DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

APR 28 2003

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RE: Health Claim Petition: Selenium and Reduced Risk of Certain Cancers and Selenium and Anticarcinogenic Effects (Docket No. 02P-0457)

Dear Mr. Emord:

This letter responds to your health claim petition dated July 10, 2002, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Wellness Lifestyles, Inc., pursuant to Section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 343(r)(5)(D)). Your petition requested that the agency authorize health claims for use on dietary supplements of selenium on the relationship between selenium and reduced risk of certain cancers, and between selenium and anticarcinogenic effects. FDA filed the petition for comprehensive review on October 28, 2002, in accordance with section 403(r)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the Act) and with Title 21 of the Code of Federal Regulations (CFR) section 101.70(j).

In a letter dated January 10, 2003, you notified FDA of your client's agreement to extend the deadline for an FDA decision on the petition from January 16, 2003 to February 20, 2003. On January 22, 2003, the agency sent you a letter explaining its concerns associated with the above referenced health claims. FDA sent another letter to you on January 24, 2003, with one additional concern regarding the need for an upper limit of daily intake for selenium dietary supplements. We discussed these concerns with you and your client at a January 27, 2003 meeting. In a letter sent to you on February 11, 2003, the agency offered two disclaimers and explained the circumstances under which it would consider the exercise of enforcement discretion for the proposed claims and disclaimers. On February 12, 2003, you sent us a letter announcing your client's agreement to the terms specified by FDA. On February 21, 2003, FDA issued a letter memorializing the agreement and announcing its intention to issue within 60 days a formal decision on the selenium health claim petition. In a letter dated April 14, 2003, you and your client agreed to a one-week extension, to April 28, 2003, for FDA to issue the formal decision. This letter sets forth that decision.

After reviewing the scientific evidence in your petition and other evidence relevant to your proposed claims, FDA evaluated the claims under the "significant scientific agreement" (SSA)

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standard. FDA's current regulations, which mirror the statutory language in 21 U.S.C. 343(r)(3)(B)(i), provide that the agency may issue a regulation authorizing a health claim only "when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence" (21 CFR 101.14(c)). For the reasons set forth below, your petition does not meet the "significant scientific agreement standard."

FDA next considered whether it would be appropriate to consider the exercise of enforcement discretion for qualified claims about this substance-disease relationship consistent with the agency's approach to evaluating proposed health claims for use on dietary supplements when the SSA standard is not met. This letter outlines FDA's rationale for its determination that the current evidence supporting the dietary supplement selenium health claims does not meet the significant scientific agreement standard, the rationale for why the evidence is appropriate for consideration of qualified claims, and the conditions under which the agency intends to consider the exercise of its enforcement discretion for certain qualified claims with respect to selenium dietary supplements.

I. Safety Review

Under 21 CFR 101.14(b)(3)(ii), the use of selenium at levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful. The safety provisions in question require, for example, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling or under ordinary conditions of use (21 U.S.C. 342(f)(1)). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (21 U.S.C. 342(f)(1)(D)).

Although selenium is known to be an essential mineral, it can also be toxic. The Institute of Medicine (IOM) recently conducted a risk assessment of dietary selenium as part of a larger project to evaluate the human requirements and safety of antioxidant nutrients (IOM, National Academy of Science (NAS) Dietary Reference Intake (DRI) Report, 2000). Adverse effects reported from high intakes of selenium included selenosis (hair and nail brittleness and loss), gastrointestinal disturbances, skin rash, garlic-breath odor, fatigue, irritability, and nervous system abnormalities. Based on considerations of causality, relevance, and the quality and completeness of the database, hair and nail brittleness and loss were selected as the critical endpoints on which to base a Tolerable Upper Intake Level (UL). The IOM recognized the lowest-observed-adverse-effect level (LOAEL) of selenium intake as 900 micrograms (μg) per day, and the no-observed-adverse-effect level (NOAEL) of selenium intake as 800 μg per day.

The IOM characterized the adverse health effects observed at the LOAEL as not severe, but likely not readily reversible and therefore justifying an uncertainty factor of 2. Dividing the NOAEL (800 μg per day) by this uncertainty factor, the IOM concluded that 400 μg per day is the UL of selenium from food and supplements likely to pose no risk of adverse health effects in almost all people. The same NAS/IOM report indicates that current average intake of selenium from foods is estimated to be approximately 100 μg per day.

