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## PETITION FOR HEALTH CLAIMS:

- LYCOPENE AND CANCER
- LYCOPENE AND PROSTATE CANCER
- LYCOPENE AND LUNG CANCER
- LYCOPENE AND GASTRIC CANCER
- LYCOPENE AND COLORECTAL CANCER
- LYCOPENE AND BREAST CANCER
- LYCOPENE AND CERVICAL CANCER
- LYCOPENE AND ENDOMETRIAL CANCER
- LYCOPENE AND OVARIAN CANCER
- LYCOPENE AND PANCREATIC CANCER
- TOMATOES AND CANCER
- TOMATOES AND PROSTATE CANCER
- TOMATOES AND LUNG CANCER
- TOMATOES AND GASTRIC CANCER
- TOMATOES AND COLORECTAL CANCER
- TOMATOES AND BREAST CANCER
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- LYCOPENE-CONTAINING TOMATO-BASED PRODUCTS AND COLORECTAL CANCER
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- LYCOPENE-CONTAINING TOMATO-BASED PRODUCTS AND CERVICAL CANCER
- LYCOPENE-CONTAINING TOMATO-BASED PRODUCTS AND ENDOMETRIAL CANCER
- LYCOPENE-CONTAINING TOMATO-BASED PRODUCTS AND OVARIAN CANCER
- LYCOPENE-CONTAINING TOMATO-BASED PRODUCTS AND PANCREATIC CANCER

SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION  
JANUARY 21, 2004

PETITIONER:  
AMERICAN LONGEVITY, INC.

2004Q-0201

QHC1

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January 21, 2004

**PETITIONER:** American Longevity, Inc.

**ADDRESS:** c/o Emord & Associates, P.C.  
5282 Lyngate Court  
Burke, VA 22015

**SUBJECT:** Petition for Health Claims:

1. Lycopene may reduce the risk of cancer.
2. Lycopene may reduce the risk of prostate cancer.
3. Lycopene may reduce the risk of lung cancer.
4. Lycopene may reduce the risk of gastric cancer.
5. Lycopene may reduce the risk of colorectal cancer.
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**Food and Drug Administration**  
**Office of Nutritional Products, Labeling, and Dietary Supplements**  
**HFS-800**  
**5100 Paint Branch Parkway**  
**College Park, MD 20740**

**I. Introduction and Statement of Purpose**

The undersigned, American Longevity, Inc. (hereinafter “Petitioner”), submits this petition pursuant to Sections 403(r)(4) and 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (“FDCA”) with respect to lycopene, tomatoes and lycopene-containing tomato-based foods<sup>1</sup> and cancer, including: prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer. The proposed claims are contained in section D below. Attached hereto, and constituting a part of this petition, are all of the items specified in 21 C.F.R. § 101.70(f).

This petition presents a logical and valid evaluation of the scientific studies and clinical trials concerning lycopene’s effect on reduction in the risk of prostate, lung, gastric, colorectal, breast, cervical, endometrial, ovarian, and pancreatic cancers. The attached scientific studies demonstrate that consumption of lycopene may reduce the risks of those cancers and justify permitting health claims that link consumption of lycopene with reduction in those risks. See Exhibit A (Scientific Report of Dr. Michael John Glade); and Exhibit B (Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids) at 342-344.

Lycopene is a member of the carotenoid family. Exhibit C (PDR for Nutritional Supplements) at 284-85. It is responsible for the red color of red tomatoes and is present in tomato-based foods such as ketchup, pizza sauce, tomato juice, and tomato paste. Id. It is also found in watermelon, papaya, pink grapefruit and pink guava. Id. at 284. The average daily intake of lycopene is approximately 25 milligrams, with 50% of this in the form of processed tomato-based foods. Id. at 285. Thus, lycopene is a safe and lawful substance within the

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<sup>1</sup> Herein what we refer to as lycopene-containing tomato-based foods include, but are not limited to: tomato juice, tomato paste, tomato sauce, pizza sauce, ketchup, salsa and picante sauce. See Exhibits A, B, and D.

meaning of 21 C.F.R. § 101.14(b)(i) and (ii). Similarly, lycopene is a substance within the meaning of 21 C.F.R. § 101.14(a)(2).

Lycopene is known to have antioxidant and anticarcinogenic properties. Thus, lycopene is associated with a disease, cancer, the particular disease that is the subject of this petition. 21 C.F.R. § 101.14(b)(i). The Scientific Report of Dr. Glade (Exhibit A), the Institute of Medicine's chapter on Vitamin C, Vitamin E, Selenium and Carotenoids (Exhibit B), and the PDR for Nutritional Supplements chapter on lycopene (Exhibit C), and all of the attached scientific articles (Exhibit F) establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims that lycopene, tomatoes, and lycopene-containing tomato-based foods may reduce the risk of prostate, lung, gastric, colorectal, breast, cervical, endometrial, ovarian, and pancreatic cancers.

This petition furthers national and DHHS policies by identifying a low cost means to help reduce the risk of certain cancers. The proposed health claims respond to a major public health concern in the United States: cancer. See 21 C.F.R. § 101.75. Cancer is the second leading cause of death in the United States. See "Cancer Facts & Figures 2003," American Cancer Society ("ACS"), 1 (2002) (Attached as Exhibit D). In the U.S., one of every four deaths is from cancer. See id. The ACS estimates that about 1,334,100 new cancer cases will be diagnosed this year alone. See id. Since 1990, about 17 million new cancer cases have been diagnosed.<sup>2</sup> See id. In 2003 about 556,500 Americans are expected to die from cancer, more than 1,500 people every day. See id.

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<sup>2</sup> This estimate does not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder, and does not include basal and squamous cell skin cancers. Id. at 2.

