., 1987; Comstock et al., 1991; Knekt et al., 1991; Breslow et al., 1995; and Karagas et al., 1997) were analyzed as nested case-control studies and used pre-diagnosis serum vitamin E data rather than dietary intake data. Two analyses of data from the Washington County Maryland Health Survey cohort, first by Comstock et al. (199 1) and subsequently by Breslow et al. (1995), found no statistically significant association of serum vitamin E and either melanoma or non-melanoma skin cancer risk. Similarly, two other prospective nested case-control studies reported no statistically significant association between serum vitamin E levels and skin cancer risk (Wald et al.,

1987 and Karagas et al., 1997). Of the six prospective studies only one (Knekt et al., 199 1) reported a statistically significant association of vitamin E and skin cancer risk. The Knekt et al. (199 1) prospective nested case-control analysis of cancer data from a Finnish cohort found significantly lower serum vitamin E-levels among melanoma skin cancer patients than among controls. However, these results must be interpreted cautiously, in part, because there were only ten melanoma cases in the cohort. A retrospective case control study (Stryker et al., 1990) found a statistically significant trend of decreasing malignant melanoma skin cancer risk with increasing dietary vitamin E intake. As previously noted in section IV.B.2. it is difficult to accurately estimate vitamin E intake, and serum vitamin E is not a reliable indicator of vitamin E nutritional status. Thus, in the available observational studies that evaluated a possible relationship between vitamin E and skin cancer, it was not possible to attribute any effects to vitamin E per se, when the data suggested such effects:

i. Consideration of Significant Scientific Agreement

Five of six prospective observational studies found no statistically significant association between vitamin E and reduced skin cancer risk (Hunter et al., 1992; Wald et al., 1987; Comstock et al., 1991; Karagas et al., 1997; and Breslow et al., 1995). A sixth prospective study did find an inverse association between plasma vitamin E and skin cancer risk (Knekt et al., 1991). However, this result found in Knekt et al. (i-991) cannot be considered conclusive, in part, because of a very limited number of skin cancer cases included iri'the risk analysis. The majority of the prospective observational studies that used pre-diagnosis serumvitamin E data are consistent with that of the one cohort study that did have dietary vitamin E as well as dietary supplement use data and also had the largest number of subjects (Hunter et al., 1992). Taken as the whole, there is consistency across the prospective studies finding no association between vitamin E and skin cancer risk. While, one retrospective case-control study (Stryker et al., 1990) also found dietary vitamin E intake inversely associated with melanoma risk, as noted previously, retrospective observational study designs are more subject to bias and are as a general rule are less persuasive than prospective observational studies. Thus, there is no strong, relevant consistent body of observational evidence to support a casual relationship between vitamin E and reduced risk of skin cancer. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E intake and reduced risk of skin cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of skin cancer.

ii. Weight of the Evidence

In evaluating the observational evidence, the agency noted that the majority of the prospective studies were consistent in finding no association of vitamin E and skin cancer risk (Hunter et al., 1992; Wald et al., 1987; Comstock et al., 1991; Breslow et al., 1995; and Karagas et al., 1997). The exception was a single prospective study reporting an

association (Knekt et al., 1991); however, this result was not convincing in that it was based upon the serum vitamin E values of only ten skin cancer patients. One retrospective study (Stryker et al., 1990) also reported an 'association of vitamin E intake and skin cancer risk.

FDA explained earlier in section IV.B.2. the difficulties in interpreting the results of observational studies of vitamin E and cancer. After reviewing the available data, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin E and a reduced risk of skin cancer. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin E and reduced risk of skin cancer.

10. Stomach Cancer

a. Vitamin C

FDA's review of the available evidence identified several reports from an intervention trial conducted in Linxian, China on effects of dietary vitamin/mineral supplementation on esophageal and gastric dysplasia and cancer (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994), as well as six prospective cohort studies (Stahelin et al., 1991; Eichholzer et al, 1996; Zheng et al., 1995; Enstrom, et al. 1992; Botterweck et al., 2000; and You et al., 2000), and six retrospective case-control studies (You et al., 1988; Buiatti et al., 1989; Boeing et al., 1991; LaVecchia et al., 1994; Kaaks et al., 1998; and Ekstrom et al., 2000) that evaluated a possible relationship between vitamin C and the risk of stomach cancer. FDA received, as a supplemental comment, a recent report of an intervention trial of progression of gastric pre-cancerous lesions (Correa et al., 2000).