FDA concludes that the use of selenium as a dietary supplement at levels no greater than 400 ug/day is safe and lawful under 21 C.F.R. § 101.14. An intake of 400 ug/day from a selenium dietary supplement and 100 ug/day from foods would provide a total estimated intake of selenium of 500 ug/day, which is below the NOAEL of 800 ug/day for selenium. Moreover, given the IOM's tolerable upper intake level, the current estimated intake of selenium from foods, and the IOM's NOAEL, FDA would likely consider a selenium dietary supplement that encourages intakes (in the labeling or under ordinary conditions of use) above the IOM's Tolerable Upper Intake Level of 400 μg/d to be misbranded under section 403(a) of the Federal Food, Drug, and Cosmetic Act (the act). Such labeling would likely be misleading under section 201(n) with respect to consequences which may result from the use of the supplement. Further, selenium dietary supplements that encourage intakes (in labeling or under ordinary conditions of use) above 400 ug/d would likely be subject to regulatory action as a misbranded food under section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)), a misbranded drug under section 502(f)(1) of the act (21 U.S.C. 352(f)(1)), and as an unapproved new drug under section 505(a) of the act (21 U.S.C. 355(a)).

One form of selenium, selenium sulfide, is reasonably anticipated to be a human carcinogen.[1] As such, the use of selenium sulfide as a dietary supplement ingredient can not be considered safe and lawful and is thus outside of this consideration for a health claim.

II. Scientific Evaluation

FDA focused its review of the evidence for the relationship between selenium and cancer risk reduction on primary reports of human experimental data, both interventional and observational. We considered results from this review to also be applicable to anticarcinogenic effects because it is synonymous with cancer risk reduction. Of the 101 references included in your petition, 30 are human studies (5 interventional and 25 observational) relating selenium to cancer-related outcome measures. The remaining 71 references were not considered because they did not directly relate diet to cancer outcomes in humans (e.g., reports of plant metabolism of selenium,

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[1] Department of Health and Human Services, National Institute of Environmental Sciences, National Toxicology Program. The Report on Carcinogens, Tenth Edition. 2002. Http://ehp.niehs.nih.gov/roc/tenth/profiles/s160sele.pdf

experimental animal model studies, human studies other than cancer studies, general review articles).

A. Assessment of Intervention Studies

Reports from five intervention cancer prevention trials[2] were submitted with the petition. Only one of these trials, the Nutritional Prevention of Cancer Trial, tested the relationship between selenium and cancer risk under conditions applicable to the U.S. population (Clark et al., 1996). This randomized, double-blind, placebo-controlled trial of 1,312 subjects (75% male) was designed to evaluate the effect of 200 μg supplemental selenium per day on reduced risk of basal and squamous cell carcinomas of skin in persons with a prior history of non-melanoma skin cancer, i.e., basal or squamous cell carcinomas. Although the trial was designed as a 5-year intervention, the actual time on treatment was 4.5 ± 2.8 years. This study found no beneficial effects of selenium supplementation on the incidence of the non-melanoma skin cancer which was the primary cancer endpoint of this study.

In addition to the primary outcome for which the study was designed, post-hoc analyses of cancer endpoints for which the study was not designed (i.e., "secondary" end points) suggested that selenium supplementation may reduce the risk of total and certain cancers (i.e., prostate, lung, and colorectal) (Clark et al., 1996). Apparent beneficial effects for secondary cancer endpoints added late in the trial require independent confirmation. Post-hoc evaluations of diet/cancer relationships for which the original study was not designed must be interpreted cautiously, because they are primarily useful for hypothesis-generation, not for demonstration of a relationship. Thus, this sole intervention trial done under conditions applicable to the U.S. population showed no benefit for the cancers for which it was designed but suggested other beneficial selenium/cancer relationships which require independent confirmation through additional studies.