NIH estimates overall costs for cancer in the year 2002 to be \$171.6 billion: \$60.9 billion for direct medical costs (total of all health expenditures); \$15.5 billion for indirect morbidity costs (costs of lost productivity due to illness); and \$95.2 billion for indirect mortality costs (costs of lost productivity due to premature death). See Exhibit D at 3.

The Petitioner believes that the truthful and succinct health information conveyed by its proposed health claims will enable consumers to make prudent and effective dietary choices, cognizant of lycopene's potential to reduce the risk of certain kinds of cancer. Labeling foods and dietary supplements with the proposed claims will inform consumers at the point of sale of current scientific evidence concerning dietary means to lessen the risk of cancer incidence.

In accordance with FDA's July 10, 2003 "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" and consistent with the decision in Pearson v. Shalala, 164 F.3d. 650 (D.C. Cir. 1999), reh'g denied en banc, 172 F.2d 72 (D.C. Cir. 1999); see also Pearson v. Shalala, 130 F. Supp. 2d 105 (D.D.C. 2001); and Whitaker v. Thompson, 248 F. Supp. 2d 1 (D.D.C. 2002), the Petitioner respectfully requests that if the agency finds that the proposed claims do not satisfy its "significant scientific agreement" standard, that the agency authorize the claim or those claims nevertheless, with such succinct and accurate disclaimer as is or disclaimers as are reasonably necessary to avoid a potentially misleading connotation.

**A. Preliminary Requirements**

**1. Lycopene meets the requirements of 21 C.F.R. § 101.14(b)**

The proposed health claims meet the relevant eligibility requirements of 21 C.F.R. §

101.14(b). Section 101.14(b) requires:

(b) Eligibility. For a substance to be eligible for a health claim:

- (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 (e.g., the elderly), is at risk, or, alternatively, the petition submitted by the proponent of the claim otherwise explains the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet and satisfies the other requirements of this section.
- (2) If the substance is to be consumed as a component of a conventional food at decreased dietary levels, the substance must be a nutrient listed in 21 U.S.C. 343(q)(1)(C) or (q)(1)(D), or one that the Food and Drug Administration (FDA) has required to be included in the label or labeling under 21 U.S.C. 343(q)(2)(A); or
- (3) If the substance is to be consumed at other than decreased dietary levels:
  - (i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and
  - (ii) 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 a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

**a. Lycopene Is Associated with a Disease Affecting the General U.S. Population**

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 (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims pertaining to such diseases are thereby not subject to § 101.13 or § 101.70).” 21 C.F.R. § 101.14(a)(5).

The proposed health claims associate lycopene,<sup>3</sup> tomatoes, and lycopene-containing tomato-based foods with reduction in the risk of nine forms of cancer: prostate, lung, gastric, colorectal, breast, cervical, endometrial, ovarian, and pancreatic. Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. See Exhibit D at 1. “Failure to control the spread of cancer cells can result in death.” Id. “Cancer is caused by both external factors (tobacco, chemicals, radiation, and infectious organisms) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism).” Id. Causal factors may act together or in sequence to initiate or promote carcinogenesis. See id. All nine forms of cancer are ones for which the general U.S. population or a specific subset of the U.S. population is at risk. Lung cancer, gastric cancer, colorectal cancer, pancreatic cancer, and breast cancer are diseases and health conditions for which the general population is at risk. Cervical cancer, endometrial cancer and ovarian cancer are diseases for which, of course, the female U.S. population is at risk; while prostate cancer is, of course, a disease for which only the male U.S. population is at risk.

Cancer is the second leading cause of death in the United States. Id. In the U.S., one of every four deaths is from cancer. See id. This year alone about 1,334,100 new cancer cases are expected to be diagnosed. See id. Since 1990 about 17 million new cancer cases have been diagnosed.<sup>4</sup> Id. In 2003 about 556,500 Americans are expected to die from cancer, more than 1,500 people a day. See id.

For prostate cancer, the American Cancer Society estimates 189,000 new cases will be diagnosed this year. Id. at 15. Prostate cancer incidence rates are significantly higher in black

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<sup>3</sup> As referred to in this Petition, lycopene includes both synthetic lycopene and lycopene purified from organic material.

<sup>4</sup> Those estimates do not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder, and do not include basal and squamous cell skin cancers. Id. at 2. More than 1 million cases of basal and squamous cell skin cancers are expected to be diagnosed this year. Id.

men than in white men. Id. Between 1988 and 1992, prostate cancer incidence increased dramatically, due to earlier diagnosis in men without symptoms (using the prostate-specific antigen blood test). Id. The American Cancer Society estimated that 30,200 deaths occurred in due to prostate cancer, the second leading cause of cancer in men. Id.

Lung cancer is the second leading cause of newly-diagnosed cancer in both males and females in the U.S. See Exhibit A at 24. The American Cancer Society estimated that there were 169,400 new cases of lung and bronchus cancers in 2002, accounting for about 13% of cancer diagnoses. See Exhibit D at 11. Moreover, the American Cancer Society estimated 154,900 deaths in 2002 from lung and bronchus cancers, accounting for 28% of all cancer deaths. See id.

Colorectal cancer is the third most common life-threatening cancer in the U.S., accounting for 10% of total cancer incidence and total cancer deaths in the U.S. See Exhibit A at 30. Colorectal cancer occurs with nearly equal frequency in men and women. See id. According to the scientific report of Michael John Glade, Ph.D., CNS, FACN (Exhibit A), the five-year survival rate following diagnosis is between 10% and 90%, depending on the stage of diagnosis. See id.

Although the prevalence of gastric cancer has been declining in the U.S., the American Cancer Society has estimated for 2003 about 22,400 new diagnoses of gastric cancer and about 12,100 gastric cancer-related deaths in 2003. See Exhibit A at 37. Gastric cancer occurs with nearly equal frequency in men and women. See id. According to the scientific report of Dr. Glade (Exhibit A), the overall five-year survival rate is 20% or less; however, the survival rate increases to 60% when the tumor is localized in the stomach. See id. Unfortunately, only a small percentage of cases are localized in the stomach. See id.

