DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

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RE: Health Claim Petition – 1) Lycopene and the following: Cancer, Prostate Cancer, Lung Cancer, Gastric Cancer, Colorectal Cancer, Breast Cancer, Cervical Cancer, Endometrial Cancer, and Pancreatic Cancer; 2) Tomatoes and the following: Cancer, Prostate Cancer, Lung Cancer, Gastric Cancer, Colorectal Cancer, Breast Cancer, Cervical Cancer, Endometrial Cancer, and Pancreatic Cancer; and 3) Lycopene-Containing Tomato-Based Foods and the following: Cancer, Prostate Cancer, Lung Cancer, Gastric Cancer, Colorectal Cancer, Breast Cancer, Cervical Cancer, Endometrial Cancer, and Pancreatic Cancer (Docket No 2004Q-0201)

Dear Mr. Emord:

This letter responds to the health claim petition received on January 1, 2004, by the Food and Drug Administration (FDA or the agency), submitted on behalf of American Longevity, Inc. pursuant to Sections 403(r)(4) and 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4) and 343(r)(5)(D)). The petition requested that the agency authorize health claims or, alternatively if FDA found that there was not significant scientific agreement, allow qualified health claims characterizing the relationship between consumption of lycopene, tomatoes, and lycopene-containing tomato-based foods, and reduction in risk of cancer, prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer. This petition proposed the following model health claims:

1) "Lycopene may reduce your risk of certain forms of cancer."
2) "Lycopene may reduce your risk of prostate cancer."
3) "Lycopene may reduce your risk of lung cancer."
4) "Lycopene may reduce your risk of gastric cancer."
5) "Lycopene may reduce your risk of colorectal cancer."
6) "Lycopene may reduce your risk of breast cancer."
7) "Lycopene may reduce your risk of cervical cancer."

8) "Lycopene may reduce your risk of endometrial cancer."
9) "Lycopene may reduce your risk of ovarian cancer."
10) "Lycopene may reduce your risk of pancreatic cancer."
11) "Tomatoes may reduce your risk of certain forms of cancer."
12) "Tomatoes may reduce your risk of prostate cancer."
13) "Tomatoes may reduce your risk of lung cancer."
14) "Tomatoes may reduce your risk of gastric cancer."
15) "Tomatoes may reduce your risk of colorectal cancer."
16) "Tomatoes may reduce your risk of breast cancer."
17) "Tomatoes may reduce your risk of cervical cancer."
18) "Tomatoes may reduce your risk of endometrial cancer."
19) "Tomatoes may reduce your risk of ovarian cancer."
20) "Tomatoes may reduce your risk of pancreatic cancer."
21) "Lycopene-containing tomato-based foods may reduce your risk of certain forms of cancer."
22) "Lycopene-containing tomato-based foods may reduce your risk of prostate cancer."
23) "Lycopene-containing tomato-based foods may reduce your risk of lung cancer."
24) "Lycopene-containing tomato-based foods may reduce your risk of gastric cancer."
25) "Lycopene-containing tomato-based foods may reduce your risk of colorectal cancer."
26) "Lycopene-containing tomato-based foods may reduce your risk of breast cancer."
27) "Lycopene-containing tomato-based foods may reduce your risk of cervical cancer."
28) "Lycopene-containing tomato-based foods may reduce your risk of endometrial cancer."
29) "Lycopene-containing tomato-based foods may reduce your risk of ovarian cancer."
30) "Lycopene-containing tomato-based foods may reduce your risk of pancreatic cancer."

FDA evaluated the scientific evidence provided with the petition and other evidence related to your proposed claims. Based on a preliminary review, FDA determined that the scientific evidence supporting the proposed health claims does not meet the "significant scientific agreement" standard under § 403(r)(3)(B)(i) of the Act for conventional food or 21 CFR 101.14(c), which is applicable to dietary supplements. FDA notified you of this decision and you submitted a letter dated April 27, 2004, stating that your client American Longevity, Inc., chose to seek FDA review of the petition as a qualified health claim petition. Thus, FDA filed the petition on May 12, 2004 as a qualified health claim petition and posted it on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedures on qualified health claims.[1]

The agency received a total of five comments pertaining to this docket, which included petitions submitted on behalf of American Longevity, Inc. and the Lycopene Health Claim Coalition . The petition submitted by the Lycopene Health Claim Coalition requested qualified health claims to characterize the relationship between tomatoes and tomato products, which contain lycopene; tomato lycopene; lycopene in tomatoes and tomato products; and lycopene in fruits and

[1] Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements, (Attachment E) July 10, 2003. (http://www.cfsan.fda.gov/~dms/nuttf-e.html).

vegetables, including tomatoes and tomato products and reduced risk of prostate cancer. Three of the comments were from individuals and two were from industry. The three comments from individuals supported the proposed claims but did not provide any data to support their conclusions and were not directed to any specific petition. One of the comments from industry was directed specifically to your petition and the other was submitted on behalf of the Lycopene Health Claim Coalition. The comment directed to your petition did not support many of the proposed claims and provided substantial data to support its conclusions. FDA considered the relevant comments in its evaluation of your petition.

This letter sets forth the basis of FDA's determination that the current scientific evidence for the proposed qualified health claims related to consumption of tomatoes and/or tomato sauce, and a reduced risk of prostate, gastric, ovarian, and pancreatic cancers is appropriate for consideration as a qualified health claim on conventional foods. This letter also sets out the basis for FDA's determination that there is no credible evidence to support qualified health claims for the following: consumption of tomato-based foods, other than tomato sauce, and a reduced risk of prostate, and ovarian cancers; consumption of all tomato-based foods and a reduced risk of gastric and pancreatic cancer; consumption of tomatoes and a reduced risk of ovarian cancer; or consumption of tomatoes or tomato-based foods and a reduced risk of lung, colorectal, breast, cervical, and endometrial cancers. This letter also sets forth the basis for FDA's determination that there is no credible evidence supporting a relationship between consumption of lycopene, either as a food ingredient, a component of food, or as dietary supplement, and reduced risk of any of the cancers specified in the petition. Finally, this letter sets forth the factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims with respect to consumption of tomatoes and/or tomato sauce, and a reduced risk of prostate, gastric, ovarian, and pancreatic cancers.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[2] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[3] FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[4]

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[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir 2004) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S.Ct. 310 (2004).

[3] See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [http://www.cfsan.fda.gov/~dms/hclmgui4.html]

[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[5] In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[6] review articles,[7] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements, such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, National Academies of Science, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker et al., 1991, Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

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[5] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999). [http://www.cfsan.fda.gov/~dms/ssaguide.html]

[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[7] Review articles summarize the findings of individual studies.

[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects -- e.g., age, smoker vs. non-smoker -- was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[9] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated[10], and the overall consistency[11] of the total body of evidence.[12] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

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[9] See *supra*, note 3.

[10] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

[11] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also Systems to rate the scientific evidence, Agency for Healthcare Research and Quality http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents, defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

[12] See *supra*, note 3.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of a food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified lycopene, tomatoes, and lycopene-containing tomato-based foods as the substances of the petition. Tomatoes and tomato-based foods are foods within the definition of food under the Act (21 U.S.C. § 321(f)(1)). Lycopene is an ingredient of foods such as red tomatoes, red tomato-based foods, red or pink grapefruit, watermelon, red sweet peppers, papaya and pink guava. Lycopene is also a member of the carotenoid family that is marketed as a dietary supplement. Therefore, lycopene is a both a food ingredient and a component of food and thus meets the definition of food under the Act (21 U.S.C. § 321(f)(3)). Therefore, the agency concludes that tomatoes, tomato-based foods, and lycopene meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified cancer, prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer as the diseases that are the subject of the proposed qualified health claim. Cancer is a constellation of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells (American Cancer Society, 2004). Cancer is categorized into different types based on the specific organ site.

Cancers at different organ sites have different risk factors, treatment modalities, and mortality risk (American Cancer Society, 2004). Both genetic and environmental risk factors may affect the risk of different types of cancers. Risk factors may include a family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, exposure to ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors. The etiology, risk factors, diagnosis, and treatment for each type of cancer are unique.[13] Since each form of cancer is a unique disease based on organ site, risk factors, treatment options, and mortality risk, each form of cancer must be individually evaluated in a health claim petition. As a result, the agency considered whether the studies supported the potential substance - disease relationship for the specific cancers requested by the petitioner, each of which constitutes a disease under 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify the claim has been demonstrated by the

[13] http://www.nci.nih.gov/cancertopics/commoncancers

proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)). For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(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 (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))).