On the basis of the hypotheses generated through these post-hoc analyses, the National Cancer Institute of the National Institutes of Health, has initiated an intervention trial to evaluate the potential benefits of selenium supplementation on reducing the risk of prostate cancer (Klein et al., 2003). The initial report from the Nutritional Prevention of Cancer Trial (Clarke et al., 1996) evaluated data available through December 1993, at which time there was an average of 6.4

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[2] These trials are: Nutritional Prevention of Cancer Trial (Clark et al., 1996); the Linxian General Population Trial (Blot et al., 1993; Blot et al., 1995; Li et al., 1993); Qidong Primary Liver Cancer Trial (Yu et al., 1991); Genova, Italy Colorectal Recurrent Adenoma Trial (Bonelli et al., 1998); and Andhra Pradesh, India Precancerous Lesions of Oral Cavity Trial (Prasad et al., 1995).

years of follow-up data. Subsequent post-hoc analyses of 7.9 years of follow- up data from this study continued to find reductions in total cancer and prostate cancer risk among the selenium-supplemented subjects (Duffield-Lillico et al., 2002; and Reid et al., 2002), but the reductions in lung and colorectal cancer risk initially reported by Clark et al. (1996) were no longer observed. Furthermore, sub-group analyses indicated that the protective effect of selenium may be confined to males and also may be confined to subjects with the lowest plasma selenium levels. In these post-hoc analyses, subjects with plasma selenium levels at the average U.S. levels experienced no reduction in risk. In fact, if the lowest and highest tertiles from these analyses were compared directly, those in the highest tertile experienced a greater than 2-fold increased risk compared with those in the lowest tertile. The authors commented that "the pattern we observed was clearly unpredicted and unsettling." Given that these data are derived from post-hoc analyses, further studies would be needed to reach any definitive conclusions regarding these findings.

Of the four remaining intervention trials, two of these studies were done in China (Blot et al., 1993; Blot et al., 1995; Li et al., 1993; Yu et al., 1991), one in India (Prasad et al., 1995), and one in Italy (Bonelli et al., 1998).

The intervention trial reported by Yu et al. (1991) of primary liver cancer represents preliminary reports of three separate trials in Quidong county of China, which has an exceptionally high rate of this cancer. The report notes that the recognized potential risk factors responsible for the high liver cancer rate in this county are aflatoxin contamination, hepatitis B viral infection, and water pollution. Supplemental selenium of 15 ppm was given as either anhydrous sodium selenite or selenium-enriched yeast tablets. The baseline blood selenium levels of the subjects in these trials was about 10 micrograms/dL, which is below the 5th percentile of blood selenium levels in the U.S. (NHANES III, 1988-1994 data). The results from these trials indicate that the extremely high incidence of primary liver cancer in some localities within this malnourished population in Quidong county could be reduced by adding selenium to the diet. Although this effect can be attributed directly to selenium *per se*, the physiological effects in malnourished individuals could be quite different from the effects of the same nutrient supplements in well nourished individuals. Moreover, the etiologies of these cancers may differ between these two countries. Thus, there is uncertainty as to whether these results are relevant to the U.S. population

The General Population phase of the Linxian Trial (Blot et al., 1993; Blot et al., 1995) examined the effect of a multi-nutrient supplement (beta-carotene, vitamin E and selenium) on stomach cancer in a malnourished Chinese population at high risk for this cancer. The General Population phase of this trial (Blot et al., 1993) reported lower stomach cancer mortality among subjects taking the selenium-containing supplement. The Dysplasia phase of the trial (Li et al., 1993), in which subjects diagnosed with esophageal dysplasia received either a multivitamin-mineral supplement or a placebo, reported no benefit of the selenium-containing supplement on esophageal or gastric cancer mortality or incidence. These results, although not consistent,

provide some evidence that a selenium-containing supplement had some effect on lowering cancer mortality in a malnourished population with a very high gastric cancer rate. However, since the supplement was a cocktail of nutrients, these results cannot provide clear evidence of an effect of selenium *per se*. The relevance of these results to the general U.S. population, which does not have the same high incidence of stomach cancer or malnutrition, is uncertain.

The intervention trial reported by Prasad et al. (1995) was designed to examine the effects of a multiple-nutrient supplement cocktail (vitamin A, riboflavin, zinc and selenium) in "reverse smokers of chutta"[3] in India on potential biomarkers of genetic damage in cells scraped from inside the subjects' cheeks. This was not a cancer risk reduction study because these endpoints (i.e., frequency of micronucleated cells and carcinogen DNA adducts as indicators of DNA damage) are not recognized as validated surrogate measures of cancer risk. Therefore, FDA did not include this study in its evaluation.