The Linxian, China intervention trial consisted of two stages, the Dysplasia Trial (Li et al., 1993; Dawsey et al., 1994) and the General Population Trial (Blot et al., 1993; and Wang et al., 1994). In the Dysplasia Trial, residents of rural Linxian County in north-central China were screened by endoscopic esophageal cytology. A total of 3,318 subjects diagnosed with esophageal dysplasia and with no history of cancer were randomized into either an active treatment group or placebo group. The active treatment consisted of a vitamin C and E-containing multivitamin and mineral tablets (Centrum, Lederle Laboratories, Inc.) plus a beta-carotene capsule. After 2.5 years and 6 years, gastric endoscopic surveys of a random sample of trial subjects found there were no statistically significant effects of the 'dietary supplement intervention on risk of developing either atrophic gastritis (a precursor of gastric cancer) or gastric cancer (Dawsey et al., 1994). Neither was there any beneficial effect of the dietary supplement treatment on reducing stomach cancer mortality (Li et al., 1993). The active treatment in this intervention trial was a multivitamin-mineral dietarysupplement consisting of 26 nutrients. Therefore, the study would not have been able to associate any potential protective effects, had any been observed, specifically with antioxidant vitamin components of the supplements. Nevertheless, these data, do show that long-term supplementation with a dietary supplement product containing vitamins C and E had no

effect on reducing stomach cancer risk. The General Population Trial was a randomized, placebo-controlled intervention trial with approximately 30,000 healthy adults in Linxian, China. The trial consisted of four intervention factors (i.e., nutrient combinations). One of the nutrient combinations consisted of vitamin C plus molybdenum. Following five years of dietary supplement intervention, there was no effect of the vitamin C-containing supplement on total cancer morality nor specifically on stomach cancer mortality (Blot et al., 1993). An esophageal/gastric endoscopy survey on a random sample of 391 subjects was performed at the end of the five year intervention to diagnose precancerous dysplasia and early invasive cancer of the esophagus and stomach (Wang et al., 1994). There was no evidence that the vitamin C and molybdenum dietary supplement decreased the prevalence of gastric dysplasia or gastric cancer. In fact, there was a statistically significant increased prevalence of gastric cancer and precursor dysplasia lesions combined (odds ratio = 2.64; 95% confidence interval 1 .01 – 6.93) (Wang et al.," 1994). The Linxian intervention trial was conducted in a population that has 1 OO-fold greater stomach cancer incidence than that of the U.S. population. Also, a nutritional survey of the Linxian population, conducted shortly before the beginning of the intervention trials, showed vitamin deficiencies by U.S. standards to be common (Yang et al., 1984). The carcinogenesissrelated effects of vitamin supplementation to correct clear vitamin deficiencies in a poorly nourished population might well be very different from effects in the well nourished U.S. population. Nevertheless, the potential effect of a vitamin C and molybdenum dietary supplement to increase gastric precancer lesions and cancer risk in a nutritional deficient population suggest there may be safety concerns. These results underscore the critical need for more research to ensure both that any suggestion of benefit or increased risk is real, and that safe conditions of use can be ascertained.

Correa et al. (2000) conducted a 6-year intervention trial in a rural region of Columbia where prevalence of *Helicobacter pylori* infection is high, precancerous lesions of the stomach common, and gastric cancer rates high. An initial screening gastrointestinal endoscopy was conducted to identify potential subjects with precancerous gastric lesions (atrophic gastritis, intestinal metaplasia, and dysplasia) but without gastric cancer. Subjects were randomized into a placebo-controlled 2x3 factorial design (8 combinations of individual and combined treatments and placebos), with the three treatments being (1) two-week anti-*Helicobacter pylori* therapy, (2) beta-carotene, and (3) vitamin C. A follow-up gastrointestinal endoscopic examination was conducted at six years to assess effects of treatment on progression of the precancerous gastric lesions. The proportion of subjects exhibiting no change or actual progression of gastric lesions was similar across all treatment groups. By contrast, the gastric lesion regression rate of the nonintervention placebo group was less than half of that of each of the seven treatment group. There were no differences in rates of gastric lesion regression among the seven single and combined treatment groups. As such, it would appear that each of the three individual treatments had the same effect on precancer gastric lesions, e.g., increased lesion regression; each individual treatment had the same magnitude of effect; and there were no interaction or additive effects of individual treatments. All of the apparent benefits for each of the three interventions hinge on the low rate of lesion regression among the

one-eighth of the participants who were in the straight placebo arm (Blot, 2000). Correa et al. (2000) comment that the trial results suggest vitamin C supplementation may interfere with the precancerous process by increasing the rate of regression of cancer precursor lesions. However, gastric cancer risk, as determined by progression rate of cancer precursor'lesions, was not affected by vitamin C supplementation in this trial. While these results may suggest vitamin C supplementation improved gastric health in a helicobacter-infected population (i.e., increased regression of gastric lesions), these results do not suggest vitamin C supplementation reduced risk of subsequent stomach cancer (i.e., progression of gastric lesions was not affected). The relevance of the of the Correa et al. (2000) intervention trial results to a reduced risk of stomach cancer and the relevance to the general U.S. population are unclear due to the fact that the trial was conducted in a population with a *high Helicobacter pylori* infection-rate at a young age and also with a very high incidence of stomach cancer,

The available prospective cohort studies do not support an association between vitamin C and reduced stomach cancer risk (Stahelin et al., 1991; Enstrom, et al. 1992; Zheng et al.,' 1995; Eichholzer et al., 1996; Botterweck et al., 2000; and You et al., 2000).