As discussed in section I.A., the three substances at issue in this petition are (1) tomatoes, (2) tomato-based foods, and (3) lycopene, both as a food ingredient in some tomato-based foods and as a dietary supplement.

1. Tomatoes and tomato-based foods

For purposes of the health claim regulation, tomatoes and tomato-based foods are not ingredients that are the source of the substance; rather tomatoes and tomato-based foods are the substance. Tomatoes are also a primary ingredient in many tomato-based foods. Tomato-based foods can thus be a source of tomatoes. Tomatoes are foods of natural biological origin that have been widely consumed in the United States for their nutrient properties prior to January 1, 1958, without known detrimental effects, which are subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists. Tomatoes themselves and tomatoes as a food ingredient in tomato-based foods are consistent with FDA's definition of food ingredients ordinarily regarded as "generally recognized as safe" (GRAS) (21 CFR 170.30(d)).

The limited scientific evidence describing the effects of tomatoes and tomato-based foods on prostate cancer, suggests that consumption of one-half to one cup of tomatoes and/or tomato sauce per week may reduce the risk of prostate cancer (discussed in section IV C). The limited scientific evidence describing the effects of tomatoes and tomato-based foods on ovarian cancer, suggests that consumption of tomato sauce twice a week may reduce the risk of ovarian cancer (discussed in section IV C). The agency could not determine an amount of tomatoes that may reduce the risk of gastric and pancreatic cancers since the scientific evidence did not yield enough information to suggest a recommended daily dietary intake level for tomatoes and these

cancers. Therefore, FDA concludes under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), that the use of tomatoes and/or tomato sauce[14] at the level necessary to justify the claims is safe and lawful.

2. Lycopene

The petition asserts that lycopene, whether consumed in food or in the form of a dietary supplement, contributes nutritive value and is safe and lawful in that there is no evidence that it has a cumulative effect in the diet that affects its safety, there are no known harmful interactions with nutritional supplements, the PDR for Nutritional Supplements indicates no significant adverse reactions except for hypersensitive individuals, and that lycopene has been shown to be safe at intake levels up to 30 mg/day. Lycopene and other carotenoids serve as a key source of antioxidants. Antioxidants are substances that can prevent or delay the oxidation of other substances and may protect against chronic disease (Institute of Medicine, 2000 p 35-57). The petition also asserts that lycopene is GRAS through experience based on common use in food. According to the petition, lycopene has been a naturally occurring ingredient in foods consumed in the United States prior to January 1, 1958, and there is no evidence that when consumed in foods there is a cumulative effect in the diet that is unsafe. The petition further states there are no known interactions with drugs in clinical practice and there are no known harmful interactions with other dietary supplements.

There are no specific intake quantities for lycopene proposed in the petition. Instead, the petition cites various articles in the scientific literature stating that, to be effective, lycopene supplementation must be at daily doses of at least 15 mg. No Dietary Reference Intakes (DRIs) have been established for the carotenoid lycopene. However, the Institute of Medicine supports existing recommendations for increased consumption of carotenoid-rich fruits and vegetables (Institute of Medicine, 2000 p. 325).

FDA has received two GRAS notifications concerning lycopene, one submitted by LycoRed for tomato lycopene extract 6 percent, tomato lycopene extract 1.5 percent, and crystallized tomato lycopene extract, (GRAS notification number 000156), and the other submitted by BASF corporation for synthetic lycopene (GRAS notification number 000119). In the "Agency Response Letter" to the GRAS notifications for the above listed subjects, the agency stated it had no questions at this time regarding the conclusions that tomato lycopene extract 6 percent, tomato lycopene extract 1.5 percent, and crystallized tomato lycopene extract or synthetic lycopene are GRAS under their intended conditions of use. FDA further stated that the agency had not made its own determination regarding the GRAS status of the use of tomato lycopene extract 6 percent, tomato lycopene extract 1.5 percent, and crystallized tomato lycopene extract or synthetic lycopene and, as always, it is the continuing responsibility of manufacturers to ensure that the food ingredients they market are safe, and are otherwise in compliance with all applicable legal and regulatory requirements (Agency Response Letters to GRAS notifications # 000156 and 000119; (http://www.cfsan.fda.gov/~rdb/opa-g156.html and

[14] Since there was no other tomato-based foods identified that purported to show an effect, the substance "tomato-based foods" is in effect limited, in this case, to tomato sauce.

http://www.cfsan.fda.gov/~rdb/opa-g119.html). Additionally, FDA has received a GRAS notification for lycopene from *Blakeslea trispora* the review of which is still pending (GRAS notification number 000173). FDA has also recently amended its color additive regulations to provide for the safe use of tomato lycopene extract and tomato lycopene concentrate as color additives in foods (70 FR 43043; July 26, 2005). The action was in response to a petition filed by LycoRed Natural Products Industries.

It is not necessary for FDA to make any determination about the safety or lawfulness of lycopene either as a food ingredient, a component of food, or as a dietary supplement in this letter because the agency is denying the proposed claims for lycopene and lycopene-containing tomato-based foods for lack of credible evidence, as discussed in section II.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified the following markers to use in identifying risk reduction for purposes of a health claim evaluation involving cancer: incident cases of the particular cancer being studied, and recurrent colon/rectal polyps for colon/rectal cancer. Colon/rectal polyp recurrence has been used as a surrogate marker for colon/rectal cancer and has been used by the National Cancer Institute as a surrogate marker for colon cancer prevention (Schatzkin et al., 1994). To evaluate the potential effects of lycopene/tomato/lycopene-containing tomato-based food consumption on cancer risk, FDA considered these markers as indicators or predictors of disease.

The petition cited 480 publications as evidence to substantiate the relationship for the claims. These publications consisted of 86 review articles; 10 abstracts; three meta-analyses; 31 *in vitro* studies; 55 animal studies; 152 articles that did not measure lycopene, tomatoes or lycopene-containing tomato-based foods and/or a type of cancer, the substances and disease that are subject of the proposed claims, (i.e., studies on lycopene bioavailability, transport, relationship to other diseases, other substance (e.g.,β-carotene)[15]; six federal reports/databases; and 137 studies on cancer and lycopene/tomato/lycopene-containing tomato-based foods (see docket # 2004Q-0201 for bibliography), of which 8 were intervention studies and 129 were observational studies. Many of the observational studies purported to evaluate both tomatoes and lycopene levels and are therefore discussed in multiple sections of the letter.

In addition to the studies in your petition, the agency considered one additional intervention study for prostate cancer and lycopene (Ansari et al., 2003) and an additional 17 observational studies found through a PubMed literature search that evaluated the substance/disease relationships: 1) tomatoes or lycopene and prostate cancer (Villeneuve et al., 1999; Deneo-Pellegrini et al., 1999; Bosetti et al., 2000; Ganmaa et al., 2002; Jian et al., 2005) ; 2) tomatoes or lycopene and lung cancer (Yuan et al., 2001; Wright et al.,2003; Darby et al., 2001; Voorrips et al., 2000a); 3) lycopene and breast cancer (La Vecchia et al., 2002); 4) tomatoes and colorectal cancer (Le Marchand et al., 1997; La Vecchia et al., 1997; Seow et al., 2002); 5) tomatoes or

[15] While both lycopene and β-carotene are classified as carotenoids, they are structurally different from each other and exhibit different physiological effects.

lycopene and gastric cancer (Graham et al., 1990; Gao et al., 1999; Terry et al., 2000) ; and 6) lycopene and endometrial cancer (Goodman et al., 1997).

A. Assessment of Review Articles, Meta-Analyses and Abstracts

Although useful for background information, the review articles, meta-analysis, and abstracts do not contain sufficient information on the individual studies that they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analysis, and abstracts supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of Animal and *In Vitro* Studies

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal or *in vitro* studies submitted with the petition as providing any supportive information about the substance - disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of any type of cancer, nor can the studies mimic the human body's response to the consumption of lycopene, tomatoes, or lycopene-containing tomato-based foods. Therefore, FDA cannot draw any scientific conclusions from the animal or *in vitro* studies regarding lycopene, tomatoes, or lycopene-containing tomato-based foods and the reduction of risk of any type of cancer.

