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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Docket No. 2007N-0464 – Health Claims and Qualified Health Claims;
Dietary Lipids and Cancer, Soy Protein and Coronary Heart Disease,
Antioxidant Vitamins and Certain Cancers, and Selenium and Certain Cancers;
Reevaluation; Opportunity for Public Comment

Dear Sir/Madam:

On behalf of Nutraceutical Corporation (Nutraceutical), we are submitting the following comments in response to the Food and Drug Administration's (FDA's) notice of intent to reevaluate the scientific evidence for two previously authorized health claims (dietary lipids and cancer; soy protein and risk of coronary heart disease) and two qualified health claims that were the subject of letters of enforcement discretion (antioxidant vitamins and risk of certain cancers; selenium and certain cancers).¹ Nutraceutical is one of the largest manufacturers and marketers of dietary supplement products sold to health food stores in the United States, with approximately 5,000 unique SKUs of dietary supplements manufactured, packaged, or distributed in or from its facilities. Nutraceutical also owns and operates retail health and natural food stores.

While Nutraceutical does not regularly make claims for the products it markets, it supports the use of sound science as the basis for health claims and qualified health claims when they are used in food and dietary supplement labeling. For a number of reasons, however, Nutraceutical believes that FDA's proposed reevaluation of the above-referenced claims is premature and unnecessary at this point in time. As discussed in greater detail below,

¹ 72 Fed. Reg. 72,738 (Dec. 21, 2007).

February 15, 2008

Page 2

the new data contained in the references cited in the Federal Register notice are unlikely to have a material impact on the continuing validity of the claims. The scientific evidence supporting each claim at issue has evolved only incrementally since FDA's prior evaluation of each claim. There will no doubt be a time when one or more previously authorized health claims or qualified health claims may need to be reevaluated to reflect then-current science. The threshold for such a reevaluation, however, should be significantly higher than that corresponding to the new data referenced in the Federal Register notice. Consumers are constantly bombarded with mixed and changing messages regarding the healthfulness of various nutrients and dietary practices, leading to confusion and a general distrust of nutritional health science. Overly-frequent reevaluation of existing authorized health claims and qualified health claims based on incremental scientific developments will only add to this growing problem.

Moreover, Nutraceutical respectfully submits that, given the limited new data impacting the validity of the existing claims, FDA's proposed reevaluation is a poor use of scarce agency resources, particularly in light of competing priorities at the agency. For example, on December 22, 2006, the Dietary Supplement and Nonprescription Drug Consumer Protection Act was signed into law.² Affected firms, such as Nutraceutical, had to comply with the new labeling requirements within one year of the Act's passage. To aid the dietary supplement industry, Congress directed FDA to issue a guidance within nine months of the Act's passage. In December of 2007, unable to issue guidance due to "competing priorities," the agency announced that it would instead give firms an additional one-year period beyond the statutory deadline to bring their labeling into compliance. Nutraceutical does not raise this episode to be critical. Indeed, industry recognizes the competing priorities FDA faces (particularly as it implements the Food and Drug Administration Amendments Act of 2007 and the President's Action Plan for Import Safety) and was grateful for the extension. Rather, Nutraceutical would simply note that during a period in which the agency struggles to accomplish even its *statutory directives*, it should not spend scarce time and money reevaluating existing health claims based on such little new evidence.

Below are Nutraceutical's specific comments regarding FDA's proposed reevaluation of each affected health claim and qualified health claim, as well as its comments on FDA's proposed approach to evaluate specific forms of cancer in conjunction with those claims.

² Pub. L. No. 109-462.

I. Dietary Lipids and Cancer

FDA is proposing to reevaluate the health claim regarding the relationship between dietary lipids (fat) and cancer that the agency authorized in 1993 after an extensive and rigorous review of the scientific evidence examining the relationship.³ The primary impetus for FDA's proposal to reevaluate this claim appears to be a report published by the Institute of Medicine (IOM) of the National Academy of Sciences for the purpose of establishing Dietary Reference Intakes (DRIs) for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (IOM Report).⁴ The purpose of the IOM Report was to establish reference values for specific nutrients. These reference values may include Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL), although it was not possible to assign all of these values for all nutrients with the data available to IOM. In the case of macronutrients, IOM also determined Acceptable Macronutrient Distribution Ranges (AMDRs), expressed as a percentage of total energy intake.