A risk analysis of 17 years of follow-up mortality data from a Basel, Switzerland male pharmaceutical employee cohort (Eichholzer et al., 1996) found that low baseline plasma vitamin C was not associated with increased risk of subsequent stomach cancer. Similarly, an earlier risk analysis of 12 years of follow-up mortality data from the same Basel, Switzerland study cohort (Stahelin et al., 1991).also found low baseline plasma vitamin C level was not associated with increased stomach cancer risk in men of all ages in the study when deaths in the first and second year of follow-up are excluded. Stahelin et al. (1991) 'noted that since men with existing undiagnosed cancer at the time of the blood sampling could not be identified, the cancer deaths occurring within two years of the blood sampling are appropriately excluded from the risk analyses. Nevertheless, they reported that by including deaths from the first two years and stratifying the risk analysis by age, they found a statistically significant association of low plasma vitamin C and stomach cancer risk among men older than 60 years at the time of blood sampling, but not for younger men.

Botterweck et al. (2000) evaluated approximately 6 years of follow-up cancer data from a large Netherlands cohort and found no statistically significant association of dietary vitamin C intake and risk of stomach cancer when cancer cases diagnosed during the first two follow-up years were excluded from the risk analysis. When the cancer cases diagnosed during the first and second follow-up years were included, there was a statistically significant inverse association of dietary vitamin C intake and stomach cancer risk (Botterweck et al., 2000). Botterweck et al. (2000) found no 'association of vitamin C supplement use and stomach cancer risk.

Zheng et al. (1995) analyzed 7 years of follow-up data from the Iowa Women's Health Study cohort. While they concluded that higher intakes of antioxidant vitamins may be related to lower risk of gastric cancer, their risk analyses show no statistically significant

association of stomach cancer risk with dietary vitamin C intake nor with vitamin C supplement use. Enstrom et al. (1992) analyzed approximately 10 years of follow-up data from the NHANES-I cohort. They found that the combined stomach and esophageal cancer mortality among males consuming at least 50 mg per day of vitamin C appeared to be substantially lower than the that of males consuming less than 50 mg per day of vitamin C. However, the investigators' interpretation of the significance of these results was that any conclusion about protective effects of high vitamin C intake is precluded by the large confidence intervals around the mortality ratios resulting from very few esophageal/stomach cancer cases in the data. No similar trend for esophageal/stomach cancers was observed among females, nor for cancer mortality in general.

One recently reported prospective cohort study found an inverse association of baseline serum vitamin C at the start of the study and subsequent risk of progression of stomach cancer precursor lesions to dysplasia or stomach cancer (You et al., 2000). You et al. (2000) performed a gastric endoscopy survey of 3433 adults in Linqu County, China, a region of high incidence of gastric cancer. Follow-up endoscopy examinations at approximately 4.5 years were obtained in 75 percent of the study subjects; of these subjects initial serum vitamin C data was available from 366 subjects. You et al. (2000) found a statistically significant association between gastric lesion progression to dysplasia or cancer and serum vitamin C. The generalizability of this result to the general U.S. population is unclear because of nutritional differences between this poorly nourished Chinese population and the U.S. population. The Linqu population was clearly vitamin C deficient by U.S. standards as evident from the reported serum ascorbic acid levels; the threshold of the highest serum vitamin C tertile was only 5.5 microgram/ml, which appears to be comparable to the 25th percentile level in the U.S. Third National Health and Nutrition Examination Survey, 1988- 1994 (IOM/FNB, 2000, Appendix F-l). Because the vitamin C serum levels for two-thirds of the study population were below the 25th percentile of the U.S. population, the relevance of the results of You et al. (2000) to the general U.S. population is unclear. In summary, the body of available prospective observational evidence does not support an association of vitamin C and reduced risk of stomach cancer for the U.S. population.

Over the last decade, a number of retrospective case-control studies reported finding statistically significant inverse associations between dietary vitamin C intake and stomach cancer risk (You et al., 1988; Buiatti et al., 1989; Boeing et al., 1991; LaVecchia et al., 1994; Kaaks et al., 1998; and Ekstrom et al., 2000). Shi et-al. (1991) reported an association between urinary vitamin C and stomach cancer risk.

