



JUL 10 2002

PETITION FOR HEALTH CLAIMS:

**SELENIUM AND REDUCTION IN THE RISK OF
CERTAIN CANCERS; SELENIUM AND ANTICARCINOGENIC
EFFECTS**

SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION

JULY 10, 2002

PETITIONER:

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02P-0457

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BACKGROUND OF THE PETITIONER

Incorporated in the state of California, Wellness Lifestyles, Inc. (d/b/a American Longevity) manufactures, distributes, and sells dietary supplements, including selenium-containing dietary supplements.

July 10, 2002

PETITIONER: Wellness Lifestyles, Inc.
ADDRESS: c/o Emord & Associates, P.C.
5282 Lyngate Court
Burke, VA 22015
SUBJECT: Petition for Health Claims: Selenium and Reduction in the
Risk of Certain Cancers; Selenium and Anticarcinogenic Effects

Food and Drug Administration
Office of Nutritional Products, Labeling, and Dietary Supplements
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I. Introduction and Statement of Purpose

Wellness Lifestyles, Inc. (hereinafter "Petitioner"), pursuant to Section 403(r)(5)(D) of the Federal Food, Drug and Cosmetic Act ("FDCA")(21 U.S.C. § 343(r)(5)(D)), submits this petition for health claims concerning the relationship between selenium and reduction in the risk of certain cancers and between selenium and anticarcinogenic effects. The proposed claims are contained in section V 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 selenium's effect on reduction in the risk of certain cancers and concerning selenium's anticarcinogenic effects. Selenium is an essential trace element in human nutrition. Exh. 2 (PDR for Nutritional Supplements) at 416. It is known to have antioxidant and anticarcinogenic activity when consumed at levels more than twice as much as in the average U.S. diet. Id. The attached scientific studies demonstrate that selenium supplementation may reduce the incidence of colon, prostate, lung, liver, and esophageal cancers. Exhibits 1 at 3-4; 2

at 418-419; and 4 at 290. The scientific evidence justifies permitting the proposed health claims. See Whanger Report attached as Exhibit (Exh.) 1.

The proposed health claims respond to a major public health concern in the United States: cancer. 21 C.F.R. § 101.75. Cancer is the second leading cause of death in the United States. “Cancer Facts & Figures 2002,” American Cancer Society, 1 (2002) (Attached as Exh. 3). In the U.S., one of every four deaths is from cancer. Id. The ACS estimates that about 1,284,900 new cancer cases will be diagnosed this year alone. Id. Since 1990, about 16 million new cancer cases have been diagnosed.¹ Id. In 2002 about 555,500 Americans are expected to die from cancer, more than 1,500 people every day. Id.

This petition furthers national and DHHS policies by identifying a low cost means to help reduce the risk of certain cancers. The truthful and succinct health information conveyed by the Petitioner’s proposed health claims will enable consumers to make prudent and effective dietary choices, cognizant of selenium’s potential to reduce the risk of certain kinds of cancer and of its anticarcinogenic activity. Labeling dietary supplements with the proposed selenium claims will inform consumers at the point of sale of current scientific evidence concerning dietary means to lessen the risk of cancer incidence.

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 (2001), 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 claims nevertheless, with such succinct and accurate disclaimers as are reasonably necessary to avoid a

¹ 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.

potentially misleading connotation. The petitioner will accept any reasonable, succinct and accurate disclaimer that avoids potential misleadingness.

II. Preliminary Requirements

A. **Selenium meets the definition of 21 C.F.R. § 101.14(a)**

The Petitioner seeks FDA approval of the proposed claims for use on dietary supplements containing selenium. Selenium meets the definition of a “substance” provided by 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.” Selenium is an essential trace element in human and animal nutrition. Exhibit 2 at 416. Selenium is a metalloid element with atomic number 34 and an atomic weight of 78.96 daltons. Id.² Selenium is found in human and animal tissues as L-selenomethionine or L-selenocysteine. The amount of selenium in foods is a function of the selenium content of the soil. Selenium enters the food chain through incorporation into plant proteins as the amino acids L-selenocysteine³ and L-selenomethionine⁴. L-selenomethionine is incorporated randomly in proteins in place of L-methionine (called selenium-containing proteins). Id. By contrast, incorporation of L-cysteine into proteins is not random and the resulting proteins are called selenoproteins. Id. L-selenocysteine does not randomly substitute for L-cysteine but has its own triplet code and is considered to be the 21st genetically coded amino acid. Id. Selenium-rich sources in foods include: organ meats and seafood (0.4 to 1.5 µg/g); muscle meats (0.1 to 0.4 µg/g), cereals and grains (less than 0.1 to greater than 0.8 µg/g), and dairy products (less than 0.1 to 0.3 µg/g). Exh. 4 at 308 (citing WHO, 1987). Plants do not require selenium, in contrast to animals. Id. Meat and seafood are more reliable sources of selenium than plants. Fruits and vegetables have less than 0.1 µg/g. Id. Selenium in dietary

