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

RE: [Docket No. 2007N-0464] 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 FR Doc. E7-24813 (December 21, 2007).

To whom it may concern,

The Council for Responsible Nutrition (CRN) appreciates the opportunity to comment on this notice provided by FDA. Health claims meeting the criteria of significant scientific agreement (SSA) and qualified health claims (QHC) represent two very important ways dietary supplement and functional food manufacturers convey to consumers the relevant health benefits of their products. These assist consumers in making informed choices about which product(s) to purchase, and therefore it is important that these claims be accurate, truthful, not misleading and based on sound science.

The science of nutrient-disease relationships is a continuously evolving process; no one study represents the definitive “final word”. We therefore recognize and appreciate FDA’s efforts to reevaluate the evidence base on which the claims and their specific language are based. With this submission to the Docket, we will attempt to provide the Agency some constructive input that we hope will be considered during the review process. Since this is relatively early in the reevaluation process (especially for the SSA claims) our comments are intended to be brief and broad in scope. These will be limited to three of the four claims presented in the notice: Soy protein and risk of coronary heart disease (CHD), antioxidant vitamins and risk of certain cancers and selenium and risk of certain cancers.

Soy protein and CHD

CRN recommendation: FDA should not alter the current language of the SSA claim related to soy protein, and should consider whether and to what extent the body of evidence supports the addition of language relating to other soy components.

On October 26, 1999, FDA published the final rule authorizing the soy and coronary heart disease (CHD) SSA claim in the *Federal Register* (<http://www.cfsan.fda.gov/~lrd/fr991026.html>). The 1999 FDA authorized SSA claim reads, “25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease”. CRN proposes that, at a minimum, this basic language remain intact, and that FDA consider, based on new science since 1999, adding additional language to describe the benefits of other soy components. We believe there is sufficient scientific evidence that has been published since 1999 that continues to support the inverse relationship between soy protein consumption and CHD risk. If a revision of the language is deemed necessary, the data suggest that it should be related to the possible contribution of other soy components (such as isoflavones) in addition to soy protein, to the reduction of CHD risk.

From a cursory review of the literature we identified approximately 50 relevant publications involving the effect of soy components on various CHD risk factors or biomarkers since the claim’s original authorization in 1999. These are largely composed of randomized, controlled trials (RCTs), followed by reviews and meta-analyses. Overwhelmingly, the conclusions of these publications are in favor of a beneficial effect of soy or soy components on various outcome measures related to cardiovascular health or disease risk. Indeed, a series of well-designed RCTs of modest size and duration have demonstrated that ≥ 15 g/day soy protein results in statistically significant beneficial effects on total serum cholesterol, LDL-C, HDL-C, triglycerides, homocysteine, blood pressure, or some combination of these (1-10, 11Tonstad, 2002 #471, 12, 13). Study populations included hypercholesterolemic adults, overweight adults, diabetics and post-menopausal women. While modest, these effects have been generally consistent, despite differences in study design, population, dosage, etc... Consistent with the outcomes obtained by these RCTs are recently published review articles (14-18) and a meta-analysis (19) which have collectively concluded that soy protein consumption results in beneficial effects on serum lipids. Complicating the matter are studies which have examined the effect of soy isoflavones alone, or in addition to soy protein on cardiovascular-related outcomes. Several studies have demonstrated that isoflavones alone (20, 21) or other soy components (22)

are effective at reducing total and LDL-C and triglycerides and improving vascular reactivity. A series of positive “combination” studies, assessing the effects of both soy protein and isoflavones has also been published since the authorization of the original SSA claim (23-28).

In contrast, a minority of studies published since 1999 have shown that soy protein does not result in a significant effect on cardiovascular related outcomes (29-32). The reason for the discrepancy between studies is not completely clear, but may relate to the processing involved in the manufacture of soy products (29), or differences in the responsiveness of the given study population. Overall, the data demonstrating a modest, but consistent effect of soy protein on serum lipids far outweighs the data suggesting no effect. We believe therefore, that the evidence base clearly meets the SSA standard and that FDA will most likely concur with this assessment and leave the present language of the SSA claim intact.