In the 1991-1993 rulemaking on an antioxidant vitamin and cancer health claim, FDA considered scientific evidence of a possible antioxidant mechanism for vitamin C effects on reducing stomach cancer risk through blocking the formation of carcinogenic N-nitroso compounds from dietary nitrites in the stomach. Because there now are intervention trial data, not available in the 199 1- 1993 rulemaking, that directly show lack of a vitamin C effect on stomach cancer-related endpoints in human subjects, as well as

several new prospective cohort studies with actual stomach cancer endpoints in human subjects, the mechanistic studies are of limited usefulness at this time.

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin C and reduced risk of stomach cancer. Evidence from the well-designed, well-conducted large Linxian intervention trial shows no protective effect of a vitamin C-containing dietary supplement against stomach cancer risk (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; Dawsey et al., 1994). In fact, evidence from the gastric endoscopic examination portion of the General Population trial (Wang et al., 1994) shows an increased risk for gastric cancer and precancerous lesions associated with the vitamin C-containing dietary supplement. The results from the Linxian trial indicating a possible increased stomach cancer incidence among vitamin C supplemented subjects (Wang et al., 1994) do raise safety concerns about vitamin C-containing supplementation and show that more research is needed to ascertain conditions of safe use for supplemental vitamin C and whether such use is associated with benefit or risk for certain cancers. The absence of a demonstrated stomach cancer protective effect of vitamin C supplementation in this sensitive population (i.e., both high stomach cancer incidence and prevalent antioxidant vitamin deficiencies) is strong evidence that a relationship between vitamin C and reduced risk of stomach cancer does not exist.

An intervention tial with Columbian subjects diagnosed with precancerous gastric lesions (Correa et al., 2000) found no beneficial effect of vitamin C supplements on suppressing precancerous gastric lesion progression. All treated groups had an apparent rate of lesion regression greater than that in the placebo group, but the rate of regression compared to placebo was of the same magnitude in all treatment groups. Therefore, the relevance of the lesion regression results to cancer risk is highly questionable and needs to be validated.

The agency also considered whether available observational data could establish a relationship between vitamin C and reduced risk of stomach cancer. With the exception of one study (You et al., 2000) the evidence from prospective cohort studies does not support an association between reduced stomach cancer risk and dietary vitamin C intake (Zheng et al., 1995; Enstrom, et al. 1992; and Botterweck et al., 2000) or serum vitamin C (Stahelin et al., 1991; and Eichholzer et al., 1996). You et al. (2000) found a statistically significant association between baseline serum vitamin C level and subsequent progression of precancerous gastric lesions. The generalizability of the results in You et al. (2000) to the general U.S. population is problematic due to nutritional differences between the U.S. population and the poorly nourished, vitamin C deficient Chinese population in this study. Therefore, none of the prospective observational data was supportive of a relationship between vitamin C and reduced risk of stomach cancer. Six retrospective case-control studies (You et al., 1988; Buiatti et al., 1989; Boeing et al., 1991; LaVecchia et al., 1994; Kaaks et al., 1998; and Ekstrom et al., 2000) found an association between vitamin C and stomach cancer risk.

The absence of a protective effect of vitamin C supplementation in reducing stomach cancer risk in intervention trials conducted in high stomach cancer risk populations is strong evidence of no relationship between vitamin C intake and stomach cancer risk. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin C and reduced risk of stomach cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin C intake and reduced risk of stomach cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency considered the results from the most persuasive type of evidence available, i.e., well-designed, randomized, double-blinded, placebo-controlled clinical intervention trial results. The Linxian, China intervention trials (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994) did not find a stomach cancer protective effect of vitamin C-containing supplements in a sensitive population; this is strong evidence that there is not a relationship between vitamin C-containing dietary supplements and reduced stomach cancer risk. The unexpected finding in the Linxian General Population Trial of an increased prevalence of gastric dysplasia and cancer in subjects taking vitamin C and molybdenum raises safety concerns. This finding underscores the need for more research to ensure that any suggestion of benefit or increased risk from vitamin C supplementation is real, and that safe conditions of use of vitamin C supplementation can be ascertained. The Correa et al. (2000) gastric lesion regression and progression results are inconsistent and the relevance to stomach cancer risk is unclear. The results of the relevant prospective cohort studies were generally consistent with the intervention trials in finding no statistically significant association between vitamin C and stomach cancer risk (Zheng et al., 1995; and Enstrom et al., 1992). Results from the least persuasive observational studies, the retrospective case-control studies, were suggestive of an association,

Based on the totality of the scientific evidence, particularly results from the well-designed Linxian intervention trials, the agency concludes that the scientific evidence against a relationship between vitamin C and reduced risk of stomach cancer outweighs the scientific evidence for such a relationship.

b. Vitamin E

FDA's review of the available evidence identified several reports from an intervention trial conducted in Linxian, China on effects of dietary vitamin/mineral supplementation on esophageal and gastric dysplasia and cancer (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994). FDA also identified reports of post hoc analyses of stomach cancer data from the ATBC lung cancer prevention trial (ATBC Study Group, 1994; and Varis et al., 1998). FDA identified reports from four prospective cohort studies (Stahelin et al., 1991; Eichholzer et al., 1996; Zheng et al., 1995; and Botterweck et al., 2000), one prospective nested case-control study (Knekt et al., 1988 and 1991), and

four retrospective case-control studies (Charpiot et al., 1989; Buiatti et al., 1990; LaVecchia et al., 1994; and Ekstrom et al., 2000) that evaluated a possible relationship between vitamin E and stomach cancer risk.