C. Assessment of Intervention Studies

Prostate Cancer

Seven intervention studies were submitted by the petitioner and one intervention study (Ansari et al., 2003) was identified by the agency to evaluate the relationship between tomatoes, lycopene-containing tomato- based foods , and/or lycopene and prostate cancer (Chen et al., 2001; Bowen et al., 2002; Van Breemen et al., 2002; Clinton et al., 1996; Kucuk et al., 2001; Kucuk et al., 2002 (republication of Kucuk et al., 2001); Matlaga et al., 2001). However, all eight of these studies used tomatoes or tomato-based foods and/or lycopene as a treatment for men diagnosed with prostate cancer. Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[16] These claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. As a

[16] See *supra*, note 2.

result, FDA considers evidence from studies in individuals already diagnosed with prostate cancer only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Given that such evidence was not available, the agency cannot draw any scientific conclusions from these seven studies.

Lung Cancer
There were no intervention studies on the effect between the intake of lycopene, tomatoes, or lycopene-containing tomato-based foods and risk of lung cancer.

Breast Cancer
One intervention study examined the effect of increased fruit and vegetable consumption on risk of breast cancer (Rock et al., 1997). This study included many types of fruits and vegetables, but it was not specified whether tomatoes or lycopene-containing tomato-based foods were included in the intervention and the study did not measure the amount of lycopene in the fruits and vegetables. Therefore, no scientific conclusions could be drawn from the study about the relationship between tomatoes, lycopene-containing tomato-based foods, or lycopene and breast cancer.

Colorectal Cancer
There were no intervention studies that evaluated the effect of tomatoes, lycopene-containing tomato-based foods, or lycopene intake and risk of colorectal cancer.

Gastric Cancer
There were no intervention studies that evaluated the effect of tomatoes, lycopene-containing tomato-based foods, or lycopene intake and risk of gastric cancer.

Ovarian Cancer
There were no intervention studies that evaluated the effect of tomatoes, lycopene-containing tomato-based foods, or lycopene intake and risk of ovarian cancer.

Endometrial Cancer
There were no intervention studies that evaluated the effect of tomatoes, lycopene-containing tomato-based foods, or lycopene intake and risk of endometrial cancer.

Cervical Cancer
There were no intervention studies that evaluated the effect of tomatoes, lycopene-containing tomato-based foods, or lycopene intake and risk of cervical cancer.

Pancreatic Cancer
There were no intervention studies that evaluated the effect of tomatoes, lycopene-containing tomato-based foods, or lycopene intake and risk of pancreatic cancer.

D. Assessment of Observational Studies

Lycopene and Cancer

A total of 81 observational studies evaluated the relationship between lycopene and a specific form of cancer. The 81 studies were categorized into three groups: 1) Studies that evaluated lycopene from dietary sources and assessed the risk of cancer based on dietary lycopene intake; 2) Prospective observational and cross-sectional studies that used a single measure of serum lycopene concentration for determining the relationship between serum lycopene and risk of cancer; and 3) Studies that evaluated serum lycopene levels in subjects diagnosed with cancer.

Forty-four observational studies calculated lycopene intake from estimated dietary intake.[17] The proposed claims regarding lycopene are for a relationship between lycopene as a dietary supplement, or lycopene as an ingredient or component of food, i.e., lycopene containing tomato-based foods. In observational studies that calculate nutrient intake from conventional food, measures of lycopene intake are based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed are estimated. Estimated lycopene concentration values are then added to the data using typical lycopene concentration values for the food product category based on the USDA National Nutrient Database for Standard Reference, SR 16. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied. Furthermore, the lycopene content of foods can vary significantly (e.g., due to food variety, ripening stage of the food, food processing/cooking procedures, or storage (duration, temperature)) (Giovannucci et al., 1999; Gartner et al., 1997; Boileau et al., 2002; Shi et al., 2000). Thus, it is difficult to ascertain an accurate amount of the nutrient consumed based on reports of dietary intake of foods.

In addition, lycopene-containing foods contain not only lycopene, but also other nutrients that may be associated with the metabolism of lycopene or the pathogenesis of certain cancers. Because lycopene-containing foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). For studies based on recorded dietary intake of such foods, it is not possible to accurately determine whether any observed effects of lycopene on cancer risk were due to: 1) lycopene alone; 2) interactions between lycopene and other nutrients; 3) other nutrients acting alone or together; or, 4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of lycopene-rich foods.

In fact, evidence demonstrates that in a number of instances, epidemiological studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient

[17] See Appendix 1.

with respect to a disease but it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually *increases* risk of the disease (Lichtenstein and Russell, 2005). For example, previous epidemiological studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996).[18] These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful.[19]

Evidence is also now available that epidemiological studies based on the recorded dietary intake of conventional foods may suggest a benefit for a particular nutrient in that food with respect to a disease but it is subsequently demonstrated in an intervention study that the nutrient itself, when isolated from other nutrients in the food, does not confer a benefit ("Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acid," Institute of Medicine of the National Academies, 2002). For example, previous epidemiological studies (38 out of 48) reported an association between dietary fiber and reduced risk of colon cancer (Lanza 1990 and Kromhout et al, 1982). Despite these and other positive findings, three

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[18] B-carotene and lycopene are both members of the carotenoid family ("Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids," A Report of the Panel on Dietary Antioxidants and Related Compounds, Food and Nutrition Board of the Institute of Medicine, 2000).

[19] With regard to dietary supplements, in *Pearson v. Shalala*, the D.C. Circuit noted that FDA had "logically determined" that the consumption of a dietary supplement containing antioxidants could not be scientifically proven to reduce the risk of cancer where the existing research had examined only foods containing antioxidants as the effect of those foods on reducing the risk of cancer may have resulted from other substances in those foods. 164 F.3d 650, 658 (D.C. Cir 1999). The D.C. Circuit, however, concluded that FDA's concern with granting antioxidant vitamins a qualified health claim could be accommodated by simply adding a prominent disclaimer noting that the evidence for such a claim was inconclusive given that the studies supporting the claim were based on foods containing other substances that might actually be responsible for reducing the risk of cancer. *Id.* The court noted that FDA did not assert that the dietary supplements at issue would "threaten consumer's health and safety." *Id.* at 656. There is, however, a more fundamental problem with allowing qualified health claims for nutrients in dietary supplements based solely on studies of foods containing those nutrients than the problem the D.C. Circuit held could be cured with a disclaimer. As noted above, even if the effect of the specific component of the food constituting the dietary supplement could be determined with certainty, recent scientific studies have shown that nutrients in food do not necessarily have the same beneficial effect when taken in the form of a dietary supplement. See Lichtenstein and Russell (2005). Indeed, not only have studies on single nutrient supplements established that the benefits associated with the dietary intake of certain nutrients do not materialize when the nutrients are taken as a supplement, but some of these studies have actually indicated an *increased* risk for the very disease the nutrients were predicted to prevent. *Id.* Thus, an observational study based on food provides no information from which scientific conclusions may be drawn for the single nutrient supplement.

recent clinical intervention trials found *no* association between dietary fiber and reduced risk of colon cancer (Alberts et al., 2000; Bonithon-Kopp et al., 2000; Schatzkin et al., 2000).

Furthermore, the observational studies that calculated lycopene intake from estimated dietary intake did not specify whether the tomato and tomato-based food intake reported derived from red tomatoes. There are three varieties of tomatoes (red, green, and yellow) and only red tomatoes contain lycopene (USDA Nutrient Database, http://www.nal.usda.gov/fnic/foodcomp/). Thus, it is not possible to know whether the tomatoes in the studies actually contained lycopene. Nor, for the reasons discussed above, would it be possible to know whether, even if the tomatoes contained lycopene, that the lycopene had any relation to the reported effects.

For the above reasons, FDA concludes that scientific conclusions cannot be drawn from observational studies on foods for the proposed claims for lycopene as a food ingredient, a component of food, or as a dietary supplement.[20]

Twenty three observational studies evaluated the relationship between serum lycopene levels and cancers.[21] Numerous studies have shown that dietary lycopene intake and serum lycopene levels are poorly correlated; correlation coefficient range r= 0.11-0.45 (Campbell et al., 1994; Michaud et al., 1998; Casso et al., 2000; Neuhouser et al., 2001)[22]. In addition, many factors can affect the serum lycopene levels including age, basal metabolic index (BMI), smoking, serum cholesterol levels, and season of the year (Casso et al., 2000; Mayne et al., 1999; Neuhouser et al., 2001). Since serum lycopene levels and dietary levels are poorly correlated and many factors (e.g., BMI, serum cholesterol, smoking, time of year) can alter the serum lycopene measures at a given point in time, scientific conclusions cannot be drawn from these 23 studies about the relationship between lycopene intake and risk reduction of any type of cancer.