The primary consideration therefore, is whether the body of data warrants addition of other soy components (isoflavones, fiber, among others) in the claim language. This, in our estimation, represents the greatest challenge for the Agency pertaining to this particular claim. While several recent studies suggest soy isoflavones positively affect serum lipid levels (20, 21, 33) or other markers of cardiovascular health (34, 35), several others show no benefit (6, 36). Data have been published suggesting isoflavones from other sources (e.g. red clover) may also exert modest cardiovascular effects (37). It is evident that, relative to soy protein, the studies are fewer in number, and of these, those indicating a cardiovascular benefit from isoflavone supplementation are substantially less consistent.

While it remains to be conclusively determined, there are many potential reasons that may explain these discrepant findings. The cardiovascular benefits of isoflavones may be dose-dependent or isoflavone-specific (e.g. genistein, diadzein, or some combination thereof). The genetic profile of the study population (38, 39), how and to what extent the isoflavones are metabolized by the gut and subsequently absorbed and utilized by the body (40), and the extraction and processing used to isolate and concentrate the isoflavones (41) all may influence the responsiveness to isoflavones. While studies on isoflavones published since 1999 appear to support a cardiovascular benefit, the uncertainties described above suggest that the data on the category of isoflavones as a whole or on specific isoflavones are unlikely to meet the required SSA standard. Our brief review and conclusions are consistent with that provided in a recent Agency for Healthcare Research Quality (AHRQ) report (42).

We urge FDA to consider carefully the contribution of other soy components, including, but not limited to, isoflavones, to the reduction of CHD risk if and when the Agency undertakes the official rulemaking process to reevaluate this claim.

Antioxidant vitamins and certain cancers

CRN recommendation: FDA should not alter the current language of the qualified health claim related to antioxidant vitamins.

On April 1, 2003 FDA issued a letter of enforcement discretion <http://www.cfsan.fda.gov/~dms/ds-ltr34.html> in which the Agency stated it would exercise enforcement discretion for the following qualified health claims (QHC) related to antioxidant vitamins and cancer:

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.

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

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

CRN proposes that FDA not modify the claim language, as there is insufficient evidence to warrant either strengthening or weakening the claim. The very nature of this particular claim renders an assessment of the evidence base extremely complex and difficult. One must consider data on the antioxidant(s) involved (i.e. vitamin C and/or E) and the strength and consistency of the data supporting a beneficial effect on cancer (of which there are hundreds of forms). From a cursory review of the literature we identified over 40 relevant publications examining the effect

of antioxidant vitamins on the risk of various cancers in the five years since FDA's letter of enforcement discretion in 2003. These publications were composed of a mixture of RCTs, observational studies (including prospective cohort, case-control and cross-sectional studies), along with reviews and meta-analyses. The conclusions reached in some studies support, while those from other studies contradict the premise of the QHC – that consumption of antioxidant vitamins reduces the risk of certain forms of cancer. Taking into account the number of studies concluding a beneficial effect with those concluding no effect (or harm in some cases), the quality of the studies and the heterogeneity of the study designs, there is a virtual “deadlock” between support and contradiction of the claim.

The primary basis for this claim is derived from observational studies indicating an inverse association between antioxidant vitamin consumption (or serum levels) and cancer risk, reviewed extensively in a number of publications (43-50). However, prospective RCTs examining this relationship have generated inconsistent and at times contradictory results. Collectively, these studies are beset with limitations, including short duration, small sample size and lack of a reliable surrogate endpoint. There are also tremendous variations in study design, antioxidant dose and combination and study population. Many studies involve chronic smokers or patients already diagnosed with cancer, assessing treatment rather than risk reduction. Therefore, there are few, if any conclusions to be drawn from the recently published RCTs.

One area that continues to emerge with relatively consistent results between trials is Vitamin E (with or without selenium, as discussed further below) and prostate cancer risk. Of the studies we identified from the past five years which examined, in one way or another, the relation between antioxidant vitamins and cancer risk, the most consistent effects appear to be with vitamin E and prostate cancer. Relevant observational trials included a cross-sectional study (51) and several prospective trials (52-55) demonstrating an inverse relationship between vitamin E intake from diet or supplementation and/or serum levels and prostate cancer risk. In a large prospective RCT, supplementation with vitamin E, along with several other antioxidants, including vitamin C, resulted in a significant reduction in prostate cancer risk. This effect was limited to those subjects with normal prostate specific antigen (PSA) levels at baseline (56). Although the data continue to emerge in a relatively consistent direction toward reduction of prostate cancer risk with vitamin E, they are not conclusive, and therefore do not support a change in the QHC language. Our position is supported both by a recently published review

article (57) and AHRQ report (58), both of which concluded that the relationship between supplemental vitamin E and prostate cancer risk has some merit, but requires further study. We and others eagerly await the results of the ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT) (59), which we hope will add substantially to the evidence base.