The Dysplasia Trial stage of the Linxian, China cancer prevention trial (Li et al., 1993; and Dawsey et al., 1994) found no effects of 6-years of intervention with a daily vitamin E-containing multivitamin-mineral dietary supplement on reducing stomach cancer risk or mortality among individuals with pre-existing precancerous esophageal dysplasia. The General Population Trial was a randomized, placebo-controlled intervention trial with approximately 30,000 healthy adults in Linxian, China. The tial consisted of four intervention factors (i.e., nutrient combinations). One of the nutrient combinations consisted of beta-carotene, vitamin E and selenium. Following 5-years of supplementation, there were no effects of the vitamin E-containing dietary supplement on prevalence of stomach cancer or dysplasia among a random subset of the study population who participated in an end-of-study endoscopic survey (Wang et al., 1994). There was however, statistically significant lower stomach cancer mortality among the individuals receiving daily supplements containing beta-carotene, vitamin E, and selenium (RR = 0.79; 95% CI= 0.64 - 0.99) (Blot et al., 1993). Because the active intervention treatment in this case consisted of three nutrients, the results would not have been able to associate any potential protective effects specifically to vitamin E. The generalizability of the Linxian intervention trial finding of a lower stomach cancer mortality is unclear due to marked differences in stomach cancer risk and nutritional status between the vitamin-deficient Linxian population and the U.S. population. The Linxian General Population Trial results for vitamin E and stomach cancer risk are inconsistent and confusing. While there appeared to be a protective effect of the vitamin E-containing dietary supplement on reducing gastric cancer mortality (Blot et al., 1993), there was no corresponding effect on the prevalence of gastric cancer and precancer dysplasia diagnosed by endoscopic examination (Wang et al., 1994). In summary, the Linxian intervention results cause confusion about the role of vitamin E dietary supplements in modifying cancer risk and thus do not support a protective effect of vitamin E supplementation towards gastric cancer risk relevant to the U.S. population.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention intervention trial (ATBC Study Group, 1994) was designed to investigate the effects of beta-carotene and vitamin E dietary supplements on lung cancer risk among male Finnish smokers; data on cancers at other sites were also reported. This 1994 ATBC trial report states that there was a higher incidence of cancers of the stomach (8.3 versus 6.6 cases per 10,000 person-years) in the participants who received vitamin E supplements than in participants who received a placebo. Because the enrollment protocols were not designed to evaluate and control for risks associated with cancers other than lung, nor systematically screen for other cancers, the results with respect to stomach cancer risk in male smokers must be interpreted with caution. With this caution in mind, FDA notes that the observation of a higher cancer incidence at two sites other than the lung (i.e., bladder and stomach), despite observation of a lower cancer incidence at two sites (i.e., prostate and colorectal), suggests that there may be potential safety concerns. The results from the ATBC lung cancer prevention

trial raise concerns about the safety of vitamin E supplementation and the ability of observational studies to predict benefit. These results underscore the critical need for more clinical research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real, and that safe conditions of use for vitamin E supplementation can be ascertained.

A follow-up of the ATBC trial subjects by Varis et al. (1998) evaluated the progression of chronic atrophic gastritis, a precursor lesion leading to stomach cancer, in selected subjects of the ATBC trial cohort, At time of entry into the trial, 2,132 subjects were found to have a low serum pepsinogen I level, indicating atrophic gastritis. A gastrointestinal endoscopic examination was performed on 1,344 of these patients after a median supplementation time of 5.1 years. Neoplastic alterations were found in 4.7 percent of the subjects. The results of the end-of-trial endoscopic examinations showed no effect of vitamin E supplementation on the occurrence of neoplastic changes of the stomach in males with atrophic gastritis (Varis et al., 1998).