Breast cancer ranks second among cancer deaths in women and is the most frequently diagnosed non-skin cancer in women. See id. at 41. Lifetime risk for breast cancer in women is 12.5% and increases with age and other factors. See id. The American Cancer Society has estimated about 211,300 new cases of invasive breast cancer will be diagnosed in 2003. See id. Over 99% of those cases are in women and 20% will lead to premature death. See id.

Finally, the American Cancer Society estimated that 108,400 new cases of cervical, endometrial, ovarian and pancreatic cancers were diagnosed in 2003.

**b. Lycopene Contributes Nutritive Value at the Levels Present in Supplements, Tomatoes, and Lycopene-Containing Tomato-Based Foods**

In accordance with section 101.14(b)(3)(i), lycopene contributes nutritive value whether in a food or in a dietary supplement. While there is no Reference Daily Intake (RDI) for lycopene, the nutritive contribution of lycopene is widely recognized. See generally Exhibits A and B. “*In vitro* studies have demonstrated that lycopene has the highest antioxidant activity of all the carotenoids.” See Exhibit C at 285. According to the Physician’s Desk Reference (“PDR”), lycopene may have anticarcinogenic and antiatherogenic activities. See id. at 285; see also Exhibit A.

Lycopene is a naturally occurring fat-soluble red pigment found in certain plants and microorganisms. See Exhibit C at 284. Although the efficiency of absorption is variable, lycopene from supplements has been reported to be highly bioavailable in humans. See Exhibit B at 354, Exhibit C at 285. The proposed health claims do not identify specific intake quantities for lycopene. Studies have shown lycopene supplementation to be effective at daily doses of at least 15 mg. See Exhibit A at 52. Lycopene is typically supplied in solid oral dosage form in capsules containing 5 mg, 6 mg or 10 mg. See Exhibit C at 287.

c. **Lycopene Is Safe and Lawful under the FDCA**

“For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of § 101.14(b)(3)(ii), e.g., that its use is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by the agency, and what the basis is for the GRAS claim, the food additive status, or prior sanctioned status.” 21 C.F.R. § 101.70(f)(A). In accordance with section 101.13(b)(3)(ii), lycopene is both a food and food ingredient and is safe and lawful at the levels necessary to reduce the risk of cancer, specifically, to reduce the risk of prostate cancer, lung cancer, gastric cancer, breast cancer and colorectal cancer. As mentioned above, lycopene is an ingredient of common foods such as tomatoes, tomato-based foods, red or pink grapefruit, raw watermelon, papaya, and pink guava all of which are known to be safely consumed for the entire length of recorded human history. See Exhibit A at 3 and Exhibit C at 284. The FDCA deems dietary supplements a food under 21 U.S.C. § 321(ff). Accordingly, lycopene is both a food and a food ingredient under 21 C.F.R. § 101.14(b)(3)(ii).

Lycopene is generally recognized as safe and lawful at the levels necessary to reduce the risk of certain cancers and to reduce the risk of prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer. General recognition of safety is based on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. 21 C.F.R. § 170.30(a). The basis for such views may be either (1) scientific procedure, or in the case of a substance used in food prior to January 1, 1958, (2) experience based on common use in food. Id.

Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is

impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

- (1) the probable consumption of the substance and of any substance formed in or on food because of its use.
- (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
- (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

21 C.F.R. § 170.3(i).

Lycopene has been a naturally occurring ingredient in foods consumed in the United States prior to January 1, 1958.<sup>5</sup> There is no evidence that lycopene consumed either in foods or as a dietary supplement has a cumulative effect in the diet that affects its safety. See Exhibit C at 286. There are no known harmful interactions with drugs in clinical practice. Id. In addition, there are no known harmful interactions with nutritional supplements. Id. The PDR for Nutritional Supplements indicates no significant adverse reactions, only a general statement that lycopene is contraindicated for persons who are hypersensitive, i.e. who are allergic to a component of the preparation. See id.

The maximum (safe) daily intake of lycopene is limited to the amount reasonably required to accomplish the intended nutritive effect. 21 C.F.R. § 172.5. The safe upper limit for lycopene has not been established, but it has been shown to be safe at intake levels up to 30 mg/day. See Exhibit B. Therefore, the proposed health claims comply with the safety and lawfulness requirements of 21 C.F.R. § 101.14(b)(3)(ii).

In summary, since lycopene meets the requirements set forth in 21 C.F.R. § 101.14(b), the preliminary requirements of 21 C.F.R. § 101.70 are fully satisfied.

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<sup>5</sup> The following are some common foods containing lycopene in the indicated amounts (mcg/gram wet weight): fresh tomatoes (8.8-42.0); cooked tomatoes (37); tomato sauce (62); tomato paste (54-1,500); pizza sauce (127); ketchup (99-134); red or pink grapefruit (141.9); raw watermelon (45.32). See Exhibit A at 3 and Exhibit C at 287.

## **B. Summary of Scientific Data Supporting the Proposed Claims**

### **1. Significant Scientific Agreement Exists to Support the Proposed Claims**

There is significant scientific agreement among experts who study the effect of lycopene on cancer (particularly prostate cancer, lung cancer, gastric cancer, breast cancer and colorectal cancer) that lycopene is an effective modifier (reducer) of the risk of those cancers. See Exhibit A at 1. The scientific literature shows that lycopene has antioxidant and anticarcinogenic effects. See Exhibit C at 286; see also Exhibit A.

The mechanism of lycopene's anticarcinogenic activity is believed to be its antioxidant activity. Id. at 286. Although the mechanism of lycopene's anticarcinogenic activity is not entirely understood, it is believed that lycopene reduces oxidative stress. See id. at 285.