The intervention trial reported by Bonelli et al. (1998) was designed to examine the effects of multiple nutrient supplements (selenium, zinc, vitamin A, vitamin C and vitamin E) on incidence of colorectal adenomatous polyps[4]. Colorectal carcinomas grow from such polyps, although most polyps remain benign. This report states that recruitment of study subjects was stopped at the end of 1995, and that the treatment period was 5 years. Thus, the results presented in 1998 represent a preliminary report from the yet uncompleted study. The report included in the petition (petition, tab 7) is a paper printed in a conference proceeding. One of the four pages of this report is missing and the paper lacks sufficient detail to evaluate study quality. FDA has not found any final or published peer-reviewed reports of this study. As such, there is no evidence that this trial was completed, and therefore there are no results for FDA to consider.

In summary, the only available intervention trial with direct applicability to the U.S. population showed no effect of selenium supplementation on the cancer endpoint for which the study was designed, i.e., non-melanoma skin cancer. Post-hoc analyses of this study for cancer endpoints not included in the initial trial design suggest possible reductions in the risk of total and certain cancers for which independent confirmation is required (i.e., prostate cancer, lung, and colorectal). One study in China (Yu et al., 1991) indicated that selenium per se reduced the risk of primary liver cancer in a malnourished population with an exceptionally high rate of this cancer. Another study in China (Blot et al., 1993; 1995) reported that a multi-nutrient supplement containing selenium reduced the risk of stomach cancer in a malnourished population with a high risk of this cancer. However, this study did not show any effect on early biomarkers of stomach cancer risk. Although the Blot, et al. (1993 and 1995) and Yu, et al., 1991

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[3] A reverse smoker of chutta is a person that inserts the lit end of a rolled tobacco leaf into their mouth

[4] According to Dorland's Medical Dictionary, 23rd edition polyp is defined as a pedunculated or sessile growth arising from the mucosa and extending into the lumen of a body cavity. Polyps are the result of hypertrophy of the mucous membrane or are true tumors (Dorland's Medical Dictionary, 23rd Edition).

studies suggest an effect of selenium on reduced risk of two types of cancer the relevance of these findings to the U.S. population is uncertain.

B. Assessment of Observational Studies

Your petition included 25 observational studies pertaining to selenium and cancer.[5] These studies included 16 prospective cohort studies, approximately one-third of which were from U.S. populations, and 3 retrospective case-control studies. The remainder of the observational studies were ecological and cross-sectional. FDA identified 11 additional observational studies through a literature search.[6] None of these studies was able to isolate the effect of selenium intakes from other nutrients. Among all 36 identified observational studies, approximately one-half support an association between selenium intake and reduced cancer risk, and one-half do not support such an association. Thus, overall the available results from observational studies are equivocal.

We do note that there was some consistency within observational study results for two cancer sites (breast and prostate). The results of the four observational studies that focused on breast cancer were consistent in finding no association of selenium intake and breast cancer risk in women.[7] The results of four other observational studies that assessed associations of breast cancer risk and selenium intake in women were also consistent in finding no association.[8] The

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[5] These include: Brooks et al. (8), Clark et al. (15), Coates et al. (20), Garland et al. (35), Glattre et al. (36), Guo et al. (38), Helzlsouer et al. (39), Hunter et al. (41), Kabuto et al. (52), Kok et al. (54), Mark et al. (57), Navarrete et al. (61), Nomura et al. (63), van Noord et al. (64), Rogers et al. (70), Russo et al. (71), Salonen et al. (72),Schrauzer et al., (73), Ujiie et al. (83), van den Brandt et al. (84), van den Brandt et al. (85), van't Veer et al. (86), Willet et al. (92), Yoshizawa et al. (97), and Yu et al. (101). The tab numbers by which these articles are filed in Exhibit 5 of the petition are given in parentheses.