In the meantime our position is that recent evidence neither strengthens nor weakens the relationship between consumption of antioxidant vitamins and the risk for prostate cancer. Therefore, we recommend at this time that FDA refrain from making any changes to the language which appears in its letter of enforcement discretion dated April 1, 2003.

Selenium and certain cancers

CRN recommendation: FDA should not alter the current language of the qualified health claim related to selenium. If an adjustment of some kind must be made, the Agency should consider adding a claim for combined antioxidants, which might include antioxidant vitamins, selenium and carotenoids such as lutein, lycopene and beta-carotene.

On April 28, 2003 FDA issued a letter of enforcement discretion <http://www.cfsan.fda.gov/~dms/ds-ltr35.html> in which the Agency stated it would exercise enforcement discretion for the following qualified health claims (QHC) related to selenium and cancer:

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."

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.

CRN proposes that FDA not modify the claim language. While we believe the evidence base supporting a link between selenium consumption and reduction of cancer risk is perhaps the strongest of the three claims addressed in these comments, it remains inadequate to warrant a

substantive strengthening of the present claim language. Correspondingly, neither should the claim language be weakened.

Most of the data supporting a beneficial effect of selenium on cancer risk are derived from observational studies, with prostate cancer being the most common cancer outcome assessed, as reviewed in several publications (57, 60-65)). We conducted a cursory review of the literature in the five years since the issuance of the letter of enforcement discretion and identified approximately 40 publications examining the relationship between selenium and cancer risk. Publications were composed of a mixture of study types, including RCTs, observational studies (prospective cohort, case-control and cross-sectional studies), along with reviews and meta-analyses. As is the case with antioxidant vitamins and cancer, the conclusions reached in some studies support, while those from other studies contradict the premise of the QHC – that consumption of selenium reduces the risk of certain forms of cancer. Of the approximately 40 publications, those concluding a beneficial effect of selenium on cancer risk outnumber those concluding no benefit by about 50%. Accounting for study quality and degree of impact renders the two sides nearly equal, with a slight edge to benefit. However, as is the case with the evidence base for antioxidants and cancer, this dataset is also beset with heterogeneous study designs and individual study limitations. Studies differed in their assessment of selenium (alone and/or in combination with other nutrients, including antioxidant vitamins), type of cancer and study population, in addition to dose and duration. Many RCTs also involved cancer patients and therefore assessed effects of treatment, not risk reduction. Thus, not surprisingly, there are widely conflicting outcomes, precluding firm conclusions.

Among types of cancer, the relationship between selenium and prostate cancer appears to be strongest (54, 56, 66-71). These findings are based largely on observational data and data derived from secondary analyses. There are also studies showing selenium may reduce the risk of cancers of the esophagus and stomach (72-74), colon (75-77), lung (78) and total cancer incidence (79). There is also a collection of studies, primarily RCTs demonstrating no effect of selenium supplementation on cancer risk (80-82) or even hinting at the possibility of an adverse effect (83). Collectively, the body of data published since, and prior to the issuance of the letter of enforcement discretion is extremely complex and difficult to interpret. Outcomes appear to be influenced by the presence of other nutrients in varying combinations, differences in dosage and duration of exposure, differences in baseline nutritional status, nature and disease state of the

study population, gender and age differences, and of course different cancers being assessed. Therefore, while many studies have been published on the relationship between selenium consumption and cancer risk, resulting in slight improvements in the evidence base over the past five years, the data do not warrant strengthening of the present claim language.