Lycopene has the ability to: (1) quench singlet oxygen, (2) trap peroxy radicals, (3) inhibit the oxidation of DNA, (4) inhibit lipid peroxidation, and (5) inhibit the oxidation of low-density lipoprotein (LDL). See id. Lycopene has been shown to have the highest antioxidant activity of all the carotenoids. See id. Human clinical trials and epidemiological studies are discussed in the following section.

### **2. Scientific Evidence Demonstrates the Public Health Benefits of Lycopene**

Genetic changes caused by oxidative damage to DNA have been linked to the initiation and progression of cancer. See Exhibit A at 10. Scientific evidence shows that the extent of oxidative DNA damage in human cells is a biomarker for predicting the risk of, and reducing the incidence of, cancer. See id. According to the attached scientific report of Dr. Glade, "lycopene has been demonstrated to be the most radical antioxidant among the carotenoids." Id.

Studies have concluded that lycopene supplements, tomatoes, and lycopene-containing tomato-based foods produce a chemopreventive effect by reducing endogenous damage to DNA.

See id. Dr. Glade’s scientific report further explains that lycopene’s chemopreventive effect is accompanied by “significant increases in plasma total lycopene concentration and lymphocyte lycopene content.” Id. Both plasma total lycopene concentration and lymphocyte lycopene content were significantly inversely correlated with the extent of exogenously-induced oxidative damage to DNA. Id.

### **Prostate Cancer**

The scientific evidence demonstrates that lycopene, tomatoes, and lycopene-containing tomato-based foods benefit public health by reducing prostate cancer incidence. Carcinogenesis in the prostate occurs in a multistage process, involving a series of genetic alterations with progression through a variety of pathways from precancerous lesions to high-grade androgen-independent metastatic disease. See Exhibit A at 12. The beneficial protective effect of lycopene supplements, tomatoes, and lycopene-containing tomato-based foods has been demonstrated repeatedly in the scientific literature. The only randomized placebo-controlled clinical trial, the only uncontrolled clinical trial, and all of the published prospective observational studies found a protective effect from lycopene. See id. at 23. The results of the above studies are bolstered by the results of ten retrospective case-control studies, a case series and a case report. See id. Furthermore, studies have found that processing or cooking tomatoes does not reduce the protective benefits of lycopene. In fact, heating tomatoes provides a higher protective benefit by improving the bioavailability of the lycopene found in tomatoes. See id.

While retrospective case-control studies have failed to observe lycopene’s protective effects, those results were likely the result of study subjects failing to consume lycopene. See id. As Dr. Glade explains in his report, a subpopulation of nonresponders can dilute the overall effect of a chemopreventive agent and obscure the association between the nutrient and the

disease. This leads to an underestimation of the effects of the nutrient on chemoprevention. See id. Hence, the results of a retrospective case-control study are not as reliable as the results of clinical trials and prospective observational studies, which in the case of lycopene, tomatoes, and lycopene-containing tomato-based foods are all positive. See id. at 14-19. Thus, the evidence strongly supports that there is significant scientific agreement that lycopene, tomatoes and lycopene-containing tomato-based foods reduce the risk of prostate cancer, thereby providing a public health benefit.

### **Lung Cancer**

The scientific evidence demonstrates that lycopene, tomatoes and lycopene-containing tomato-based foods have public health benefits in relation to their effect on lung cancer. Carcinogenesis in the lung occurs in a multistage process involving a series of genetic alterations with progression through a variety of pathways from initial reversible lesions to the development of metastatic disease. See Exhibit A at 24. The scientific literature has shown that the risk of developing lung cancer is reduced by lycopene. That conclusion is supported by the findings of two prospective observational studies, a retrospective cohort study and five retrospective case-control studies. See id. at 25.

The results of the Health Professionals Follow-Up Study and the Nurses' Health Study found that both men and women with a median daily lycopene intake of 14.7 mg had a significantly reduced risk of developing lung cancer than the men and women with a median daily intake of 4.4 mg. See id. Although there have been reports of prospective observational studies and retrospective case-control studies that have failed to observe this protective effect, Dr. Glade's scientific report explains that most of those studies examined subjects with very little routine consumption of tomatoes or lycopene. See id. at 30. For example, the Netherlands

Cohort Study on Diet and Cancer found that daily lycopene intake had no effect on the multivariate-risk of developing lung cancer; however, fewer than five percent (5%) of the 58,279 men in the study consumed more than 4 mg of lycopene per day. That is the equivalent of 1.5 tablespoons of ketchup per day. See id. at 28. Thus, the results of the prospective observational studies and retrospective case-control studies that did not show a positive correlation between lycopene and lung cancer are not indicative of lycopene's protective benefits against lung cancer. The Health Professionals Follow-Up Study and the Nurses' Health Study, along with the Alpha-Tocopherol, Beta-Carotene Cohort Study and the results of a retrospective cohort study and five retrospective case-control studies, demonstrate that there is significant scientific agreement that lycopene, tomatoes and lycopene-containing tomato-based foods reduce the risk of lung cancer, thereby providing a public health benefit.

### **Colorectal Cancer**

The scientific evidence demonstrates that lycopene, tomatoes, and lycopene-containing tomato-based foods have public health benefits in relation to their effect on colorectal cancer. As explained in Dr. Glade's scientific report, the intestinal epithelium is in a constant state of renewal with a continuous high rate of cell proliferation, differentiation, and apoptotic cell death. See Exhibit A at 30. Colorectal carcinogenesis is a complex, multi-step process involving initiation, promotion, expansion, and progression stages that are not necessarily discrete or well-defined. See id. at 31. It is believed that mutations in the adenomatous polyposis colici ("APC") gene may be the initiating event in the development of most or all colorectal neoplasia. See id. at 32. In normal colorectal mucosa, exposure to carcinogenic compounds produces damage to the epithelium; however, in cells with the mutated APC gene, unrestrained hyper-proliferation produces aberrant crypt foci. See id. According to Dr. Glade's scientific report, "aberrant crypt

focci are preneoplastic lesions predictive of increased risk of colon cancer.” Id. Other factors contributing to the initiation or promotion of colorectal cancer are discussed in further detail in Dr. Glade’s scientific report. See id. at 30-37.