Although an examination of chronic disease risks associated with dietary intakes of each nutrient was considered in conjunction with IOM's determination of the DRI values, a critical analysis of these substance/disease relationships in the context of health claims was *not* an area of focus or the purpose of the IOM Report. This is perhaps best illustrated by the fact that the discussion of the relationship between intake of total dietary fat and risk of cancer is limited to a fraction of a page (discussing a handful of studies) out of this 1,331 page report.⁵ The references cited within this brief section do not disprove a relationship between total fat intake and cancer. Some recent studies cited in the IOM report have failed to detect a relationship between total fat intake and specific cancers, while others did detect such a relationship. The failure to detect a relationship in a study, however, does not necessarily indicate that no such relationship exists; it may be that the study was not sufficiently powerful to detect a relationship with statistical significance or that it was flawed in design. Thus, when results are "mixed," as was the case with colon cancer, prostate cancer, and lung cancer, the studies detecting a relationship through the background "noise" of the data are more

³ 58 Fed. Reg. 2,787 (Jan. 6, 1993); 21 C.F.R. § 101.73.

⁴ Institute of Medicine, National Academy of Sciences "Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids," National Academy Press, Washington, D.C. (2005).

⁵ *See id.* at 808.

February 15, 2008

Page 4

convincing as to the existence of the relationship than are the studies that merely failed to do so. Moreover, a meta-analysis of 23 studies cited in the IOM report reported a small but significant association between fat intake and breast cancer with a relative risk of 1.01 and 1.21 from cohort and case-control studies, respectively.⁶

Although IOM found the data regarding the relationship between total fat and cancer (and other chronic diseases) to be unsuitable for establishing a UL for this nutrient, this is not tantamount to a finding that no such relationship exists. Nutraceutical respectfully submits that it would be premature to call into question the rigorous literature review and analysis that led to the 1993 rulemaking (which focused specifically on the nutrient/disease relationship and examined well over 100 scientific papers) based on the cursory review and discussion on this topic found in the IOM report.

II. Soy Protein and Coronary Heart Disease (CHD)

In response to a petition filed under 21 C.F.R. § 101.70, FDA conducted a rigorous and comprehensive literature review of the relationship between soy protein and risk of coronary heart disease, primarily using blood total cholesterol and low density lipoprotein (LDL) cholesterol levels as endpoints.⁷ FDA published a final rule in 1999 authorizing a health claim describing the relationship between a diet including 25 grams of soy protein per day (as part of a diet low in saturated fat and cholesterol) and reduced risk of heart disease.⁸ FDA gave particular weight to 14 clinical trials that met rigorous selection criteria based on the comprehensive report "Diet and Health" issued by the National Academy of Sciences and "The Guide to Clinical Preventive Services" issued by the U.S. Preventive Services Task Force.⁹ These inclusion criteria resulted in the consideration of studies that: (1) included subjects representative of the U.S. population; (2) were well controlled; (3) reported information on intakes of saturated fat and cholesterol; and (4) avoided the problems associated with small

⁶ *Id.*; Boyd NF, Martin LJ, Noffel M, Lockwood GA, & Trichler DL (1993), "A meta-analysis of studies of dietary fat and breast cancer risk," BR. J. CANCER 68:627-636.

⁷ See 63 Fed. Reg. 62,977 (Nov. 10, 1998).

⁸ 64 Fed. Reg. 57,700 (Oct. 26, 1999); 21 C.F.R. § 101.82.