² Selenium was discovered in 1817 by Berzelius who named it after Selene, the Greek goddess of the moon. Id.

³ Selenocysteine is the form of selenium that accounts for the biological activity of the element. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids, Institute of Medicine, 284-324, at 285 (National Academy Press, 2000) (Attached as Exh. 4 is a copy of the chapter on selenium).

supplements is typically selenium-enriched yeast. Thus, selenium is a “substance” as defined by 21 C.F.R. § 101.14(a).

B. Selenium meets the definition 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.

1. Selenium 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

⁴ Selenomethionine cannot be synthesized by humans and is initially synthesized in plants. Exh. 4 at 284. It is the major dietary form of selenium. *Id.* at 285.

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 the substance, selenium, with reduction in the risk of certain kinds of cancer, a disease, and state its anticarcinogenic activity.

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. Exh. 3. 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. Id.

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. Id. This year alone, about 1,284,900 new cancer cases are expected to be diagnosed. Id. Since 1990, about 16 million new cancer cases have been diagnosed.⁵ Id. In 2002 about 555,500 Americans are expected to die from cancer, more than 1,500 people a day. Id.

Colorectal cancers (cancers of the colon and rectum combined) are the third most common site of new cancer cases and deaths in both men and women. Exh. 3 at 20. ACS estimates that in 2002 there will be 148,300 new colorectal cancer cases and 56,600 deaths from the disease. In the United States, while colorectal cancer deaths have decreased from 1992 to 1998 by 1.8%, a person’s lifetime risk of developing colorectal cancer is nearly 6%, with over 90% of cases occurring after age 50. Id.

For prostate cancer ACS estimates 189,000 new cases will be diagnosed this year. Id. at 15. Prostate cancer incidence rates are significantly higher in black men than in white men. Id.

Between 1988 and 1992, prostate cancer incidence rates increased dramatically, due to earlier diagnosis in men without symptoms (using the prostate-specific antigen blood test). Id. Prostate cancer incidence rates subsequently declined and have leveled off, especially in the elderly. Id. ACS estimates that 30,200 deaths in 2002 will occur due to prostate cancer, the second leading cause of cancer in men. Id. Although mortality rates are declining in white and black men, rates in black men are more than twice as high as rates in white men. Id.

ACS estimates that there will be 169,400 new cases of lung and bronchus cancers in 2002, accounting for about 13% of cancer diagnoses. Id. at 11. While the incidence of lung and bronchus cancers is declining significantly in men (from a high of 86.5 per 100,000 in 1984 to 69.8 in 1998), in the 1990s the increase among women reached a plateau (with incidence in 1998 at 43.4 per 100,000). Id. ACS estimates 154,900 deaths in 2002 from lung and bronchus cancers, accounting for 28% of all cancer deaths. Id. Decreasing lung cancer incidence and mortality rates are mostly attributed to decreased smoking rates over the past 30 years. Id. However, declines in adult tobacco use have slowed and tobacco use among youth increased considerably during the 1990s except in a few states. Id. at 12.

The National Institutes of Health estimates overall costs for cancer in the year 2001 at \$156.7 billion: \$56.4 billion for direct medical costs (total of all health expenditures); \$15.6 billion for indirect morbidity costs (cost of lost productivity due to illness); and \$84.7 billion for indirect mortality costs (cost of lost productivity due to premature death). Id. at 3. Reduction in cancer risk is, thus, a health and economic policy necessity for the United States.

2. Selenium contributes nutritive value at the levels present in supplements

⁵ 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.