Fifteen studies evaluated the relationship between serum lycopene levels in subjects with cancer compared to controls.[23] In addition to the problem that serum lycopene levels are poorly correlated with dietary intake (see above), these studies used subjects diagnosed with different forms of cancer. Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[24] These claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. As a

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[20] Therefore, observational studies in foods do not provide any credible evidence for a claim for risk reduction for a single food component because, in fact, the single food component form may decrease, have no effect, or actually *increase* risk of the disease or health related condition. Additionally, such studies do not provide credible evidence for the single food component as discussed above. For the reasons set forth in Section V, we have concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances because observational studies in food do not provide credible evidence for the proposed claims for lycopene, tomatoes and tomato-based foods and there is no other credible evidence to support these claims.

[21] See *supra*, note 17.

[22] Correlation coefficients range from -1(negative correlation) through +1 (positive correlation). The closer to 1 the coefficient the stronger the correlation; the closer to zero the weaker the correlation.

[23] See *supra*, note 17.

[24] See *supra*, note 2.

result, FDA considers evidence from studies in individuals already diagnosed with a particular form of cancer only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Given that such evidence was not available, the agency cannot draw any scientific conclusions from these studies.

Tomatoes and tomato-based foods

Prostate Cancer

There were 19 observational studies on tomato and/or tomato-based food consumption and risk of prostate cancer, consisting of three prospective cohort studies[25], one sub-cohort study,[26] 13 case-control studies[27], and two ecological studies.[28] Three studies were a republication of studies already being used in evaluating the proposed claim.[29] One study compared insulin-like growth factors (IGF) and tomato intake.[30] IGF is not a surrogate endpoint for prostate cancer. Therefore, the agency could not draw any scientific conclusions from this study. Finally, two case-control studies provided no information as to whether the food frequency questionnaires in the studies, which were used for the collection of tomato consumption data from study subjects, had been appropriately validated.[31] Validation of the food frequency questionnaire method is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[32] As a result, these studies provided no information on the accuracy of how tomato intake was measured, and hence, no scientific conclusions could be drawn from them.[33]

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[25] In a cohort study, a group of healthy people or cohort is identified and followed up for a certain time period to ascertain the occurrence of disease and or health related events. (Epidemiology Beyond the Basics, page 24, Aspen Publishers, 2000).

[26] A sub-cohort study uses subjects from a defined cohort study. Cases are subjects diagnosed with the disease (i.e. cancer) in the cohort and controls are subjects selected randomly from a sample of the entire cohort at baseline. (Epidemiology Beyond the Basics, Aspen Publishers, 2000.)

[27] In a case-control study, a group of cases are identified as the individuals in whom the disease of interest was diagnosed during a given year and controls are selected from individuals who do not have the disease in the same time period (Epidemiology Beyond the Basics, page 29 Aspen Publishers, 2000).

[28] An ecological study examines a possible association between aggregate measure of exposure and disease or mortality (Epidemiology Beyond the Basics, page 17, Aspen Publishing 2000).

[29] See Appendix 2.

[30] See *supra*, note 29.

[31] See *supra*, note 29.

[32] "Validation of the food frequency questionnaire method is essential, as incorrect information may lead to false associations between dietary factors and disease or disease-related markers." Cade, J., Thompson, R., Burley, V., and Warm D. Development, Validation and Utilization of Food-Frequency Questionnaires-A Review. *Public Health Nutrition*, 5: page 573, 2002. See, also, Subar, A., et al., Comparative validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires, *American Journal of Epidemiology*, 154: 1089-1099, 2001.

[33] "Food frequency questionnaires require validation prior to or as a part of dietary research. The approach taken in most studies is to examine the concordance of food frequency responses with reference instruments such as multiple

Thus, there were 13 observational studies evaluating the relationship between tomatoes or tomato-based foods and prostate cancer. Two large cohort studies conducted in the United States evaluated tomato/tomato sauce intake and prostate cancer risk (Giovannucci et al., 2002; Mills et al., 1989). Both studies received a high methodological quality rating. Giovannucci et al. (2002) used the Health Professionals Follow-Up Study cohort that contained 47,365 males followed for approximately 12 years. In this cohort 2,481 prostate cancer cases were identified during follow-up. Tomato sauce intake was evaluated using three different food frequency questionnaires given at the beginning of the study and at four-year intervals. Consuming one, or greater than one, serving of tomato sauce per week was associated with significant decreased risk of prostate cancer; relative risk 0.80 (95% Confidence Interval (CI) of 0.70-0.91) and 0.77 (95% CI of 0.66-0.90)[34], respectively. Mills et al. (1989) followed a cohort of 14,000 Seventh Day Adventist males for six years, 180 prostate cancer cases were identified during the follow-up. Consuming tomatoes one to four times per week, or greater than five times per week was associated with a significant decrease in prostate cancer incidence; relative risk 0.62 (95% CI of 0.40-0.96) and 0.57 (95% CI of 0.35-0.93), respectively.

One sub-cohort study evaluated tomatoes and prostate cancer risk in 642 prostate cancer cases and 1,668 random healthy subjects from a cohort in the Netherlands (Schuurman et al., 1998). This study was of high methodological quality. Tomato intake (per 25 grams tomatoes) was not associated with prostate cancer, with a relative risk of 1.05 (95% CI of 0.90-1.22). Tomato juice intake (per 25 grams) was not associated with prostate cancer incidence; relative risk of 1.12 (95% CI of 0.96-1.29).

Eight case-control studies evaluated tomatoes and prostate cancer risk and all of the studies received high to moderate methodological quality ratings. Jain et al. (1999) reported that consuming greater than 109 grams of tomatoes per day was associated with a reduced risk of prostate cancer; odds ratio of 0.64 (95% CI of 0.45-0.91). This case-control study was conducted in Canada with 617 prostate cancer cases and 636 controls. Bosetti et al. (2000) conducted a case-control study that included 320 prostate cancer cases and 246 controls in Greece. Decreased intake of cooked tomatoes was associated with an increased risk of prostate cancer; odds ratio of 1.91 (95% CI of 1.20-3.04). However, there was no association between raw tomato intake and prostate cancer risk. Jian et al. (2005) conducted a case-control study in 130 prostate cancer cases and 274 controls from China. Tomato intake was associated with a reduced risk of prostate cancer; odds ratio of 0.16 (95% CI of 0.07-0.38).

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24 hour recalls or diet records using measurement error models to estimate the correlations between nutrient intakes measured by food frequency questionnaires and truth." Subar, A., et al., Comparative validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires, *American Journal of Epidemiology*, 154: 1089-1099, 2001.

[34] Relative risk is expressed as the ratio of the risk (incidence) in exposed individuals to that in unexposed individuals (Epidemiology Beyond the Basics, page 93, Aspen Publishers, 2000).
It is calculated in prospective studies by measuring exposure (e.g. lycopene intake) in subjects with and without disease (e.g. specific type of cancer). An adjusted relative risk controls for potential confounders. Confidence intervals provide a statistical analysis (p value) of relative risk. 95% Confidence intervals that include 1.0 are not statistically significant. "CI" stands for a Confidence interval.

Five of the eight case-control studies found no association between tomato consumption and prostate cancer risk (Villeneuve et al., 1999; Key et al., 1997; Hayes et al., 1999; Kolonel et al., 2000; LeMarchand et al., 1991). One case-control study conducted in Canada included 1,623 prostate cancer cases and controls and found no association between prostate cancer and tomatoes or tomato juice consumption; odds ratio of 1.0 (95% CI of 0.7-1.3) (Villeneuve et al., 1999). Another case-control study conducted in England included 328 prostate cancer cases and controls and found no association between prostate cancer and raw or cooked tomato intake; odds ratio of 1.06 (95% CI of 0.55-1.62) and 0.92 (0.59-1.42), respectively (Key et al., 1997). Hayes et al. (1999) conducted a case-control study in the United States with 932 prostate cancer cases and 1,201 controls. Tomato juice and raw/cooked tomatoes had no association with prostate cancer risk. Kolonel et al. (2000) conducted a case-control study using 1,619 prostate cancer cases and 1,618 controls from a multi-ethnic population from the United States and Canada. There was no association between raw tomato consumption or cooked tomato consumption and prostate cancer risk. Le Marchand et al. (1991) conducted a case-control study in Hawaii with 452 prostate cancer cases and 899 controls. Tomato consumption had no association with prostate cancer risk.