As evidenced by the findings of seven retrospective case-control studies, the risk of developing colorectal cancer is reduced by lycopene. See id. at 34. The individual results of the retrospective studies are fully vetted in Dr. Glade’s attached scientific report. See id. at 34-37. Moreover, the results of a prospective observational study confirm that lycopene reduces the risk of colorectal cancer. See id. at 37. Thus, the evidence demonstrates that there is significant scientific agreement that lycopene, tomatoes and lycopene-containing tomato-based foods reduce the risk of colorectal cancer, thereby providing a public health benefit.

### **Gastric Cancer**

The scientific evidence demonstrates that lycopene, tomatoes and lycopene-containing tomato-based foods have public health benefits in relation to their effect on gastric cancer. Gastric cancer is differentiated into two categories: (1) intestinal, with well-differentiated tissue, and (2) diffuse, consisting largely of undifferentiated cells. See Exhibit A at 37. As explained in Dr. Glade scientific report, the pathogenesis of gastric cancer depends on its initiating mutations. See id. Diffuse-type gastric cancer follows mutations in the E-cadherin gene, while intestinal-type gastric cancer appears to follow a multistage model. See id. The results of seven retrospective case-control studies support the proposition that lycopene reduces the risk of gastric cancer. See id. at 38. The study parameters and results vary. They are fully vetted in Dr. Glade’s attached scientific report. See id. at 38-40.

A prospective observational study and several retrospective case-control studies did not find a correlation between lycopene the risk of gastric cancer. See id. at 39. However, there was

an absence or virtual absence of lycopene in the diets of those studied. Hence, Dr. Glade concludes that “the failure of [the] investigators to observe the beneficial effect of the consumption of lycopene and tomatoes and tomato-based foods on the risk for developing gastric cancer [is] both predictable and irrelevant.” Id.

The prospective observational study and retrospective case-control studies that did not find a beneficial effect on gastric cancer are irrelevant to an evaluation of the scientific support for lycopene’s ability to reduce the risk of gastric cancer because the diets of almost all subjects in those studies did not include adequate amounts of lycopene. Hence, those studies do not measure lycopene’s protective effects against gastric cancer.

The results of seven retrospective case-control studies did demonstrate a beneficial effect of lycopene on the risk of developing gastric cancer. The subjects in those studies consumed varying amounts of lycopene. See id. at 38-39. Thus the evidence shows that there is significant scientific agreement that lycopene reduces the risk of gastric cancer, thereby providing a public health benefit.

### **Breast Cancer**

The scientific evidence demonstrates that lycopene, tomatoes and lycopene-containing tomato-based foods have public health benefits in relation to their effects on breast cancer incidence. While the pathogenesis of breast cancer is multifactorial and understood incompletely, the continued biosynthesis of polyamines is required for cellular proliferation in the breast. See Exhibit A at 41.

The scientific literature has shown that the risk of developing breast cancer is reduced by lycopene. That conclusion is supported by the findings of six retrospective case control studies. See id. at 42. In one such study, lycopene intakes greater than 5 mg daily were associated with

significantly reduced risk of developing breast cancer, compared to the risk associated with lycopene intakes of less than 2 mg daily (OR: 0.43; 95% CI: 0.28, 0.66; adjusted for age, education, parity, menopausal status, body mass index, alcohol consumption and dietary daily total caloric intake). See id. Similarly, another study found that women who consumed more than 4.3 mg of lycopene daily experienced significantly reduced risk of developing breast cancer, compared to the risk among women who consumed less than 2.3 mg of lycopene daily (OR: 0.30; 95% CI: 0.19, 0.47; adjusted for age, area of residence, urban or rural status, family history of breast cancer in a first-degree relative, body mass index, age at menarche, parity, menopausal status and dietary daily total caloric intake). Hence, the results of that study suggest that simply doubling the daily consumption of lycopene may significantly reduce an individual woman's risk of developing breast cancer. Id.

Contrary to the above findings, one prospective observational study, an analysis of pooled prospective epidemiological data and several retrospective case-control studies do not support the conclusion that lycopene reduces the risk of breast cancer. See id. at 44-45. The failure of those studies to find a correlation between lycopene and reduction in the risk of breast cancer is attributable to low lycopene consumption. The prospective observational study and retrospective case-control studies that did not find a beneficial effect on breast cancer incidence are irrelevant to an evaluation of the scientific support for lycopene's ability to reduce the risk of breast cancer because the diets of almost all subjects in those studies did not include adequate amounts of lycopene. Hence, those studies are not a measure of lycopene's protective effects against breast cancer.

The results of six retrospective case-control studies did demonstrate a beneficial effect of lycopene on the risk of developing breast cancer. The subjects in those studies consumed

varying amounts of lycopene. See id. at 43-46. Thus the evidence shows that there is significant scientific agreement that lycopene reduces the risk of breast cancer, thereby providing a public health benefit.

### **Cervical Cancer**

The scientific evidence demonstrates that lycopene reduces cervical cancer incidence. Cervical cancer begins as preneoplastic lesions that may progress to cervical intraepithelial neoplasia grade II and III, which is a recognized immediate precursor of invasive cervical cancer. See Exhibit A at 46. Carcinogenesis in the cervix is characterized by multiple genetic events, and human papillomavirus-induced disruptions in cell cycle regulation appear to be involved in the progression of cervical dysplasia to invasive cervical cancer. See id.