In accordance with section 101.14(b)(3)(i), selenium contributes nutritive value. The Institute of Medicine's Food and Nutrition Board established a Recommended Dietary Allowance (RDA) for selenium for both men and women of 55 μg (0.7 μmol)/day. Exh. 4 at 284.⁶

The nutritive value of selenium is widely recognized. See Exhs. 1-2 and 4. According to the Institute of Medicine the known biological functions of selenium include defense against oxidative stress, regulation of thyroid hormone action, and regulation of the redox status of vitamin C and other molecules. Exhibit 4. The PDR for Nutritional Supplements also includes antioxidant activity among selenium's actions and states that selenium may have immunomodulatory, anti-carcinogenic and anti-atherogenic activities. Exhibit 2.

As mentioned above, the selenium content of food depends upon the selenium content of the soil where the animal was raised or the plant grown. It is believed that plants do not require selenium and most selenium metabolism by plants occurs through sulfur pathways where selenium substitutes for sulfur. Exh. 4 at 308. That lack of requirement causes the plant to reflect the selenium content of the soil. By contrast animals require selenium. Id. Meat and seafood are considered reliable dietary sources of selenium and contain selenium in its functional form as selenoproteins. Moreover, virtually all animal proteins contain selenomethionine, because animals consume selenium when they eat plants. Thus, meat varies in selenium content depending upon the animals' selenomethionine intake from the plants they consume.

⁶ The RDA figure for selenium is based on the amount of selenium needed to maximize synthesis of the selenoprotein glutathione peroxidase. Id. Glutathione peroxidases use reducing equivalents from glutathione to detoxify hydroperoxides. Exh. 2 at 417. There are four different glutathione peroxidases and they are present in most cells of the body, helping prevent oxidative damage to membranes, and in the extracellular fluid. Id. Glutathione peroxidases detoxify hydrogen peroxide and fatty-acid-derived hydroperoxides. Id. Selenium also performs an antioxidant function in its role in selenium-dependent thioredoxin reductases that reduce intramolecular disulfide bonds and regenerate ascorbic acid from dehydroascorbic acid. Id.

The most common dietary supplement form of selenium is selenium-enriched yeast. High-selenium yeast contains L-selenomethionine in proteins. Exh. 2 at 417. Proteins in high-selenium yeast are enzymatically digested in the small intestines to yield amino acids, oligopeptides, and L-selenomethionine. Id. L-selenomethionine is efficiently absorbed from the small intestine to the liver where a fraction is extracted by the hepatocytes and the remaining amount is transported by circulation to the various tissues of the body. Id. Selenium homeostasis is achieved by the kidney's regulation of selenium excretion. Id. at 418. As selenium intake increases so does urinary excretion of selenide metabolites. Id.

Dietary selenium intakes in the United States have been estimated in several studies. Exh. 4 at 309. In one study of 22 Maryland residents using direct selenium analysis, selenium intake was 81 ± 41 (SD) μg (1.0 ± 0.5 μmol) per day. Id. The FDA purchased foods in different regions of the United States from 1982 to 1991 and calculated dietary selenium intake as 87 μg (1.1 μmol)/day with a range of 79 to 104 μg (1.0 to 1.3 μmol) per day in different years. Id. The Third National Health and Nutrition Examination Survey (NHANES III) intake data reported median selenium intakes of 106 μg (1.3 μmol) per day from food and 108 μg per day from food and supplements for all individuals based on dietary recall and food tables, but that method has low accuracy. Id.

Dietary intake of selenium varies tremendously among different populations. Id. Factors affecting intake include origin of the food and meats. Id. The lowest selenium intakes are in populations that eat vegetarian diets consisting of plants grown in low-selenium areas. Id. Dietary intake in the U.S. varies by region but is rendered more uniform by the food distribution system where there is extensive transport of food throughout the country, preventing low-selenium geographic areas from having low dietary selenium intakes. Id.

The proposed claims do not identify specific intake quantities for selenium. Studies have shown selenium supplementation to have risk reduction value from 50 to 200 µg a day, with most studies supplementing at 200 µg per day, more than twice as much as is in the average U.S. diet. Exh. 1 at 3-4; Exh. 2 at 418-419; Exh. 4 at 290-291. Selenium is typically supplied in solid oral dosage form in capsules containing 50 µg, 100 µg, and 200 µg; extended release tablets containing 200 µg; and tablets containing 20 µg, 100 µg, 126 µg, 150 µg, and 200 µg. Exh. 2 at 421.

3. Selenium 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), selenium is both a food and food ingredient and is safe and lawful at the levels necessary to reduce the risk of certain cancers. As mentioned above, selenium is an ingredient of common foods such as meats, seafoods, and plants. The FDCA deems dietary supplements a food under 21 U.S.C. § 321(ff). Accordingly, selenium is both a food and a food ingredient under 21 C.F.R. § 101.14(b)(3)(ii).