From a nutrition perspective, inclusion of multiple nutrients in a test formula makes logical sense – nutrients do not work or function in isolation and therefore should not be studied as such (i.e. like drugs). However, in this case, where the claim language centers around a single nutrient, selenium, FDA is restricted to assessing the effects of that nutrient. Therefore, the results from studies incorporating selenium together with other nutrients in the test formula are inherently confounded. For this reason, it may be prudent to add an additional claim for “combined” antioxidants and reduction of cancer risk. Indeed from a research perspective, most prospective RCTs examining the effect of these nutrients on cancer risk (and other chronic diseases) have included combinations of antioxidants in the intervention (e.g. vitamin E, selenium, beta-carotene). Therefore, the logical approach might be to base claim language on the combination of antioxidants, rather than attempt to “extract” from these complex studies, the contribution of a single nutrient (which is virtually impossible).

FDA’s evidence-based reviews

Our primary concern pertaining to the reevaluation of these claims (and future claims) is FDA’s employment of the evidence-based review. In FDA’s draft guidance *Evidence-Based Review System for the Scientific Evaluation of Health Claims* published in July 2007 <http://www.cfsan.fda.gov/~dms/hclmogui5.html>, the Agency appears to be describing how the effects of drugs, rather than nutrients, should be assessed.

We respectfully disagree with aspects of the draft guidance in which the Agency maintains broadly that RCTs “trump” observational studies. As indicated in our comments to the Docket (Appendix A), the majority of RCTs have addressed different questions than the observational studies, so their results are not directly comparable, and one cannot be used to refute (or confirm) the other. The example used in the draft guidance is particularly concerning:

“For example, previous observational studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981)(84). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996) (85, 86). These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful. For the above reasons, scientific conclusions from observational studies cannot be drawn about a relationship between a food component and a disease.”

This is a poor example to cite to support the Agency’s contention that observational data are not conclusive. The observational studies linking beta-carotene consumption and serum levels to a reduction in lung cancer risk tested the question of whether a diet high in fruits and vegetables (and correspondingly high in beta-carotene) or high beta-carotene serum levels over the course of decades led to a reduction of cancer risk whereas the ATBC and CARET trials test the question of whether treatment with relatively high doses of an isolated nutrient, beta-carotene, over a relatively short period of time in a very high risk population might reverse the effects of decades of exposure to a carcinogen. These are two completely different types of studies asking and answer two very different questions, and therefore the two sets of studies are not comparable.

We caution FDA against over reliance on and over-interpretation of results from recently published RCTs, not because they are all “negative” (on the contrary, we identified the total number of “positive” and “negative” RCTs conducted since these claims were approved/authorized to be nearly equal). Rather, it is our view that the data derived thus far from RCTs assessing the effect of nutrient consumption and chronic disease risk are insufficient to

influence either way a decision on the language for these claims. The majority of these studies failed to address the fundamental question, “Do modest levels of supplemental antioxidant vitamins or selenium reduce the risk of cancer in a US population that is cancer-free at baseline?” This question, we would argue, has not been answered yet to date, and therefore has not rebutted in any way the conclusions made previously based on a vast body of strong observational data. Unfortunately, such studies are unlikely to be conducted. There is a paucity of prospective RCTs examining the effect of antioxidant nutrients on cancer risk (or chronic disease in general). Unlike drugs, which tend to act acutely with high impact, nutrients act chronically and in combination, with a modest impact. The effects of nutrient consumption on chronic disease risk are subtle, and manifest over decades. For an RCT to assess such effects requires enormous sample sizes and trials of long duration. Practical and fiscal limitations have largely prevented large-scale, long-term RCTs from being conducted to a sufficient extent. The Women’s Health Study (WHS) (87), Women’s Health Initiative (WHI) (88) and SELECT (59) trials are examples of the few long-term, large-scale prospective RCTs examining the effect of nutrient consumption on chronic disease risk starting with a healthy US population at baseline. All have limitations that make (or may make) their results less conclusive and generalizable. WHS reported significant effects of vitamin E supplementation on secondary cardiovascular outcomes, but found no effect on cancer (87). This study has the limitation of having studied a single nutrient in isolation. The WHI study is an example of the difficulty associated with administering such large trials, where compliance was poor and calcium and vitamin D use was nearly identical in the intervention and placebo groups (88). The outcome was then inappropriately interpreted to mean that these interventions provide no benefit (or in the case of dietary fat, was inconsequential). We are currently awaiting the results of the SELECT trial (59). Although well designed with a multifactorial approach, it too may suffer from the practical limitations inherent in such large prospective RCTs. Our comments should not be misconstrued to mean we find no value in RCTs. On the contrary, RCTs can decisively establish causality, whereas observational studies cannot. Our point is that FDA should recognize the limitations inherent in all studies, including RCTs, when assessing the evidence base. The very type and standard of evidence the Agency appears to demand (large-scale, long-term RCTs examining the effect of one or more nutrients on chronic disease risk in a healthy population) is often not feasible.