[6] (1) Menkes et al. NEJM 315:1250-1254. 1986. (2) Kok et al. NEJM 316:1416. 1987. (3) Meyer and Verreault. Am J Epidemiology. 125:917-919. 1987. (4) Schober et al. Am J Epidemiology. 126:1033-1041. 1987. (5) Virtamo et al., Cancer. 60:145-148. 1987. (6) Michaud et al., Cancer Epidemiol Biomarkers Prev. 11:1505-1506. 2002. (7) Nelson et al., Diseases of the Colon and Rectum. 38:1306. 1995. (8) Peleg et al., Med Oncol Tumor Pharmacother. 2:157-163. 1985. (9) Knekt, et al., J National Cancer Inst. 82:864-868. 1990. (10) Zeegers et al., Cancer Epidemiology, Biomarkers & Prevention. 11:1292-1297. 2002. (11) Hardell et al., European J Cancer Prevention. 4:91-95. 1995.

[7] Hunter et al. (41), van Noord et al. (64), van't Veer et al. (86), and Meyer and Verreault, 1987.

[8] Garland et al. (35), Kok et al., (54), Knekt et al., 1990, and Rogers et al. (70).

four observational studies that focused on prostate cancer were consistent in finding a significant inverse association between prostate cancer and selenium intake.[9]

The equivocal nature of these results overall from the observational studies is observed both within types of observational studies (e.g., within prospective cohort or within retrospective case control studies) and across types of observational studies. Therefore, although there can be found, within the observational results, some evidence in support of a relationship of selenium intake and reduced risk of certain cancers (e.g., prostate cancer), the whole body of observational evidence does not provide strong evidence for such a relationship.

C. Assessment of Authoritative Statements

FDA also considered whether other authoritative bodies had reviewed the scientific evidence on dietary supplement selenium intakes and reduced risk of certain cancers. The Food and Nutrition Board of the Institute of Medicine, the National Academy of Sciences, as part of an evidence-based process to update Dietary Reference Intakes (DRIs) for the U.S. population, evaluated the relationship of selenium intakes to cancer risk reduction (IOM, NAS DRI Report, 2000). It concluded that the available evidence was insufficient to develop a DRI for selenium based on reduction in cancer risk and that additional intervention trials are required before the validity of this relationship can be confirmed. This strongly suggests that there is not significant scientific agreement among qualified experts that a relationship exists between selenium intake and reduction in risk of certain cancers.

III. Agency's Consideration of Significant Scientific Agreement

There were reports from 5 intervention and 36 observational studies available for evaluating the relationship of selenium intake to reduced risk of certain cancers. In general, intervention studies are more persuasive than observational studies (Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplement. December 22, 1999). Of the 5 intervention studies, only the Nutritional Prevention of Cancer Trial had direct applicability to the general U.S. population. This study found no benefit of selenium supplementation on reducing the risk of non-melanoma skin cancer, the cancer endpoint for which the study was designed. Post-hoc analyses of secondary cancer endpoints for which the study was not designed suggested risk reduction for certain cancers. However, post-hoc analyses are primarily useful for hypothesis-generation, not documentation of a relationship. One study in China indicated that selenium *per se* reduced primary liver cancer in a malnourished population with a high rate of this cancer (Yu et al., 1991). In another study in China (Blot et al., 1993; 1995), selenium containing multi-nutrient supplements reported a reduction in stomach cancer in a malnourished population with a high risk for this cancer. However, applicability of results from these two studies to a well nourished U.S. population in

[9] Brooks et al. (8), Willet et al. (92), Yoshizawa et al. (97), and Hardell et al., 1995.

which the etiologies of these cancers may differ from those in China is uncertain. Additionally, results from the Blot et al. studies (1993; 1995) may not be attributed with certainty to selenium *per se*. The two remaining intervention trials were not considered useful for this review, because the Prasad et al. (1995) trial did not study cancer risk, and there is no evidence that the trial by Bonelli et al. (1998) was ever completed, thus, there are no results to consider from these studies. Thus, evidence from intervention trials in support of a relationship between dietary selenium and reduced cancer risk is limited to results from the two studies conducted in China. Because the subjects were malnourished and cancer etiologies in these two countries may differ, the relevance to the general healthy U.S. population is uncertain. The evidence from observational studies with respect to overall cancer risk in both males and females is equivocal. The IOM expert panel recently found insufficient evidence to base a selenium DRI on a relationship between selenium intake and reduction in cancer risk (NAS DRI Report, 2000). Therefore, based on its evaluation of the totality of the publicly available scientific evidence, the agency concludes that there is not SSA among qualified experts that a relationship exists between dietary supplement selenium intake and reduced cancer risk.