Selenium is generally recognized as safe and lawful at the levels necessary to reduce the risk of certain cancers. 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 (2) in the case of a substance used in food prior to January 1, 1958, through 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).

Selenium has been a naturally occurring ingredient in foods consumed in the United States prior to January 1, 1958. There is no evidence that selenium consumed either in foods or as a dietary supplement has a cumulative effect in the diet that is unsafe. See Exh. 2 at 420. There are no known interactions with drugs in clinical practice. Id. Moreover, there are no known harmful interactions with nutritional supplements. Id. Intake of selenium at less than 900 micrograms a day (for adults) is unlikely to cause adverse reactions. Id. Prolonged intakes of selenium in doses of 1,000 micrograms (or one milligram) or greater daily may cause adverse reactions. The PDR for Nutritional Supplements states that the most frequently reported adverse reactions of selenosis or chronic selenium toxicity are hair and nail brittleness and loss. Other symptoms include skin rash, garlic-like breath odor, fatigue, irritability and nausea and vomiting. Id. The PDR indicates no significant contraindications, only a general statement that selenium is contraindicated for persons who are hypersensitive, i.e. who are allergic to a component of the preparation. Id.

The maximum (safe) daily intake of selenium is generally well above the amount reasonably required to accomplish the intended nutritive effect. 21 C.F.R. § 172.5. The PDR

recommends a safe upper limit for selenium of 900 micrograms a day, Exh. 2 at 420, although some suggest a more conservative 400 micrograms a day, Exh. 1 at 13. Nutritive effect in reducing the risk of certain cancers has been recorded in daily doses ranging from 50 to 200 μg a day, with most studies supplementing at 200 μg per day. Exh. 1 at 3-4; Exh. 2 at 418-419; Exh. 4 at 290-291. 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 selenium 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.

III. Summary of Scientific Data Supporting the Proposed Claims

A. **Significant scientific agreement exists to support the proposed claims**

There is significant scientific agreement among experts who study the effect of selenium on cancer that selenium is an effective modifier of the risk of certain cancers and that it has anticarcinogenic effects. See Exh. 1 at 1. The scientific literature shows that selenium has both antioxidant and anticarcinogenic effects. Exh. 2 at 416.

The mechanism of selenium's anticarcinogenic activity is believed to be its antioxidant activity and its immune-enhancing activity. Id. at 417. Selenium has been shown to up-regulate apoptosis in tumor cells *in vitro* and increase macrophage killing *in vitro*. Id. Selenium's antioxidant activity is mainly due to its role in the formation and function of the selenium-dependent glutathione peroxidases (GSHPx). Id. at 416. GSHPxs detoxify hydroperoxides. There are four different types of GSHPX: (1) GSHPx-1 present in most cells in the body; (2) GSHPx-2 found mainly in gastrointestinal tract cells; (3) GSHPx-3 found extracellular; and (4) GSHPx-4 a membrane-bound hydroperoxide glutathione peroxidase, detoxifying phospholipid hydroperoxides and preventing oxidative damage to membranes with d-alpha-tocopherol. Id. GSHPxs perform an antioxidant role and detoxify hydrogen peroxide and fatty acid-derived hydroperoxides.

Selenium's antioxidant activity is also attributed to its role in selenium-dependent thioredoxin reductases. Those enzymes reduce intramolecular disulfide bonds and regenerate ascorbic acid from dehydroascorbic acid. Id. at 417. They also affect the redox regulation of a number of factors including ribonucleotide reductase, the glucocorticoid receptor and transcription factors AP-1 and NF-KappaB.

Of the more than 100 trials on small animals on the relationship between tumor incidence and selenium status, two-thirds have shown significant tumor incidence reductions. One half showed reductions of 50% or more. Exh. 1 at 8. Evidence indicates that the likely mechanism of action is apoptosis. Id. Human clinical trials and epidemiological studies are discussed in the following section.

B. Scientific evidence demonstrates the public health benefits of Selenium

Six human clinical trials have evaluated the effects of selenium supplementation on the incidence of cancer. The study by Clark et al. measured the effect of a daily oral supplement of selenium enriched yeast at 200 µg per day on 1312 Americans with histories of basal and/or squamous cell carcinomas of the skin. Id. at 7. Supplementation did not reduce the risk of recurrent skin cancers but did significantly reduce the incidence of lung, colon and prostate cancers, respectively by 46%, 58% and 64%. Id.