We are pleased to note that FDA places minimal reliance on meta-analyses in the review process. When used and applied correctly, meta-analysis can be an enormously useful tool to identify trends resulting from a collection of similarly designed studies (key word, similar). However, several recently published meta-analyses have revealed how abuse and distortion of accepted methods can result in erroneous conclusions. Two in particular generated sensational headlines in the media and needlessly alarmed consumers (89, 90). Selective modification of study inclusion and exclusion criteria and unconventional use of statistical methods allowed these researchers to arrive at preconceived conclusions. Both analyses were heavily criticized by experts both privately and publicly. We trust that FDA will not interpret these publications at face value and will instead see them as they are – fabrications for the sake of notoriety – and assess the contributions of the individual studies to the evidence base.

We recognize the continuing emergence of science and appreciate and support the need to periodically reassess the state of the science for health claims. The process of reevaluation is a long one, and FDA must wade through enormous volumes of information and data. Understanding that it is relatively early in the process, our present position is that we believe overall that the claim language for the three claims covered here need not be altered. In the case of soy there may be the possibility of adding other components to the SSA claim language. In the case of antioxidant vitamins and selenium and certain cancer, there may be the possibility of adding a new claim that combines antioxidants into one QHC. We hope our comments provide the Agency with constructive input.

Sincerely,



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REFERENCES

1. Welty FK, Lee KS, Lew NS, Zhou JR. Effect of soy nuts on blood pressure and lipid levels in hypertensive, prehypertensive, and normotensive postmenopausal women. *Arch Intern Med* 2007;167:1060-7.
2. Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr* 2007;85:960-6.
3. St-Onge MP, Claps N, Wolper C, Heymsfield SB. Supplementation with soy-protein-rich foods does not enhance weight loss. *J Am Diet Assoc* 2007;107:500-5.
4. Hanson LN, Engelman HM, Alekel DL, Schalinske KL, Kohut ML, Reddy MB. Effects of soy isoflavones and phytate on homocysteine, C-reactive protein, and iron status in postmenopausal women. *Am J Clin Nutr* 2006;84:774-80.
5. Siefker K, DiSilvestro RA. Safety and antioxidant effects of a modest soy protein intervention in hemodialysis patients. *J Med Food* 2006;9:368-72.
6. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr* 2006;83:244-51.
7. Lukaczer D, Liska DJ, Lerman RH, et al. Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women. *Nutrition* 2006;22:104-13.
8. Hoie LH, Graubaum HJ, Harde A, Gruenwald J, Wernecke KD. Lipid-lowering effect of 2 dosages of a soy protein supplement in hypercholesterolemia. *Adv Ther* 2005;22:175-86.
9. Hoie LH, Morgenstern EC, Gruenwald J, et al. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr* 2005;44:65-71.
10. Teixeira SR, Tappenden KA, Carson L, et al. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes mellitus and nephropathy. *J Nutr* 2004;134:1874-80.
11. Sagara M, Kanda T, M NJ, et al. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Coll Nutr* 2004;23:85-91.
12. Hori G, Wang MF, Chan YC, et al. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem* 2001;65:72-8.
13. Jenkins DJ, Kendall CW, Vidgen E, et al. The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy, and vegetable protein foods. *Metabolism* 2000;49:67-72.
14. Torres N, Tovar AR. The role of dietary protein on lipotoxicity. *Nutr Rev* 2007;65:S64-8.
15. Torres N, Torre-Villalvazo I, Tovar AR. Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders. *J Nutr Biochem* 2006;17:365-73.