The scientific literature has shown that the risk of developing cervical cancer is reduced by lycopene. That conclusion is supported by the findings of five retrospective case-control studies. See id. One retrospective case-control study found that consumption of tomatoes more than twice a week significantly reduced the risk of developing cervical dysplasia, a well-recognized precursor to cervical cancer. See id. While eight retrospective case-control epidemiologic studies did not find a significant relationship between lycopene or tomatoes and cervical cancer, Dr. Glade explains that those reports “likely reflect confounding by related factors,” such as very low lycopene intakes by study participants or heterogeneity of effect. Id. at 48. Those factors result in underestimation of lycopene as chemopreventive. See id. Hence, those studies are not a good measure of lycopene’s protective effects against cervical cancer.

The results of five retrospective case-control studies did demonstrate a beneficial effect of lycopene on the risk of developing cervical cancer. The subjects in those studies consumed varying amounts of lycopene. See id. at 47-48. Thus the evidence shows that there is significant

scientific agreement that lycopene reduces the risk of cervical cancer, thereby providing a public health benefit.

### **Endometrial Cancer**

The scientific evidence demonstrates that lycopene benefits public health by reducing endometrial cancer incidence. Endometrial carcinogenesis results from the progression of hyperestrogenic endometrial hyperproliferation, perhaps secondary to defective DNA mismatch repair systems. The loss of expression of one of the DNA mismatch repair enzymes (usually hMLH1 or hMSH2) can result in microsatellite instability and produce predisposition to endometrial cancer. See Exhibit A at 48.

The scientific literature has shown that the risk of developing endometrial cancer is reduced by lycopene. That conclusion is supported by the findings of two retrospective studies of cohorts of women with and without endometrial cancer. See id. at 49. In one study, women who consumed at least 14 mg/day of lycopene significantly reduced their risk of developing endometrial cancer, compared to the risk in women who consumed less than 4.5 mg of lycopene/day (RR: 0.63; 95% CI: 0.43, 0.94; adjusted for age, body mass index, smoking status, oral contraceptive use, hormone replacement therapy use, education, parity, age at menarche and dietary daily total caloric intake). See id. Similarly, the results of the second study suggest that the routine daily intake of more than 7.3 mg of lycopene significantly reduces the risk of developing endometrial cancer, compared to the risk in women with routine daily lycopene intakes less than 3.5 mg. See id. Thus there is significant scientific agreement that lycopene reduces the risk of endometrial cancer, thereby providing a public health benefit.

## Ovarian Cancer

The scientific evidence demonstrates that lycopene benefits public health by reducing ovarian cancer incidence. Ovarian cancer usually begins in a single layer of the epithelia that line the surface of the ovary when that layer has lost the regulation of its normal post-ovulatory proliferative phase. See Exhibit A at 49. The loss of cell cycle regulation in the ovarian epithelium results from multiple genetic alterations in proto-oncogenes as well as mutation of the p53 tumor-suppressor gene. See id.

The scientific literature has shown that the risk of developing ovarian cancer is reduced by lycopene. That conclusion is supported by the findings of a retrospective case-control study. That study found that daily consumption of at least 15 mg of lycopene significantly reduced the risk of developing ovarian cancer, compared to the risk in women consuming less than 5 mg of lycopene daily (OR: 0.53; 95% CI: 0.35, 0.82; adjusted for age, body mass index, oral contraceptive use, family history of breast, ovarian or prostate cancer in a first-degree relative, tubal ligation, education, parity, marital status and dietary daily total caloric intake). See id. at 50. Moreover, the consumption of tomato sauce more than once a week significantly reduced the risk of developing ovarian cancer, compared to the risk in women consuming tomato sauce less than once a month. See id. This study also concluded that heating or cooking the organic matrix of plant sources of lycopene substantially increased the bioavailability and chemopreventive effectiveness in the ovary of naturally-occurring lycopene. See id. Hence, the study's results did not depend on whether the women consumed raw tomatoes or tomato juice (or some other processed tomato food). Thus the published scientific evidence supports the conclusion that lycopene reduces the risk of endometrial cancer, thereby providing a public health benefit.

## **Pancreatic Cancer**

The scientific evidence demonstrates that lycopene benefits public health by reducing pancreatic cancer incidence. The pathogenesis of pancreatic cancer is characterized by mutation in cellular proto-oncogenes and tumor suppressor genes. See Exhibit A at 50.

The scientific literature has supported the hypothesis that the risk of developing pancreatic cancer is reduced by lycopene. That conclusion is supported by the findings of three retrospective studies. In one study of over 600 men and women, the researchers concluded that daily consumption of the highest quintile of raw tomatoes significantly reduced the risk of developing pancreatic cancer, compared to the risk in subjects consuming the lowest quintile (OR: 0.23; significantly difference from OR = 1.0,  $p < 0.05$ ; adjusted for age, sex, smoking status and dietary daily total caloric intake). Consistent with the conclusion that tomato consumption has chemopreventive effects, another retrospective study found that mean serum total lycopene concentration was significantly higher among subjects without pancreatic cancer than among subjects with pancreatic cancer. See id. at 51. Moreover, subjects with the serum total lycopene concentrations greater than  $1.01 \times 10^{-6} M$  experienced significantly less risk of developing pancreatic cancer than did subjects with serum total lycopene concentrations less than  $0.66 \times 10^{-6} M$  (unadjusted OR: 0.19; significantly different from OR = 1.0,  $p < 0.05$ ). See id.