Two ecological studies of moderate methodological quality evaluated tomato consumption and prostate cancer risk (Grant., 1999; Ganmaa et al., 2002). Grant (1999) compared prostate cancer mortality data from 41 countries to the tomato supply for each country. Of the 28 countries that reported consumption of more than five kilocalories per day from tomatoes, there was a strong protective correlation between tomato intake and prostate cancer mortality. Ganmaa et al. (2002) evaluated prostate cancer incidence rates and tomato consumption (based on country intake) for 44 countries. There was no correlation between tomato consumption and prostate cancer.

Lung Cancer

FDA identified a total of 18 observational studies on tomato and/or tomato based-food intake and risk of lung cancer, consisting of four prospective cohort studies, two nested case-control studies[35], one sub-cohort study and 11 case-control studies. One study used patients diagnosed with cancer.[36] Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.[37] These claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. As a result, FDA considers evidence from studies in individuals already diagnosed with lung cancer only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in

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[35] A nested-case control study uses subjects from a defined cohort. Cases are subjects diagnosed with the disease (i.e. cancer) in the cohort and controls are subjects selected from individuals at risk each time a case (i.e. cancer) is diagnosed. (Epidemiology Beyond the Basics, Aspen Publishers, 2000.)

[36] See *supra*, note 29.

[37] See *supra*, note 2.

the same way in both diseased people and healthy people. Given that such evidence was not available, the agency cannot draw any scientific conclusions from this study.

Two studies used subjects who were not relevant to the general U.S. population (i.e., tin miners from China).[38] The studies themselves detail how these subjects are not relevant to a general population because of the unique environmental exposures (i.e., arsenic and severe pollution) that increase the incidence of lung cancer (Forman et al., 1992). Therefore, conclusions could not be drawn from these studies about the relationship between lycopene/tomatoes and lung cancer in the general U.S. population.

Seven case-control studies included a greater proportion of smokers in the cases compared to the controls and the results were not stratified by smoking status. Smoking is a causal factor of lung cancer (Montesano and Hall, 2001) and smoking can lead to many dietary changes including decreased weight and appetite (Jo et al., 2002) which may affect food intake and bias the results of these studies. Thus, it was not possible to determine whether differences in the consumption of lycopene, tomato, and/or tomato-based food, independently contributed to the results in the lung cancer cases.[39] Therefore, scientific conclusions could not be drawn from these studies about the relationship between tomatoes, tomato-based foods, or lycopene consumption and lung cancer.

Five studies provided no information as to whether the food frequency questionnaires in the studies, which were used for the collection of tomato consumption data from study subjects, had been appropriately validated.[40] Validation of the food frequency questionnaire method is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[41] As a result, these studies provided no information on the accuracy of how tomato intake was measured; and, hence, no scientific conclusions could be drawn from them.[42]

Thus, 3 observational studies evaluated the relationship between tomato consumption and lung cancer. One cohort study evaluated tomato intake and lung cancer risk and received a moderate methodological quality rating (Speizer et al., 1999). This study followed a cohort of 89,284 nurses for approximately 16 years and identified 593 cases of lung cancer. Eating one or more servings of tomatoes per day had no effect on lung cancer incidence.

One nested case-control study (Voorrips et al., 2000) and one sub-cohort study (Steinmetz et al., 1993) also evaluated tomato consumption and lung cancer risk. Both studies were of moderate methodological quality. Steinmetz et al. (1993) used a sub-cohort of 2,814 female controls and

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[38] See *supra*, note 29.
[39] See *supra*, note 29.
[40] See *supra*, note 29.
[41] See *supra*, note 32.
[42] See *supra*, note 33.

138 cases from Iowa to evaluate tomato intake and lung cancer risk. Tomato intake had no association with lung cancer risk. Voorrips et al. (2000) was a nested-case control study that included a sub-cohort study with 2,953 controls and 1,010 lung cancer cases from the Netherlands. This study observed no association between raw tomato consumption (25 grams per day) and lung cancer risk.

Breast Cancer

There were four case-control studies on tomato intake and risk of breast cancer (Graham et al., 1991; Levi et al., 1993; Ewertz and Gill, 1990; Ronco et al., 1999). Graham et al. (1991) did not measure the association between tomato consumption and breast cancer.[43] Without such a measurement, it is not possible to determine whether an association between tomato consumption and breast cancer was statistically significant. As a result, this study provided no information about how tomatoes may reduce the risk of breast cancer; hence, no scientific conclusions could be drawn from it. Levi et al. (1993) provided no information as to whether the food frequency questionnaires in this study, which were used for the collection of tomato consumption data from study subjects, had been appropriately validated. Validation of the food frequency questionnaire method is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[44] As a result, this study provided no information on the accuracy of how tomato intake was measured, and hence no scientific conclusions could be drawn from it.[45]

Thus, there were 2 case-control studies evaluating the relationship between tomato consumption and breast cancer and of high and moderate methodological quality, respectively (Ronco et al., 1999; Ewertz and Gill., 1990). Ewertz and Gill (1990) evaluated tomato intake and breast cancer risk in 1,486 breast cancer cases and 1,336 controls from Denmark. Tomato consumption had no association with breast cancer risk; odds ratio of 1.04 (95% CI of 0.79-1.34). Ronco et al. (1999) conducted a case-control study in Uruguay with 400 breast cancer cases and 405 controls. Tomato consumption had no association with breast cancer risk; odds ratio of 0.62 (95% CI of 0.36-1.06).

Colorectal Cancer

There were eight case-control observational studies on tomato or tomato-based food intake and risk of colorectal cancer. One study was a republication of study already being used in evaluating the proposed claim.[46] Five studies provided no information as to whether the food frequency questionnaires in the studies, which were used for the collection of tomato consumption data from study subjects, had been appropriately validated.[47] Validation of the food frequency questionnaire method is essential in order to be able to draw conclusions from

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[43] Measures of association between exposure and disease are based on either an absolute difference between groups being compared or on relative differences or ratios (e.g. relative risk). (Epidemiology Beyond the Basics, Aspen Publishers, 2000.)

[44] See *supra*, note 32.

[45] See *supra*, note 33.

[46] See *supra*, note 29.

[47] See *supra*, note 29.

the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[48] As a result, these studies provided no information on the accuracy of how tomato intake was measured, and hence no scientific conclusions could be drawn from them about the relationship between tomatoes/tomato-based-based foods and colorectal cancer.[49]

There were two studies evaluating the relationship between tomato consumption or tomato-based foods and colon/rectal cancer (Le Marchand et al., 1997; Franceschi et al., 1997). Le Marchand et al. (1997) was of high methodological quality and included 1,192 colorectal cancer cases and controls from the United States to evaluate tomato intake and colorectal cancer risk. Increased consumption of tomato-based foods had no association with colorectal cancer in male or females; odds ratio 0.8 (95% CI 0.5-1.2) or 0.9 (95% CI 0.5-1.4), respectively. Franceschi et al. (1997) was a case-control study of moderate methodological quality that included 1,225 colon cases and 4,154 controls in evaluating the relationship between pizza consumption and colon cancer. There was no significant relationship between pizza consumption and colon cancer; odds ratio 0.8 (95% CI 0.7-1.0).

Gastric Cancer

There were a total of 14 case-control observational studies on tomato, tomato-based foods, and risk of gastric cancer. One study was a republication of a study already being used in evaluating the proposed claim.[50] One study combined many forms of cancer (gastric, colon/rectal, and other intestinal cancers) into one single analysis.[51] As discussed in Section I, each form of cancer is a unique disease based on organ site, risk factors, treatment options, and mortality risk. As a result, it is not possible to draw any scientific conclusions regarding individual cancer risks from a study that combine multiple forms of cancer into a single analysis. Therefore, scientific conclusions could not be drawn from these studies about the relationship between the consumption of tomatoes or tomato-based foods and gastric cancer.