⁹ 63 Fed. Reg. at 62,980-81.

sample size, lack of a placebo, and other design problems.¹⁰ Although the lowering of total and LDL cholesterol generally observed in the studies was “modest,” FDA determined that it could result in a significant reduction in CHD risk.¹¹ The 25 g per day intake of soy protein was deemed to be a “reasonable, effective amount,” and correlated with an estimate suggested by a meta-analysis and confirmed by a subsequent study that established a dose-response relationship and found reductions in total and LDL cholesterol of 4 and 6 percent, respectively, with ingestion of 25 g per day of soy protein.¹²

In response to a July 2004 report published by the Agency for Healthcare Research and Quality (AHRQ), “Effects of Soy on Health Outcomes,” FDA now proposes to reevaluate the scientific evidence on soy protein and the risk of CHD. The AHRQ meta-analysis yielded median reductions of 2.5 and 3 percent, respectively, for total and LDL cholesterol, for consumers of *soy products* generally, including refined soy proteins, soy-derived isoflavones, whole soy beans, soy flour, soy milk, soy drink, tofu, miso, and other processed soy bean products.¹³ Moreover, AHRQ noted that a net negative effect on total and LDL cholesterol attributable to soy products was found in “most studies.”¹⁴

Of particular importance, the AHRQ report did not attempt to quantify the reduction in total or LDL cholesterol attributable to soy protein *per se*. As a result, the AHRQ report on soy products is of little utility in reevaluating the continuing validity of the significant scientific agreement previously found to support the authorized health claim on soy protein and risk of CHD. To the extent the AHRQ report has any bearing on the claim, it would be to maintain the status quo. The modest but significant reductions in total and LDL cholesterol found by the AHRQ report to be attributable to soy product intervention suggest that modification of the current health claim, which may serve to increase consumption of soy products in general, would not be beneficial to the public health. Nutraceutical therefore respectfully submits that the AHRQ report is not an appropriate trigger for reevaluation of the existing health claim.

¹⁰ 64 Fed. Reg. at 57,707.

¹¹ *Id.* at 57,709.

¹² *Id.* at 57,712; 63 Fed. Reg. at 62,991.

¹³ AHRQ, “Effects of Soy on Health Outcomes” at 32, 42.

¹⁴ *Id.* at 31, 42.

February 15, 2008
Page 6

III. Antioxidant Vitamins and Risk of Certain Cancers

FDA's enforcement discretion letter of April 1, 2003 regarding qualified health claims for antioxidant vitamins (specifically, vitamins E and C) and risk of certain cancers was the result of over a decade of agency deliberation on the matter and judicial intervention.¹⁵ The qualifying language approved in the claims clearly conveys the inconclusive nature of the scientific evidence. For example, one of three similar claims approved in the letter is:

Some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive.

[Emphasis added.] Citing the May 2006 AHRQ report "Multivitamin/Mineral Supplements and Prevention of Chronic Disease," FDA now proposes to reevaluate the approved qualified health claims.

As an initial matter, we would note that the AHRQ report does not even address the efficacy of vitamin C on cancer prevention. As for vitamin E, the AHRQ report cites only two studies that were published subsequent to FDA's 2003 enforcement discretion letter.¹⁶ One of those two studies found "moderate" but temporary protective effects on colorectal cancer.¹⁷ The other study, which failed to detect any effect on cancer risk, involved only healthy women age 45 or older and supplementation with vitamin E every other day.¹⁸ Such a study hardly seems the basis to revisit a decision that resulted from an order of the DC Circuit Court of Appeals and a decade of agency deliberation.

¹⁵ See also FDA Letter, "Re: Petition for Health Claim: Antioxidants and Cancer (Docket No. 91N-0101)," (May 4, 2001) (citing *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)).

¹⁶ See AHRQ, "Multivitamin/Mineral Supplements and Prevention of Chronic Disease" at 39.

¹⁷ J. Virtamo, P. Pietinen, and JK. Huttunen, *et al.*, "Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up," *JAMA* (2003), 290:(4) 476-85.

¹⁸ IM. Lee, NR. Cook, and JM. Gaziano, *et al.*, "Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial," *JAMA* (2005), 294:(1) 56-65.

February 15, 2008
Page 7

In light of the discussion above, Nutraceutical believes that the AHRQ report does not have any material impact on the continuing validity of the existing approved qualified health claims for antioxidant vitamins and risk of certain cancers. Indeed, based on the differing conclusions of the two cited studies, it is clear that the qualifying language in the approved claims still accurately describes the inconclusive nature of the scientific evidence. Nutraceutical, therefore, respectfully submits that agency resources would be better spent in other endeavors, such as prompt review and decisions on future health claim and qualified health claim petitions.