Nonetheless, the results of a 6-year prospective study of 34,556 Seventh Day Adventists suggested that tomato consumption had no effect on the age and sex adjusted incidence of pancreatic cancer. See id. Dr. Glade concludes that “although the results of the only published prospective study of the relationship between tomato intake and pancreatic cancer did not observe a relationship, all of the published retrospective epidemiologic data consistently indicate

the presence of a chemopreventive relationship.” Id. Thus the published scientific evidence supports the conclusion that lycopene reduces the risk of pancreatic cancer, thereby providing a public health benefit.

### 3. Scientific Summary Issues

a. **Is There an Optimum Level of Lycopene to Be Consumed Beyond Which No Benefit Would Be Expected?**

There is no evidence of an optimum level of lycopene to be consumed beyond which no benefit would be expected. See Exhibit A. The scientific literature indicates that dietary supplementation with lycopene or the daily consumption of tomatoes or lycopene-containing tomato-based foods is effective with doses of at least 15 mg of lycopene per day. See Exhibit A at 52. Moreover, there are no reports of overdosage. See Exhibit A at 53, Exhibit C at 287.

b. **Is There Any Level at Which an Adverse Effect from the Substance or from Foods Containing the Substance Occurs for Any Segment of the Population?**

There is no level identified at which adverse events occur for any segment of the population. See Exhibit A at 52, Exhibit C at 286-87. There is an absence of reports of adverse reactions in the published scientific literature and the safety of oral supplementation with lycopene has been documented in detail by several investigators. See id. Moreover, the PDR for Nutritional Supplements reports no side effects associated with lycopene. See Exhibit C at 287.

c. **Are There Certain Populations that Must Receive Special Consideration?**

The PDR for Nutritional Supplements has two general warnings. See Exhibit C at 286. It cautions that pregnant women and nursing mothers should only consume lycopene contained in common foods and not via dietary supplements. Id. It also states that lycopene is contraindicated in those who are hypersensitive to any component of a lycopene-containing preparation. Id. Adults treated with either cholestyramine or probucol have exhibited significant

decreases (30%) in serum total lycopene concentrations, suggesting that individuals receiving those medications require restorative dietary supplementation with lycopene. See Exhibit A at 52.

**d. What Other Nutritional or Health Factors (Both Positive and Negative) Are Important to Consider When Consuming the Substance?**

There are no known harmful interactions with drugs in clinical practice for lycopene. See Exhibit C at 286. Concomitant intake of cholestyramine, colestipol, mineral oil, orlistat, or pectin may decrease the absorption of lycopene. See id. at 286-287. Concomitant intake of beta-carotene or medium-chain triglycerides may increase the absorption of lycopene. See Exhibit A at 52, Exhibit C at 287.

**4. Potential Effect of the Use of the Proposed Claims on Food Consumption, including Significant Alterations in Eating Habits and Corresponding Changes in Nutrient Intakes**

The proposed claims may increase use of oral lycopene supplements, tomatoes, and lycopene-containing tomato-based foods among the general population, including populations at greater risk of cancer. The Petitioner does not anticipate substantial dietary changes in the general population but does expect there to be some increase in consumer preferences for lycopene-containing foods and supplements. The effect on such people is expected to be beneficial: reducing the risk of certain cancers, prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer.

**5. Prevalence of the Disease or Health-Related Condition in the U.S. Population and the Relevance of the Claims in the Context of the Total Daily Diet.**

As discussed above, the proposed health claims respond to a major public health concern in the United States: the incidence and mortality of cancer. 21 C.F.R. § 101.75(b). Cancer is

the second leading cause of death in the United States. See Exhibit D at 1. In the U.S., one of every four deaths is from cancer. Id. This year alone, about 1,334,100 new cancer cases are expected to be diagnosed. Id. Since 1990, about 17 million new cancer cases have been diagnosed.<sup>6</sup> Id. In 2002 about 556,500 Americans are expected to die of cancer, more than 1,500 people a day. Id.

The American Cancer Society estimates that 189,000 new cases of prostate cancer will be diagnosed this year. It also estimated that 30,200 deaths in 2002 occurred due to prostate cancer, the second leading cause of cancer in men. Id. The American Cancer Society estimated that there were 169,400 new cases of lung and bronchus cancers in 2002, accounting for about 13% of cancer diagnoses. Id. at 11. Finally, the American Cancer Society estimated 154,900 deaths in 2002 from lung and bronchus cancers, accounting for 28% of all cancer deaths. Id.

Most studies have shown lycopene to be effective in cancer risk reduction at levels of at least 15 mg per day, while the average U.S. diet for lycopene intake ranges from 5 mg to 15 mg. See Exhibit A at 52, Exhibit C at 287. Thus, increased intake of lycopene offers a safe, inexpensive, readily accessible means for reducing population wide the risk of certain cancers, specifically: prostate cancer; lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer and pancreatic cancer.

**6. Lycopene, Tomatoes and Lycopene-Containing Tomato-Based Foods Conform to the Definition of 21 C.F.R. § 101.14(a)(2).**

The Petitioner seeks FDA approval of the proposed claims for use in connection with lycopene supplements, tomatoes, and lycopene-containing tomato-based foods. Lycopene, tomatoes, and lycopene-containing tomato-based foods<sup>7</sup> meet the definition of a “substance” in

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<sup>6</sup> That estimate does not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder, and does not include basal and squamous cell skin cancers. Id. at 2.

<sup>7</sup> The specific foods are fresh tomatoes, tomato sauce, tomato paste, pizza sauce and ketchup.