Three other trials were conducted, the first two in regions of China with high incidences of primary liver cancer (PLC). Id. at 6. In the first trial daily supplementation with 30 to 50 µg for eight years resulted in a drop of PLC incidence to almost one-half (27.2 per 100,000 versus 50.4 per 100,000). Id. Upon withdrawal of selenium from the treated group, PLC incidence rose. Id. In the second trial, members of families with risk of PLC were given either 200 µg daily or a placebo. Id. Over the 2 year study, 1.26% of the controls developed PLC versus 0.69% of those given the selenium supplement. Id. In the third China study, selenium supplementation at 50 µg per day, in a region with the highest mortalities from esophageal cancer in the world, produced a modest protective effect against esophageal and stomach cancer mortality in the general population. Id.

In the remaining two studies, one in India and one in Italy, supplementation with selenium as part of a multi-nutrient-containing supplement resulted in cancer incidence reduction. Id. at 7 In the India study, subjects had precancerous lesions in the oral cavity and were given multi-nutrient supplements containing 100 µg selenium daily for six months and selenium enriched yeast at 50 µg daily for the final six months. Id. The frequency of micronuclei and DNA adducts decreased by 95% in subjects taking selenium with all categories of lesions and by 72% in subjects without lesions. Id. at 4.

The Italian study test subjects supplemented with 200 µg of selenium for five years; the incidence of metachronous adenomas of the large bowel was 5.6% in the group given the supplement versus 11% in the placebo group. Id. There are at least three human trials presently underway examining selenium's cancer risk reduction effects.

Epidemiological studies associate reduced selenium status in humans with increased risk of some cancers. Id. at 4-5. Studies reveal mortality due to lymphomas and cancer of the gastrointestinal tract, peritoneum, lung and breast are lower for men and women in the U.S. in areas that have high concentrations of selenium in forage crops as compared to men and women in areas with low selenium in forage crops. Id. A 27-country comparison revealed that total cancer mortality rate and age-corrected mortality due to leukemia and cancers of the colon, rectum, breast, ovary, and lung varied inversely with estimated per capita selenium intake. Id.

Low selenium levels in serum have been shown in individuals later diagnosed with gastrointestinal and prostatic cancers, thyroid cancer, malignant oral cavity lesions, esophageal and gastric cancers, cervical cancer mortality rates, and colorectal adenomas. Id. at 5. A decade long prospective study on selenium status and cancer incidence indicated that initial plasma

selenium concentrations are inversely related to subsequent risks of both non-melanoma skin cancer and colonic adenomatous polyps. Id. at 5.

C. Scientific Summary Issues

1. Is there an optimum level of selenium to be consumed beyond which no benefit would be expected?

Clinical trials have tested selenium's effectiveness with doses at 200 µg per day. E.g., exh. 1 at 6-7. There is no evidence of an optimum level of selenium to be consumed beyond which no benefit is expected.

Overdosage of nutritional supplements (produced by manufacturing error) and daily intake of selenium in regions of high selenium have been associated with toxicity. Exh. 2 at 420. The most frequently reported adverse reactions of selenosis (or chronic selenium toxicity) are hair and nail brittleness and loss. Id. Other symptoms include skin rash, garlic-like breath odor, fatigue, irritability, and nausea and vomiting. Id. In one recorded overdose case, manufacturing error caused a woman to consume selenium at 27 milligrams per tablet (182 times higher than labeled). Id. That individual's symptoms included almost total alopecia, fingernail loss, nausea, vomiting, sour-milk breath odor, and increased fatigue. In another overdose record, Chinese subjects taking 3.20 to 6.69 milligrams (average of 4 mg) daily lost hair and nails and experienced skin rashes, garlic breath, fatigue, irritability and hyperreflexia. Id.

2. 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?

Selenium intake less than 900 µg daily (for adults) is unlikely to cause adverse reactions. Exh. 2 at 420. Prolonged intakes of selenium in doses of 1,000 µg (or one mg) or more daily may cause the adverse reactions recited above. Id.

3. Are there certain populations that must receive special consideration?

The PDR for Nutritional Supplements cautions that pregnant women and nursing mothers should avoid selenium intakes greater than RDI amounts (60 and 70 µg daily, respectively). Id. It also states that selenium is contraindicated in those who are hypersensitive to any component of a selenium-containing preparation. Id.

4. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

There are no known interactions with drugs in clinical practice for selenium. Id. Intake of selenium and iodide may have synergistic activity in the treatment of Kashin-Beck disease. Id. Concomitant intake of vitamin C and the selenite form of selenium may decrease the absorption of selenium. Intake of vitamin E and selenium may produce synergistic beneficial effects. Id.

D. 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 selenium supplements among the general population, including populations at greater risk of cancer. The Petitioner does not believe that the proposed claims will have an effect on food consuming or eating habits. The only change in nutrient intake resulting from the proposed claims would be for those who choose to supplement their diets with selenium. The effect on such people is expected to be beneficial, reducing the risk of certain cancers and enhancing immune system function.

E. 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. Exh. 3 at 1. In the U.S., one of every

four deaths is from cancer. Id. This year alone, about 1,284,900 new cancer cases are expected to be diagnosed. Id. Since 1990, about 16 million new cancer cases have been diagnosed.⁷ Id. In 2002 about 555,500 Americans are expected to die of cancer, more than 1,500 people a day. Id.

Colorectal cancers (cancers of the colon and rectum combined) are the third most common kind of new cases and deaths in both men and women. Exh. 3 at 20. ACS estimates that in 2002 there will be 148,300 new cases and 56,600 deaths from the disease that year alone. In the United States, while colorectal cancer deaths have decreased from 1992 to 1998 by 1.8%, a person's lifetime risk of developing colorectal cancer is nearly 6%, with over 90% of cases occurring after age 50. Id. For prostate cancer ACS estimates 189,000 new cases will be diagnosed this year. It also estimates that 30,200 deaths in 2002 will occur due to prostate cancer, the second leading cause of cancer in men. Id. ACS estimates that there will be 169,400 new cases of lung and bronchus cancers in 2002, accounting for about 13% of cancer diagnoses. Id. at 11. Finally, ACS estimates 154,900 deaths in 2002 from lung and bronchus cancers, accounting for 28% of all cancer deaths. Id.

Most studies have shown selenium supplementation to be effective in cancer risk reduction at levels of 200 µg per day while the average U.S. diet for selenium intake ranges from 87 to 108 by estimates. Exh. 1 at 3-4; Exh. 2 at 418-419; Exh. 4 at 290-291; and Exh. 4 at 309. Thus, selenium offers a safe, inexpensive, readily accessible means for reducing the risk of certain cancers population wide.

IV. Analytical Method

⁷ 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.

The amount of selenium contained in a dietary supplement that may be a candidate for bearing the health claims can be ascertained by (1) Fluorometric Method or Continuous Hydride Generation Atomic Absorption (HGAA) Method according to the Association of Official Analytical Chemists (AOAC); (2) Fluorometric Determination of Selenium in Biological Material with 2,3-Diaminonaphthalene; (3) Critical Re-appraisal of Fluorometric Method for Determination of Selenium in Biological Materials; (4) Dry Ashing, Hydride Generation Atomic Absorption Spectrometric Determination of Arsenic and Selenium in Foods. See Exhibit 7. The assay methods described in Exhibit 7 are applicable to finished products.

V. Proposed Model Claims

Petitioner proposes the follow model claims for selenium:

Selenium may reduce the risk of certain cancers.

Selenium may produce anticarcinogenic effects in the body.

Multiple studies have shown that oral supplementation with selenium reduces the risk of certain cancers and that selenium has anticarcinogenic effects in the body. Moreover, clinical trials have proven its safety for use by the general population.

VI. Attachments

Attached are copies of the scientific studies (Exhibit 5) and other information 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 eq seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

VII. Environmental Impact

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

VIII. Conclusion and Certification

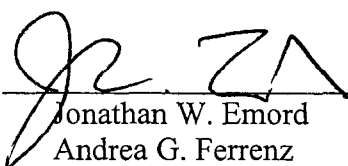
For the foregoing reasons, the Petitioner requests that the FDA approve the proposed health claims. The Petitioner looks forward to working with the FDA in promulgating a regulation authorizing the use of dietary supplement health claims concerning selenium's effect on reducing the risk of certain cancers and its anticarcinogenic effects.

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 their knowledge and belief, the Petition includes all information and views on which the Petitioner relies and is a representative and balanced submission that includes unfavorable information as well as favorable information known by the Petitioner to be pertinent to evaluation of the proposed health claims.

Sincerely,

WELLNESS LIFESTYLES, INC.

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Date submitted: July 10, 2002