One study did not do statistical analysis of the data.[52] Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming tomatoes and those not consuming tomatoes, to determine whether there is a reduction in cancer risk. Thus

when statistics are not performed on the specific substance disease relationship we are unable to determine if there is a difference between the two groups. As a result, this study provided no information about how tomatoes may reduce the risk of gastric cancer; hence, no scientific conclusions could be drawn from it.

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[48] See *supra*, note 32.
[49] See *supra*, note 33.
[50] See *supra*, note 29.
[51] See *supra*, note 29.
[52] See *supra*, note 29.

Four studies provided no information as to whether the food frequency questionnaires in the studies, which were used for the collection of tomato consumption data from study subjects, had been appropriately validated.[53] Validation of the food frequency questionnaire method is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.[54] As a result, these studies provided no information on the accuracy of how tomato intake was measured, and hence no scientific conclusions could be drawn from them.[55]

Thus, 7 case-control studies of moderate methodological quality were identified as evaluating the relationship between tomatoes or tomato-based foods and gastric cancer. Graham et al. (1990) conducted a study in 293 gastric cancer cases and controls from upstate New York. Tomato intake was associated with a reduced risk of gastric cancer in males, but not in females. Correa et al. (1985) conducted a case-control study in Louisiana with 391 gastric cancer cases and controls. The consumption of tomatoes was associated with a decreased risk of gastric cancer in blacks but not in whites. Hansson et al. (1993) conducted a case-control study in Sweden with 456 gastric cancer cases and 669 controls. Tomato intake during adolescence (15-18 years of age) was protective against gastric cancer, but intake during adulthood had no association.

Gonzalez et al. (1991) carried out a case-control study in Spain with 354 gastric cancer cases and controls. Tomato intake had no association with gastric cancer risk. A case-control study from Sweden found that four to 12 servings of tomatoes per week had no effect on gastric cancer incidence in 258 cancer cases and 815 controls (Terry et al., 2000). A case-control study from Belgium using 449 gastric cancer cases and 3,524 controls found no association between tomato intake and risk of gastric cancer (Tuyns et al., 1992). Ramon et al. (1993) found that tomato intake had no effect on gastric cancer risk reduction in 117 cases and 234 controls from Spain.

Ovarian Cancer

One case-control study evaluated the relationship between tomato and tomato-based food intake and ovarian cancer and received a high quality methodological rating (Cramer et al., 2001). This study included 549 ovarian cancer cases and 516 controls from the United States and found no association between tomato and tomato juice intake and ovarian cancer risk; odds ratio of 0.88 (95% CI of 0.50-1.54) and 0.65 (95% of CI 0.34-1.22), respectively. However, eating tomato sauce two of more times per week was associated with a significant reduction in ovarian cancer risk; odds ratio of 0.60 (95% CI of 0.37-0.99).

Endometrial Cancer

There were no studies that evaluated the relationship between tomato or tomato-based food intake and endometrial cancer risk.

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[53] See *supra*, note 29.
[54] See *supra*, note 32.
[55] See *supra*, note 33.

Cervical Cancer
There were two case-control studies examining tomato intake and cervical cancer risk (Marshall et al., 1983; DeVet et al., 1991). DeVet et al. (1991) evaluated the relationship between tomato intake and incidence of cervical dyplasia. Cervical dysplasia is not a recognized surrogate endpoint for cervical cancer (see section II, paragraph 1); therefore, no scientific conclusions could be drawn from this study about tomato intake and the risk of cervical cancer. Marshall et al. (1983) analyzed the mean differences of tomato consumption between controls and cervical cancer cases. This mean difference was not significantly different between the two groups. There were no studies evaluating the relationship between tomato-based food intake and cervical cancer.

Pancreatic Cancer
There were three observational studies on tomato and/or tomato based-food intake and risk of pancreatic cancer risk, consisting of one cohort study and two case-control studies. Baghurst et al. (1991) did not calculate the odds ratio for pancreatic cancer incidence and tomato intake. Without an odds ratio, it is not possible to determine if tomato intake reduced the risk of colon/rectal cancer. As a result, this study provided no information about the relationship between tomato consumption and risk of pancreatic cancer; hence, no scientific conclusions could be drawn from it.

Thus, there were 2 studies evaluating the relationship between tomato intake and pancreatic cancer. One cohort study (Mills et al., 1988) and one case-control study (Bueno De Mesquita et al., 1991) evaluated the relationship between tomato intake and pancreatic cancer risk and studies received moderate methodological quality ratings. Mills et al. (1988) followed a cohort of 34,000 Seventh Day Adventists from California for seven years, which included 162 pancreatic cancer deaths. Tomato consumption had no association with pancreatic cancer death. A case-control study from the Netherlands included 164 pancreatic cancer cases and 480 controls (Bueno De Mesquita et al., 1991). Raw tomato intake had no association with pancreatic cancer risk when all of the subjects completed a food frequency questionnaire. However, when a subset of the subjects (n=421), not including proxy respondents, were interviewed by a dietitian using the same food frequency questionnaire, raw tomato intake was significantly associated with a decreased risk of pancreatic cancer.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body

of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated[56], and the overall consistency[57] of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

Lycopene and Cancers

As discussed in Section II of this letter, no studies provided information about whether lycopene intake may reduce the risk of any of the specific forms of cancer. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between lycopene consumption, either as a food ingredient, a component of food, or as a dietary supplement, and any of these cancers.

Tomatoes and tomato-based foods

Prostate Cancer
As discussed in Section II of this letter, there were 13 observational studies that evaluated the relationship between the consumption of tomatoes or tomato-based foods, and prostate cancer: two cohort studies, one sub-cohort study, eight case-control studies, and two ecological studies. Both cohort studies reported a significant reduction in prostate cancer risk with increased consumption of tomato sauce or tomatoes, respectively (Giovannucci et al., 2002; Mills et al., 1989). Furthermore, prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.[58] The cohort studies were conducted in the United States, received high methodological quality ratings, and contained a large number of subjects (greater than 14,000 per study). Two case-control studies (Jain et al., 1999; Bosetti et al., 2000) and one ecological study (Grant, 1999) also reported a protective association between tomatoes and prostate cancer risk. However, five case-control studies (Villeneuve et al., 1999; Key et al., 1997; Hayes et al., 1999; Kolonel et al., 2000; and LeMarchand et al., 1991), one sub-cohort study (Schuurman et al., 1998) and one ecological study (Ganmaa et al., 2002) found no association between tomato intake and prostate cancer risk. Several of these case-control studies were conducted in the United States, received high methodological quality ratings, and each study contained greater than 1,000 subjects.

Based on the above, FDA finds that there is very limited credible evidence for a qualified health claim. FDA concludes that there is a very low level of comfort that a relationship exists between tomatoes and/or tomato sauce and prostate cancer.[59]

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[56] See *supra*, note 10.
[57] See *supra*, note 11.
[58] See *supra*, note 3.
[59] See *supra*, note 3.

Lung Cancer
As discussed in Section II of this letter, the evidence for a relationship between tomato or tomato-based foods intake and a reduced risk of lung cancer is from one cohort study (Speizer et al., 1999), one sub-cohort study (Steinmetz et al., 1993), and one nested case-control study (Voorrips et al., 2000). None of these 3 studies supported a relationship between tomato or tomato-based food intake and lung cancer risk reduction. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between tomato or tomato-based food consumption and lung cancer.

Breast Cancer
As discussed in Section II, the evidence for a relationship between tomato intake and reduced risk of breast cancer is based on two case control studies. Neither of the studies found a relationship between tomato or tomato-based food intake and breast cancer risk (Ewertz and Gill, 1990; Ronco et al., 1999). Based on the above, FDA concludes that there is no credible evidence supporting a relationship between tomato or tomato-based food consumption and breast cancer.

Colorectal Cancer
As discussed in Section II, the evidence for a relationship between tomato or tomato-based food consumption and reduced risk of colorectal cancer is based on two case-control studies from the United States and Italy. Neither case-control study found a relationship between tomato or pizza consumption and colorectal cancer risk reduction (Le Marchand et al., 1997; Franceschi et al., 1997). Based on the above, FDA concludes that there is no credible evidence supporting a relationship between tomato or tomato-based food consumption and colorectal cancer.