21 C.F.R. § 101.14(a): “Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances.”

Lycopene is a component of food, and tomatoes and lycopene-containing tomato-based foods (e.g., fresh tomatoes, tomato sauce, tomato paste, pizza sauce, and ketchup) are, of course, foods. Lycopene is a natural fat-soluble pigment (red) found in certain plants and microorganisms where it acts as an accessory light-gathering pigment and protects those organisms against the toxic effects of oxygen and light. See Exhibit C at 284. Its molecular formula is C<sub>40</sub>H<sub>56</sub> and its molecular weight is 536.88 daltons. Lycopene is an acyclic isomer of beta-carotene. Id. at 284. Unlike beta-carotene, lycopene has no vitamin A activity and thus is a nonprovitamin A carotenoid. Id. at 285. Lycopene is a 40 carbon atom, open chain polyisoprenoid with 11 conjugated double bonds. Id. All-*trans* lycopene is the predominant geometric isomer found in plants. Id. However, *cis*-lycopene is found in nature. Id. Lycopene found in human plasma is a mixture of approximately 50% *cis* lycopene and 50% all-*trans* lycopene. Id. Lycopene in processed foods is mainly the *cis*-isomer. Id. *Cis*-lycopene is more bioavailable than *trans*-lycopene. Id. at 285.

The bioavailability of synthetic lycopene has been compared to the bioavailability of lycopene found in raw tomatoes and processed tomato products. See Exhibit A at 4. According to the Scientific Report of Dr. Glade, the bioavailability of synthetic lycopene, the extracted “natural source” lycopene and lycopene in cooked tomato soup were found to be nearly identical. See id. at 5. Moreover, like the bioavailability comparison between lycopene in raw tomatoes and lycopene in processed tomato-based foods, the bioavailability of synthetic lycopene is

significantly greater than the bioavailability of lycopene in unprocessed (raw) tomato juice. See id.

Lycopene is found in tomatoes and tomato-based foods (such as ketchup, pizza sauce, and tomato juice). Id. at 284, see also Exhibit A at 3. Processed tomato foods are more available dietary sources of lycopene than fresh tomatoes. Id. The improved availability of lycopene from processed foods is due to its release from the ruptured plant cells following mechanical and thermal processing, as well as heat induced-*trans* to *cis*-isomerization. Lycopene in dietary supplements is in the form of an oleoresin, in phospholipids, complexes and oils. Id. at 285. According to USDA, the average daily intake of lycopene is estimated to be 9-28 milligrams. See Exhibit A at 7.

Thus, lycopene and lycopene-containing foods are “substances” as defined by 21 C.F.R. § 101.14.

C. **Analytical Method**

The amount of lycopene contained in a dietary supplement and in food products that may be candidates for bearing the health claims can be ascertained by High-Performance Liquid Chromatography (HPLC) according to the Institute for Nutraceutical Advancement. See Exhibit E. The assay method described in Exhibit E is applicable to finished products.

**D. Proposed Model Claims**

Petitioner proposes the follow model claims:

**Lycopene may reduce the risk of certain forms of cancer.**

**Lycopene may reduce the risk of prostate cancer.**

**Lycopene may reduce the risk of lung cancer.**

**Lycopene may reduce the risk of gastric cancer.**

**Lycopene may reduce the risk of colorectal cancer.**

**Lycopene may reduce the risk of breast cancer.**

**Lycopene may reduce the risk of cervical cancer.**

**Lycopene may reduce the risk of endometrial cancer.**

**Lycopene may reduce the risk of ovarian cancer.**

**Lycopene may reduce the risk of pancreatic cancer.**

**Tomatoes may reduce the risk of certain forms of cancer.**

**Tomatoes may reduce the risk of prostate cancer.**

**Tomatoes may reduce the risk of lung cancer.**

**Tomatoes may reduce the risk of gastric cancer.**

**Tomatoes may reduce the risk of colorectal cancer.**

**Tomatoes may reduce the risk of breast cancer.**

**Tomatoes may reduce the risk of cervical cancer.**

**Tomatoes may reduce the risk of endometrial cancer.**

**Tomatoes may reduce the risk of ovarian cancer.**

**Tomatoes may reduce the risk of pancreatic cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of certain forms of cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of prostate cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of lung cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of gastric cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of colorectal cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of breast cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of cervical cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of endometrial cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of ovarian cancer.**

**Lycopene-containing tomato-based foods may reduce the risk of pancreatic cancer.**

As discussed above, multiple studies have shown that consumption of lycopene reduces the risk of the above cancers. Moreover, clinical trials and current usage have proven the safety of lycopene for the general population.

**E. Attachments**

Attached are copies of the scientific studies (Exhibit F) and other information (Medline search results attached as Exhibit G) referenced in, and constituting the basis for, this Petition. To the best of the Petitioner's knowledge, all non-clinical studies relied upon were conducted in compliance with the good laboratory practices regulations set forth in 21 C.F.R. Part 58, and all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review set forth at 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. § 56.104 or 56.105, and were conducted in conformance with the requirements for informed consent set forth in 21 C.F.R. § 50 et seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

**F. Exclusion from Environmental Assessment**

The requested health claims contained in this petition are categorically excluded from the environmental impact statement requirements under 21 C.F.R. § 25.24.

**G. Conclusion and Certification**

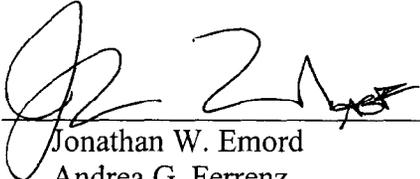
For the foregoing reasons, the Petitioner requests that the FDA approve the proposed health claims. The Petitioner looks forward to working with the FDA to promulgate a regulation authorizing on food and dietary supplement labels and in their labeling the health claims concerning lycopene's effects on reducing the risk of certain cancers; prostate cancer, lung cancer, gastric cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, and pancreatic cancer.

Any questions concerning this Petition may be directed to Jonathan W. Emord, Esq., Emord & Associates, P.C., 5282 Lyngate Court, Burke, VA 22015, (202) 466-6937.

The undersigned certify on behalf of the Petitioner that to the best of Petitioner's knowledge, this Petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known to it to be pertinent to the evaluation of the proposed health claims.

Sincerely,

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