IV. Selenium and Risk of Certain Cancers

FDA's enforcement discretion letter of April 28, 2003 authorizes two similar qualified health claims regarding selenium and the risk of certain cancers:

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."

The May 2006 AHRQ report, "Multivitamin/Mineral Supplements and Prevention of Chronic Disease," examined the evidence on the efficacy of selenium in cancer prevention and characterized the overall strength of the evidence as "moderate."¹⁹ (As an initial matter, Nutraceutical notes that the Federal Register notice that is the subject of these comments incorrectly states that the AHRQ report characterized the strength as "low."²⁰) The AHRQ summary on selenium and cancer discussed one paper that was published subsequent to FDA's enforcement discretion letter. This was a subgroup analysis of a previously published study,

¹⁹ AHRQ, "Multivitamin/Mineral Supplements and Prevention of Chronic Disease" at 46.

²⁰ 72 Fed. Reg. at 72,739.

February 15, 2008
Page 8

which showed that the effect of selenium on prostate cancer was greatest in those with a baseline prostate specific antigen (PSA) level of less than 4 ng/mL.²¹

Nutraceutical is of the opinion that the data discussed in the AHRQ report do not materially change the strength of the evidence relating to selenium and cancer risk, as compared to the state of the evidence in 2003. If anything, AHRQ's conclusion may support a stronger positive statement than is reflected in the existing approved qualified health claims. Nutraceutical assumes that this is what the agency had contemplated when commenting in the Federal Register notice that the more recent evidence may have the effect of strengthening the substance-disease relationship for one or more of the qualified health claims.²² Nutraceutical does not object to the strengthening of qualified health claims to reflect new scientific evidence. In this instance, however, Nutraceutical respectfully submits that the incremental effect of the more recent evidence does not justify an expenditure of agency resources on its own initiative to reevaluate the health claim on selenium and cancer risk. Rather, this is a task better left until such time as marketing interests inspire a manufacturer or distributor to petition the agency for such a claim.

V. Comments on Claims Relating to Specific Cancers as Opposed to "Certain" Cancers

In the Federal Register notice that is the subject of these comments, FDA noted that its "current approach is to evaluate each form of cancer individually in a health claim or qualified health claim."²³ Nutraceutical does not disagree that, going forward, this is an appropriate approach in situations where there is good evidence for a preventive effect as to specific types of cancer, but an absence of effect as to others. With respect to the health claims and qualified health claims that are the subject of these comments, however, Nutraceutical does not believe that specific cancer claims are appropriate. For each of these nutrient/disease relationships, there are varying degrees of evidence regarding the association between the nutrient and

²¹ AHRQ, "Effects of Soy on Health Outcomes" at 45; AJ. Duffield-Lillico, BL. Dalkin, and ME. Reid, *et al.*, "Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial," *BJU INT.* (2003), 91:(7) 608-12.

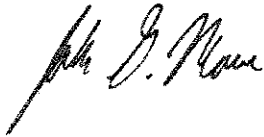
²² 72 Fed. Reg. at 72,738.

²³ *Id.* at 72,740.

February 15, 2008
Page 9

various specific cancers. Attempting to describe the strength of the relationship in conjunction with each type of cancer would result in unwieldy verbiage that would be bewildering to the consumer and difficult to include on product labels. Moreover, where modest evidence exists as to a preventive effect on each of several types of cancers, collectively, this may synergize to stronger evidence of a general anti-carcinogenic effect. This is especially true where, as here, there are plausible mechanisms for a general protective effect from a reduction in total fat intake or an increase in intake of antioxidant vitamins and selenium. If FDA does ultimately decide to authorize specific cancer claims for the nutrient/disease relationship claims that are the subject of these comments, Nutraceutical requests that FDA should continue to permit the current claims as well.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "John G. Moore". The signature is written in a cursive style with a large initial "J" and "M".

John G. Moore