Most of the available prospective cohort studies have not found statistically significant associations of vitamin E with reduced stomach cancer risk. Neither of two cohort studies with dietary intake data (Zheng et al., 1995; and Botterweck et al., 2000) found any statistically significant association of stomach cancer risk and either vitamin E from dietary intake or from dietary supplement use. In two successive risk analyses of 12-year and 17-year follow-up data from a cohort of Swiss men, no statistically significant association of serum vitamin E levels and stomach cancer risk was found (Stahelin et al., 1991; and Eichholzer et al., 1996). Conversely, a nested case-control analysis of mortality data from a Finnish cohort, did find a statistically significant association of stomach cancer risk and low baseline serum vitamin E (Knekt et al., 1988, and 1991). Among the four available retrospective case-control studies two have found a statistically significant association of vitamin E and stomach cancer risk (Buiatti et al., 1990; and Charpiot et al., 1989), while two other studies found no association (LaVecchia et al., 1994; and Ekstrom et al., 2000).

i. Consideration of Significant Scientific Agreement

The agency considered whether the available scientific evidence could establish a relationship between vitamin E and reduced risk of stomach cancer. Data from the Linxian intervention trial and the followup of the ATBC trial subjects (Varis et al., 1998) indicated that vitamin E-containing supplements have no protective effect against stomach cancer (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; Dawsey et al., 1994; and Varis et al., 1998). Further, data from the ATBC trial (ATBC Study Group, 1994) suggest potential safety concerns related to vitamin E supplementation. There was no effect of vitamin E-containing dietary supplements on prevalence of gastric cancer or dysplasia in either stage of the Linxian intervention trials (Dawsey et al., 1994; and Wang et al., 1994), nor on gastric cancer mortality in the Dysplasia Trial (Li et al., 1993). Although Blot et al. (1993) reported a reduced stomach cancer mortality in the Linxian General Population Trial when a beta-carotene, vitamin E, selenium supplement

combination was used, this result is confusing in light of contradictory findings by Li et al. (1993) and is not generalizable to the general U.S. population because of the vitamin-deficient, high stomach cancer risk nature of the Linxian population. Further, any protective effect of the combination beta-carotene, vitamin E and selenium supplement cannot be attributable specifically to vitamin E. Four of the prospective cohort studies found no significant association between vitamin E and reduced stomach cancer risk (Botterweck et al., 2000; Stahelin, et al. 1991; Eichholzer et al., 1996; and Zheng et al., 1995), whereas a prospective nested case control study (Knekt et al., 1988 and 199 1) did find a vitamin E - stomach cancer association. Two retrospective case-control studies (La Vecchia et al., 1994; and Ekstrom et al., 2000) found no association between vitamin E and stomach cancer risk, whereas two others (Buiatti et al., 1990; and Charpiot et al., 1989) did find an association. There is no strong, relevant, consistent body of observational evidence from which to support a causal relationship between vitamin E and stomach cancer. Therefore, based on its review, FDA concludes that the totality of available scientific evidence does not support a relationship between vitamin E intake and a reduced risk of stomach cancer. Accordingly, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between supplemental vitamin E intake and reduced risk of stomach cancer.

ii. Weight of the Evidence

In weighing the evidence, the agency first considered the results of intervention trials. The Linxian, China intervention trials (Li et al., 1993; Blot et al., 1993; Wang et al., 1994; and Dawsey et al., 1994) found no protective effect of vitamin E-containing dietary supplements against development of precancerous stomach dysplasia or stomach cancer, but did report reduced stomach cancer mortality among vitamin E-containing dietary supplement recipients of the General Population Trial (Blot et al., 1993). The lower stomach cancer mortality associated with vitamin E-containing supplements reported in the Linxian General Population Trial (Blot et al., 1993) was not corroborated by mortality data in the Linxian Dysplasia Trial (Li et al., 1993) nor in the endoscopy results of either Linxian trial (Dawsey et al., 1994; and Wang et al., 1994). Furthermore, the finding of lower stomach cancer mortality associated with the vitamin E-containing supplement was given less weight in the current review because the generalizability of the vitamin supplementation effects in this under-nourished population to the U.S. population is questionable. The initial reported results from the ATBC intervention trial (ATBC Study Group, 1994) suggested vitamin E supplementation to be associated with increased stomach cancer risk. However, an adjunct study of atrophic gastritis progression in the ATBC cohort (Varis et al., 1998) provided no evidence of any effect of vitamin E for stomach cancer risk. The agency observed that four prospective studies found no significant association of vitamin E intake and stomach cancer risk (Botterweck et al., 2000; Stahelin et al., 1991; Eichholzer et al., 1996; and Zheng et al. 1995). A prospective nested case-control study (Knekt et al., 1988 and 1991) and three out of four retrospective case-control studies (Buiatti et al., 1990; Charpiot et al., 1989; and Gey et al., 1987) reported finding an inverse association of serum vitamin E with stomach

cancer risk. FDA explained earlier in section IV.B.2. the difficulties in interpreting the results of results of observational studies of vitamin E and cancer.