Gastric Cancer
As discussed in Section II, the evidence for a relationship between tomato consumption and reduced risk of gastric cancer is based on seven case-control studies from various developed countries, including the United States. All seven studies received moderate methodological quality ratings. Four of the studies found no association between tomato intake and gastric cancer risk (Terry et al., 2000; Tuyns et al., 1992; Ramon et al., 1993; Gonzalez et al., 1991). Three studies reported some type of protective association between tomato intake and lung cancer risk. Graham et al. (1990) observed that tomato consumption was associated with a reduced risk of gastric cancer in males, but not females; Hansson et al. (1993) reported a protective association with gastric cancer and tomatoes if the tomatoes were consumed during adolescence, but not during adult life; and Correa et al. (1985) reported that tomato intake was protective for blacks, but not Caucasians. The three studies are all retrospectively designed (case-control). Prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.[60] Moreover, consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence;[61] these studies did not provide consistent findings among different groups of subjects in the studies. Based on FDA's review of the strength of the total body of publicly available scientific evidence for a claim about tomatoes or tomato-based food, and reduced risk

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[60] See *supra*, note 3.
[61] See *supra*, note 11.

of gastric cancer, FDA finds that there is very limited credible evidence for a qualified health claim about tomatoes and gastric cancer and no credible evidence for a qualified health claim about tomato-based foods and gastric cancer since none of the studies evaluated tomato-based foods. FDA ranks the evidence for tomatoes and gastric cancer as the lowest level for a qualified health claim.[62] For the reasons given above, FDA concludes that it is unlikely that tomatoes reduce the risk of gastric cancer.

Ovarian Cancer
As discussed in Section II, the evidence for a relationship between tomato consumption and reduced risk of ovarian cancer is based on one case-control study from the United States. The study received a high methodological rating. Cramer et al. (2001) found no association between tomatoes or tomato juice intake and ovarian cancer risk; however, tomato sauce consumption was associated with a reduced risk of ovarian cancer. The findings by Cramer et al. (2001) have not been replicated and replicating scientific findings is important to substantiate results.[63] Furthermore, this study is retrospectively designed (case-control). Prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.[64] Therefore, FDA finds that there is very limited credible evidence for a qualified health claim about tomato sauce and reduced risk of ovarian cancer and no credible evidence for a qualified health claim about tomatoes and ovarian cancer. Based on FDA's review of the strength of the total body of publicly available scientific evidence for a claim about tomatoes or tomato-based food and reduced risk of ovarian cancer, FDA ranks this evidence as the lowest level for a qualified health claim about tomato sauce and ovarian cancer.[65] For the reasons given above, FDA concludes that it is highly uncertain whether tomato sauce reduces the risk of ovarian cancer.

Endometrial Cancer
As discussed in Section II, there were no studies that evaluated the relationship of tomatoes or tomato-based foods and endometrial cancer risk. Based on the above, FDA concludes that there is no credible evidence supporting a relationship between tomato or tomato-based food consumption and endometrial cancer.

Cervical Cancer
As discussed in Section II, there was one observational study that showed that the consumption of tomatoes was not significantly different between control and cervical cancer cases (Marshall et al., 1983) and no studies showing a relationship between tomatoes or tomato-based foods and risk of cervical cancer. Therefore, FDA concludes that there is no credible evidence to support a relationship between the consumption of tomatoes or tomato-based foods and cervical cancer risk.

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[62] See *supra*, note 3.
[63] See *supra*, note 10.
[64] See *supra*, note 3.
[65] See *supra*, note 3.

Pancreatic Cancer
As discussed in Section II, the evidence for a relationship between tomatoes or tomato-based food intake and reduced risk of pancreatic cancer is based on one cohort and one case-control study. The cohort study was conducted in the United States and showed no association between tomato intake and pancreatic cancer risk (Mills et al., 1988). The case-control study by Bueno De Mesquita et al. (1991) found no association between tomato intake and pancreatic cancer when the subject's entire intake was evaluated by a food frequency questionnaire in the Netherlands. However, when a subset of the subjects were directly interviewed (not including proxy interviews), a significant protective association was reported for tomato consumption. The findings by De Mesquita et al. (1991) have not been replicated and replicating scientific findings is important to substantiate results.[66] Furthermore, this study is retrospectively designed (case-control). Prospectively designed studies provide stronger evidence for an association than case-control studies since there are fewer forms of bias.[67] Therefore, FDA finds that there is very limited credible evidence for a qualified health claim about tomatoes and reduced risk of pancreatic cancer and no credible evidence for a qualified health claim about tomato-based foods and pancreatic cancer since none of the studies evaluated tomato-based foods. Based on FDA's review of the strength of the total body of publicly available scientific evidence for a claim about tomatoes or tomato-based foods and reduced risk of pancreatic cancer, FDA ranks this evidence as the lowest level for a qualified health claim about tomatoes and pancreatic cancer.[68] For the reasons given above, FDA concludes that it is highly unlikely that the consumption of tomatoes reduces the risk of pancreatic cancer.

IV. Other Enforcement Discretion Factors

For the purposes of this section of the letter, the term "tomato" includes raw, cooked, dried, or canned tomatoes. FDA has not established a standard of identity for tomato sauce; however, the agency's policy on tomato sauce is that it should consist of a spiced tomato product concentrated to contain not less than 8.37 percent salt-free tomato solids, and that it can be made by adding spices to tomato puree (CPG 7109.21). For the purposes of this letter the term "tomato sauce" means a spiced or not spiced tomato product that contains at least 8.37% of salt-free tomato solids.

Factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims about tomatoes and/or tomato sauce and prostate, gastric, ovarian, and pancreatic cancers used on the label or in the labeling of tomatoes and/or tomato sauce are discussed below.

A. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4). Disqualifying total fat levels for

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[66] See *supra*, note 10.
[67] See *supra*, note 3.
[68] See *supra*, note 3.

individual foods are above 13.0 g per reference amount customarily consumed (RACC), per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying saturated fat levels for individual foods are above 4.0 g per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying cholesterol levels for individual foods are above 60 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying sodium levels for individual foods are above 480 mg per RACC, per label serving size, and, for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g.

Tomatoes and most tomato sauces would not exceed the disqualifying levels for total fat, saturated fat, and cholesterol as specified in 21 CFR 101.14(a)(4). However, some tomatoes or tomato sauces may be disqualified based on their sodium level. FDA intends to consider the exercise of its enforcement discretion for qualified health claims about consumption of tomatoes and/or tomato sauce and reduced risk of prostate, gastric, ovarian, and pancreatic cancers on the label or in the labeling of tomatoes and/or tomato sauce when the food does not exceed any disqualifying nutrient levels (i.e., total fat, saturated fat, cholesterol and sodium) as specified in 21 CFR 101.14(a)(4).

B. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value (DV) for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC (21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods with minimal nutritional value.

FDA notes that most tomatoes and tomato sauces will contain at least 10 percent of vitamin A, vitamin C, or both. Therefore, FDA intends to consider the exercise of its enforcement discretion for qualified health claims about tomatoes and/or tomato sauce and prostate, gastric, ovarian, and pancreatic cancers, used on the label or in the labeling of tomatoes and/or tomato sauce when the food complies with the 10 percent minimum nutrient contribution requirement as specified in 21 CFR 101.14(e)(6).

C. Minimum Effective Amount of Tomatoes Eligible for the Claim

The general requirements for health claims require that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in the appropriate form to justify the claim. Where no definition of high has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)). However, the agency finds that this provision cannot be applied to the qualified health claims about consumption of tomatoes and a reduced risk of gastric and pancreatic cancer because the scientific evidence for these relationships is so uncertain and does not yield enough information to suggest a recommended daily dietary intake level that might result in reduction in risk of gastric and pancreatic cancers. The agency also

finds that this provision cannot be applied to qualified health claims about consumption of tomato sauce and reduced risk of ovarian cancer. While it was not possible to determine a daily dietary intake amount necessary to achieve the claimed effect, the evidence in the petition suggests a frequency of tomato sauce consumption per week.

After considering the available scientific evidence, the agency determined that the minimum effective amount of tomatoes and/or tomato sauce that may result in a reduced risk of prostate cancer is one-half to one cup per week. The frequency of tomato sauce consumption that may result in a reduced risk of ovarian cancer is twice a week. The agency, however, intends to consider the exercise of its enforcement discretion for qualified claims described in Section VI because the claims cannot not specify a daily dietary intake necessary to achieve the claimed the effect consistent with 21 CFR 101.14(d)(2)(vii) because not such daily dietary intake has been established.

V. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims for which we found no credible evidence, i.e., for tomatoes or tomato-based foods and lung, colorectal, breast, cervical, and endometrial cancers; for tomato-based foods, other than tomato sauce, and prostate, and gastric cancers; for all tomato-based foods and gastric and pancreatic cancer; for tomatoes and ovarian cancer; and for lycopene, as a food ingredient, a component of food, or as a dietary supplement, and any of the cancers specified in the petition. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances, where there is no credible evidence to support the claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."); *Pearson v. Shalala*, 164 F.3d 650, 659 (D.C. Cir. 1999) (the court stated that, where the weight of the evidence was against the claim, FDA could rationally conclude that the disclaimer "The FDA has determined that no evidence supports this claim" would not cure the misleadingness of a claim). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th

Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

VI. Conclusions

Based on FDA's consideration of the scientific evidence submitted with your petition, and other pertinent scientific evidence, FDA concludes that there is no credible evidence to support qualified health claims for tomatoes or tomato-based foods and a reduced risk for lung, colorectal, breast, cervical, and endometrial cancers. Thus, FDA is denying these claims. FDA also concludes that there is no credible evidence to support qualified health claims for tomato-based foods, other than tomato sauce, and prostate, and gastric cancers, for tomato-based foods and pancreatic cancer, or for tomatoes and ovarian cancer. Therefore, FDA is also denying these claims. FDA further concludes that there is no credible evidence to support qualified health claims for lycopene, as a food ingredient, component of food, or as a dietary supplement, and reduced risk of any of the cancers specified in the petition. Thus, FDA is denying these claims. However, FDA concludes that there is very limited credible evidence for qualified health claims for tomatoes and/or tomato sauce and prostate, gastric, ovarian, and pancreatic cancers provided that the qualified claims are appropriately worded so as to not mislead consumers. Thus, FDA intends to consider exercising its enforcement discretion for the following qualified health claims:

> Prostate Cancer
> "Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer. FDA concludes that there is little scientific evidence supporting this claim."
>
> Gastric Cancer
> "Four studies did not show that tomato intake reduces the risk of gastric cancer, but three studies suggest that tomato intake may reduce this risk. Based on these studies, FDA concludes that it is unlikely that tomatoes reduce the risk of gastric cancer."
>
> Ovarian Cancer
> "One study suggests that consumption of tomato sauce two times per week may reduce the risk of ovarian cancer; while this same study shows that consumption of tomatoes or tomato juice had no effect on ovarian cancer risk. FDA concludes that it is highly uncertain that tomato sauce reduces the risk of ovarian cancer."

Pancreatic Cancer
"One study suggests that consuming tomatoes does not reduce the risk of pancreatic cancer, but one weaker, more limited study suggests that consuming tomatoes may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that tomatoes reduce the risk of pancreatic cancer."

FDA intends to consider exercising its enforcement discretion for the above qualified health claims when all factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will support a qualified health claim for those claims that were denied, that will no longer support the use of the above qualified health claim, or that may raise safety concerns about the substance that is the subject of the claim.

Sincerely,

Barbara O. Schneeman, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Appendix 1
Lycopene Studies

See petition (docket #2004Q-0201) for complete reference citation

Observational Studies that estimate lycopene intake from dietary sources

Prostate Cancer
Giovannucci et al., 2002
Key et al., 1997
Hayes et al., 1999
Norrish et al., 2000
Cohen et al., 1999
Schuurman et al., 2002
Meyer et al., 1997
Deneo-Pellegrini et al., 1999
Jian et al., 2005

Lung Cancer
Holick et al., 2002
Michaurd et al., 2000
Rohan et al., 2002
Voorrips et al., 2000
Candelora et al., 1996
Le Marchand et al., 1993
De Stefani et al., 1999
Garcia-Closas et al., 1998
Wright et al., 2003
Ziegler et al., 1996
Kneckt et al., 1991

Breast Cancer
Jarvinen et al., 1997
Zhang et al., 1999
Terry et al., 2002
Freudenheim et al., 1996
Levi et al., 2001
Ronco et al., 1999
La Vecchia et al., 2002

Colorectal Cancer
Malila et al., 2002
Slattery et al., 2000

Levi et al., 2000
Le Marchand et al., 1997
La Vecchia et al., 1997
Enger et al., 1996

Gastric Cancer
De Stefani et al., 2000
Garcia-Closas et al., 1999
Botterweck et al., 2000

Ovarian Cancer
Cramer et al., 2001
La Vechhia et al., 2002

Endometrial Cancer
Jain et al., 2000
Goodman et al., 1997
McCann et al., 2000

Cervical Cancer
VanEenwyk et al., 1991
Kanetsky et al, 1998
Sedjo et al., 2002

Serum lycopene levels measured as a biomarker of lycopene intake
Prostate Cancer
Gann et al., 1999
Huang et al., 2003
Hsing et al., 1990
Nomura et al., 1997

Lung Cancer
Yuan et al., 2001
Ito et al., 2003
Comstock et al., 1997

Breast Cancer
Dorgan et al., 1998
Sato et al., 2002
Hulton et al, 2001
Tonilo et al., 2001

Gastric/Oral Cancer
Nagao et al., 2000
Nomura et al., 1997

Ovarian Cancer
Helzlsouer et al., 1996

Cervical cancer
Batieha et al., 1993
Giuliano et al., 1997
Schiff et al., 2001
Nagata et al., 1999
Goodman et al., 1998
Palan et al., 1996

Pancreatic Cancer
Burney et al., 1989

Serum lycopene levels measured as biomarker of lycopene intake
Gastric cancer
Tsubono et al., 1999
Tsugane et al., 1992

Serum lycopene levels measured in subjects diagnosed with cancer
Prostate Cancer
Lu et al., 2001
Vogt et al., 2002
Rao et al, 1999
Cinton et al., 1996

Breast Cancer
Zhang et al., 1997
Ito et al., 1999
Potischman et al., 1992
Potischman et al., 1990
London et al., 1992
Ching et al., 2001
Simon et al., 2000

Cervical Cancer
Potischman et al., 1994
Peng et al., 1998
Potischman et al., 1991
Palan et al., 1996

Appendix 2
Tomatoes and Tomato-based Foods Studies

See petition (docket #2004Q-0201) for complete reference citation

Prostate Cancer
Republication
Giovannucci et al., 1995
Norrish et al., 2000
Tzonou et al, 1999

Used non validated endpoints of cancer
Mucci et al., 2001

No Information on Validation of Food Frequency Questionnaire
Norrish et al., 2000
Cohen et al., 1999

Lung Cancer

Not Relevant to the US population
Forman et al., 1992
Swanson et al., 1992

Studies had disproportionate amount of smokers in cases versus the controls or smoking status not detailed
Axelsson et al., 1996
Agudo et al, 1997
Le Marchand et al., 1989
Darby et al., 2001
Harris et al., 1991
De Stefani et al, 1999
Sankaranarayanan et al, 1994

Study done in diseased subjects
Goodman et al., 1992

No Information on Validation of Food Frequency Questionnaire
Fraser et al., 1991
Kvale et al., 1983
Bond et al., 1987
Brennan et al., 2000
Mayne et al., 1995

Breast Cancer
No measure of relative risk
Graham et al., 1991

No Information on Validation of Food Frequency Questionnaire
Levi et al., 1993

Republication
La Vecchia et al., 1997

No Information on Validation of Food Frequency Questionnaire
Hu et al., 1991
Seow et al., 2002
Tajima et al., 1985
Tuyns et al., 1988
Francheschi et al., 1994

Gastric Cancer
Republication
La Vecchia et al., 1987

No Statistical Analysis
Boeing et al., 1991

Studies did not evaluate disease incidence of specific cancer
Modan et al., 1981

No Information on Validation of Food Frequency Questionnaire
Franceschi et al., 1994
Haenszel et al., 1972
Tajima et al., 1985
Ramon et al., 1992

Cervical Cancer
Used non validated endpoints of cancer
De Vet et al., 1991

No measure of risk
Marshall et al, 1983

Pancreatic Cancer
No measure of risk
Baghurst et al., 1991

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