IV. Agency's Consideration of Qualified Health Claims

For claims that do not meet the significant scientific agreement standard, FDA considers whether the exercise of enforcement discretion might be appropriate for qualified health claims about the relationship between the substance and the disease. After reviewing the scientific evidence in your petition and other relevant scientific evidence, FDA concludes that much of the data do not support a relationship between selenium dietary supplement intake and reduced risk of certain cancers. Although there is some basis for qualified health claims for dietary supplement selenium intake and reduced risk of certain cancers, the evidence is limited and not conclusive. There was only one intervention study that showed an effect of selenium *per se* on reduced risk of primary liver cancer (Yu et al., 1991). This study does suggest a relationship of selenium dietary supplement intake and reduced risk of this cancer in the select population studied, but its relevance to the U.S. population is uncertain because of differences in population nutritional status and in cancer etiologies between the two countries. One other intervention trial suggests a relationship between selenium dietary supplement intake and reduced risk of stomach cancer (Blot et al., 1993; 1995). However, similar to the Yu et al., 1991 study the relevance of the results from the Blot, et al. studies to the U.S. population is uncertain. Additionally because the Blot et al. studies used a test product that was a multi-nutrient supplement, it is not possible to attribute these effects to selenium *per se*. There are four observational studies that show an association between selenium intake and reduced risk of prostate cancer. These findings from observational studies are consistent with the post-hoc analyses of secondary cancer end points in a U.S. intervention trial (Clarke et al., 1996). Therefore, although much of the available evidence is either not supportive of, or equivocal relative to, the effect of selenium intake on cancer risk reduction, some evidence from two of the intervention trials and from four of the observational studies provide limited and inconclusive evidence to suggest a possible relationship between selenium intake and reduced risk of certain cancers.

V. Other Requirements

Selenium dietary supplements bearing the qualified claims for which FDA has indicated that it intends to consider the exercise of its enforcement discretion must still meet all applicable statutory and regulatory requirements under the act. For example, such supplements must be labeled consistent with 21 CFR § 101.36(b)(3). Dietary supplements also must not pose an unreasonable risk of illness or injury to the consumer or contain substances that may render the product injurious to health, or be otherwise adulterated or misbranded.

VI. Conclusions

We have considered the scientific evidence submitted with your petition and, as appropriate, have also considered other pertinent scientific evidence. Our conclusion is that there is not significant scientific agreement about the science underlying the statements that "Selenium may reduce the risk of certain cancers" and that "Selenium may produce anticarcinogenic effects in the body." However, the science provides sufficient evidence for qualified health claims provided that the qualified claims are appropriately worded so as to not to mislead consumers. Thus, FDA proposed the qualified claims as presented below, which your clients agreed to as reflected in your letter dated February 12, 2003.

> Claim 1:
> "Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive."
>
> Claim 2:
> "Selenium may produce anticarcinogenic effects in the body. Some scientific evidence suggests that consumption of selenium may produce anticarcinogenic effects in the body. However, FDA has determined that this evidence is limited and not conclusive."

FDA intends to consider exercising enforcement discretion for the above qualified claims when: (1) the applicable disclaimer is placed immediately adjacent to and directly beneath your claim(s), with no intervening material, in the same size, typeface, and contrast as the claim itself; (2) the supplement does not recommend or suggest in its labeling, or under ordinary conditions of use, a daily intake exceeding 400 μg of selenium per day; and (3) the claim meets the general requirements for health claims in 21 CFR 101.14, except for the requirement that the evidence for the claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether

it necessitates a change in this decision. For example, scientific evidence may later become available that will support significant scientific agreement or that will no longer support the use of a qualified claim, or that may raise safety concerns about the level of intake that FDA has outlined for the safe use of selenium supplements. If and when such information becomes available, FDA intends to inform you of this new information and its implications by letter.

Sincerely,

Virginia Z. Williams

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

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