The effects of vitamin supplementation in a vitamin-deficient population are not generalizable to the U.S. population, and the mixed findings of the Linxian intervention trial confuses the issue of what role antioxidant vitamins may play in modifying cancer risk. Post-hoc ATBC trial results (ATBC Study Group, 1994; and Varis et al., 1998) with respect to effects of vitamin E supplementation on stomach cancer risk did not confirm the Linxian report of decreased risk for stomach cancer mortality (Blot et al., 1993). Furthermore, the ATBC studies were inconsistent among themselves, with the ATBC Study Group (1994) results suggesting vitamin E supplementation may increase stomach cancer incidence while Varis et al. (1998) could not find an effect of vitamin E supplementation on atrophic gastritis progression, an indicator of stomach cancer risk. Furthermore, as previously noted, the results from the ATBC lung cancer prevention trial raise concerns about the safety of vitamin E supplementation and the ability of observational studies to predict benefit. These results underscore the critical need for more clinical research to ensure that any suggestion of benefit or increased risk from vitamin E supplementation is real, and that safe conditions of use for vitamin E supplementation can be ascertained.

The results of available intervention trials are sufficiently inconsistent and contradictory so as to confuse the real role, if any, of antioxidant vitamin E supplements in modifying stomach cancer risk. Therefore, no disclaimer could render a claim regarding vitamin E and reduced risk of stomach cancer non-misleading. Further, FDA explained earlier in section IV.B.2. the difficulties in interpreting the results of observational studies of vitamin E and cancer, After reviewing the available data, the agency concludes that the quality and quantity of the available scientific evidence do not support the use of a qualified claim for a relationship between vitamin E and reduced stomach cancer risk. Therefore, the agency is not providing for the use of a qualified claim about the use of vitamin E and reduced risk of stomach cancer.

V. FDA's Consideration of Significant Scientific Agreement

As discussed in section IV.A., a major factor in FDA's 1993 decision not to authorize a health claim for antioxidant vitamins and cancer was that the scientific evidence was not sufficient to attribute a decreased risk of some cancers specifically to vitamin C or vitamin E, alone or in combination, or to other specific components of the diet. The evidence at that time only supported significant scientific agreement for a link between diets rich in fruits and vegetables, which are generally low in fat and high in vitamin A (as beta-carotene), vitamin C, and dietary fiber, with decreased risk of several types of cancer. See 21 C.F.R. 101.78. In the 1993 final rule, FDA concluded that there was significant scientific agreement that diets high in fruits and vegetables and low in fat are associated with reduced risk of cancer. 58 Fed. Reg. 2622. However, the agency found that the evidence was not sufficient to attribute the reduction in cancer risk specifically to

antioxidant vitamins (i.e., vitamin A (as beta-carotene)[14], vitamin C, or vitamin E, alone or in combination) or to other components of diets high in fruits and vegetables. *Id.* at 2634. Thus, the studies lacked specificity for the substance that was the subject of the claim in relationship to cancer. In evaluating whether there is significant scientific agreement among experts to support a claim about a relationship between antioxidant vitamins and reduced risk of certain kinds of cancer, FDA focused on studies that could address whether there is specificity for vitamin C or vitamin E, alone or in combination, in relation to certain kinds of cancer, or individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, and stomach).

FDA finds that the more recent data for some of the vitamin-cancer relationships that the agency evaluated, which included well-designed intervention trials, do not demonstrate a causal relationship between vitamin C or E, alone or in combination, and a reduced risk of certain cancers. Therefore, the available evidence that is the most capable of demonstrating a relationship between diet and disease risk does not support a relationship between vitamin C or vitamin E intakes and reduced risk of certain cancers. Further, FDA finds that the more recent data for the other vitamin-cancer relationships that the agency evaluated, which consisted of primarily of observational data, do not alter the previous 1993 determination that the scientific evidence is not sufficiently conclusive or specific for vitamin C or vitamin E, alone or in combination, to justify the use of a health claim relating the intake of such vitamins to a reduced risk of certain cancers. Much of the observational data does not support a relationship between vitamin C or vitamin E and reduced cancer risk. The data from the observational studies that suggest an association between vitamin C or vitamin E and reduced cancer risk cannot isolate these vitamins from other substances in the diet and in the dietary supplements consumed by the study subjects, and thus cannot demonstrate that vitamin C *per* se, vitamin E *per se*, or these vitamins in combination reduce the cancer risk. Moreover, as previously discussed in section IV., assessment of subjects' intake of vitamins C and E (whether from dietary measures or from serum or plasma measures) in an observational study design is subject to significant limitations.

FDA's conclusion from its review of the available scientific data is consistent with the recent conclusions of the IOM/NAS (April 2000 DRI report).

In sum, the totality of the publicly available scientific evidence does not demonstrate a causal relationship between the specific substance (vitamin C or vitamin E, alone or in combination) and reduction of the risk of the specific disease or health-related condition (certain kinds of cancer or of individual cancers, i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, or stomach) in the general population. Therefore, based on the agency's review of the

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[14] As explained in section IV.B., FDA has considered only vitamins C and E to be antioxidant vitamins in this evaluation.

totality of the publicly available scientific evidence, including the studies newly discussed in this letter and those evaluated in the 1993 rulemaking, FDA concludes that there is not significant scientific agreement among qualified experts that the available evidence supports a relationship between intake of vitamin C or vitamin E, alone or in combination, and certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, or stomach).

VI. FDA's Consideration of a Qualified Claim

The agency stated in the October 6 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 21 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 standard and the requirement that the claim be made in accordance with an authorizing regulation. The first condition does not apply to this decision because the agency is complying with an instruction by the court to reconsider the claim, as discussed earlier. 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.

Based on its review of the totality of the scientific evidence as discussed in detail above, FDA concludes that the scientific evidence against a claim relating vitamin C or vitamin E, alone or in combination (i.e., antioxidant vitamins) and reduced risk of certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, or stomach) outweighs the scientific evidence for a claim about such a relationship. For example, some antioxidant vitamin and cancer relationships have intervention trial data that provide strong and compelling evidence against the relationship. In addition, for some antioxidant vitamin and cancer relationships, the quality and quantity of the available scientific evidence are insufficient to support a qualified claim. In some relationships, there are some observational data that suggest an association between an antioxidant vitamin and reduced risk off cancer, However, in none of these latter cases is 'the evidence considered sufficient, on balance, to support a qualified claim. Therefore, a claim for a relationship between vitamin C and vitamin E dietary supplements (alone or in combination) and a reduced risk of certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, or stomach) cannot be qualified in such a way as not to mislead consumers.

Because FDA does not intend to exercise enforcement discretion with respect to the use of a qualified claim on vitamin C or vitamin E dietary supplements, it was not necessary for FDA to evaluate the safety of vitamin C or vitamin E with respect to the use of a health claim, including a qualified claim. The agency has noted in section II. of this letter that there are potential safety concerns with the use of vitamin C and 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 concluded that there is no significant scientific agreement for a relationship between antioxidant vitamins (i.e., vitamin C or vitamin E, alone or in combination) and certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, stomach) and that the scientific evidence against a relationship outweighs the scientific evidence for a relationship. Therefore, FDA finds that health claims relating antioxidant vitamins (i.e., vitamin C or vitamin E, alone or in combination) and reduced risk of certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, stomach) 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 C or vitamin E, alone or in combination, and reduced risk of certain kinds of cancer or of individual cancers (i.e., cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, or stomach) will be subject to regulatory action as a misbranded food under 21 U.S.C. 343(a)(l) and (r)(l)(B); as a misbranded drug under 21 U.S.C. 352(a) and (f)(l); and as an unapproved new drug under 21 U.S.C. 355(a).

Sincerely yours,

Virginia L. Dillaway

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

Enclosure: References

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Tab 1	Citations and references for letter dated May 4, 2001, from Christine J. Lewis, FDA, to Jonathan W. Emord, Emord and Associates, P.C.
Tab 2	Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999).
Tab 3	***Federal Register,*** March 28, 1991, Vol. 60, No. 56, pp. 12932-12933; "Food Labeling; Health Claims and Label Statements; Submission of Scientific Data for Ten Topic Areas. "
Tab 4	***Federal Register,*** November 27, 1991, Vol. 56, No. 229, pp. 60624-6065 1; "Food Labeling: Health Claims and Label Statements; Antioxidant Vitamins and Cancer. "
Tab 5	***Federal Register,*** January 6, 1993, Vol. 58, No. 3, pp. 2622-2660; "Food Labeling: Health Claims and Label Statements: Antioxidant Vitamins and Cancer. "
Tab 6	***Federal Register,*** October 14, 1993, Vol. 58, No. 197, pp. 53296-53305; "Food Labeling; Health Claims for Dietary Supplements. "
Tab 7	***Federal Register,*** January 4, 1994, Vol. 59, No. 2, pp. 436-437; "Food Labeling; Health Claims for Dietary Supplements. "
Tab 8	***Federal Register,*** September 8, 1999, Vol. 64, No. 173, pp. 48841-48842; "Food Labeling; Health Claims and Label Statements; Request for Scientific Data and Information. "
Tab 9	***Federal Register,*** December 22, 1999, Vol. 64, No. 245, pg. 71794; "Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements; Availability. "
Tab 10	***Federal Register,*** January 26, 2000, Vol. 65, No. 17, pp. 4252-4253; "Food Labeling; Health Claims and Label Statements; Request for Scientific Data and Information; Reopening of Comment Period. "
Tab 11	***Federal Register,*** October 6, 2000, Vol. 65, No. 195, pp. 59855-59857; "Food Labeling Health Claims and Label Statements for Dietary Supplements; Update to Strategy for Implementation of Pearson Court Decision. "

Tab 12 U. S . Dept. of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, "Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements, " 1999.

Tab 13 Memorandum to file, "Replication of Research Findings," prepared by L.A. Larsen, FDA, April 30, 2001.

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