16. Vega-Lopez S, Lichtenstein AH. Dietary protein type and cardiovascular disease risk factors. *Prev Cardiol* 2005;8:31-40.
17. Clarkson TB. Soy, soy phytoestrogens and cardiovascular disease. *J Nutr* 2002;132:566S-569S.
18. Hecker KD. Effects of dietary animal and soy protein on cardiovascular disease risk factors. *Curr Atheroscler Rep* 2001;3:471-8.
19. Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol* 2006;98:633-40.
20. Clerici C, Setchell KD, Battezzati PM, et al. Pasta naturally enriched with isoflavone aglycons from soy germ reduces serum lipids and improves markers of cardiovascular risk. *J Nutr* 2007;137:2270-8.
21. Lissin LW, Oka R, Lakshmi S, Cooke JP. Isoflavones improve vascular reactivity in post-menopausal women with hypercholesterolemia. *Vasc Med* 2004;9:26-30.
22. Kohno M, Hirotsuka M, Kito M, Matsuzawa Y. Decreases in serum triacylglycerol and visceral fat mediated by dietary soybean beta-conglycinin. *J Atheroscler Thromb* 2006;13:247-55.
23. Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. *Diabetes Care* 2002;25:1709-14.
24. Washburn S, Burke GL, Morgan T, Anthony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause* 1999;6:7-13.
25. Jenkins DJ, Kendall CW, Garsetti M, et al. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity--a controlled crossover trial. *Metabolism* 2000;49:537-43.
26. Jenkins DJ, Kendall CW, Vidgen E, et al. Effect of soy-based breakfast cereal on blood lipids and oxidized low-density lipoprotein. *Metabolism* 2000;49:1496-500.
27. Urban D, Irwin W, Kirk M, et al. The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen. *J Urol* 2001;165:294-300.
28. Steinberg FM, Guthrie NL, Villablanca AC, Kumar K, Murray MJ. Soy protein with isoflavones has favorable effects on endothelial function that are independent of lipid and antioxidant effects in healthy postmenopausal women. *Am J Clin Nutr* 2003;78:123-30.
29. Hoie LH, Sjöholm A, Guldstrand M, et al. Ultra heat treatment destroys cholesterol-lowering effect of soy protein. *Int J Food Sci Nutr* 2006;57:512-9.
30. Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. *Am J Clin Nutr* 2005;81:590-6.
31. Ma Y, Chiriboga D, Olendzki BC, Nicolosi R, Merriam PA, Ockene IS. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: a randomized controlled trial. *J Am Coll Nutr* 2005;24:275-85.
32. Dent SB, Peterson CT, Brace LD, et al. Soy protein intake by perimenopausal women does not affect circulating lipids and lipoproteins or coagulation and fibrinolytic factors. *J Nutr* 2001;131:2280-7.
33. Goodman-Gruen D, Kritiz-Silverstein D. Usual dietary isoflavone intake is associated with cardiovascular disease risk factors in postmenopausal women. *J Nutr* 2001;131:1202-6.

34. Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2007;92:3068-75.
35. Wiseman H, O'Reilly JD, Adlercreutz H, et al. Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. *Am J Clin Nutr* 2000;72:395-400.
36. Hale G, Paul-Labrador M, Dwyer JH, Merz CN. Isoflavone supplementation and endothelial function in menopausal women. *Clin Endocrinol (Oxf)* 2002;56:693-701.
37. Atkinson C, Oosthuizen W, Scollen S, Loktionov A, Day NE, Bingham SA. Modest protective effects of isoflavones from a red clover-derived dietary supplement on cardiovascular disease risk factors in perimenopausal women, and evidence of an interaction with ApoE genotype in 49-65 year-old women. *J Nutr* 2004;134:1759-64.
38. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: interactions with genotype and equol production. *Am J Clin Nutr* 2006;83:592-600.
39. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: interactions with genotype and equol production. *Am J Clin Nutr* 2005;82:1260-8; quiz 1365-6.
40. Yuan JP, Wang JH, Liu X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora--implications for health. *Mol Nutr Food Res* 2007;51:765-81.
41. Clair RS, Anthony M. Soy, isoflavones and atherosclerosis. *Handb Exp Pharmacol* 2005:301-23.
42. Balk E, Chung M, Chew P, et al. Effects of Soy on Health Outcomes. Evidence Report/Technology Assessment No. 126. Prepared by the Tufts-New England Medical Center Evidence-based Practice Center, Boston, Massachusetts. Rockville, MD: Agency for Healthcare Research and Quality, 2005.
43. Borek C. Dietary antioxidants and human cancer. *Integr Cancer Ther* 2004;3:333-41.
44. Ruano-Ravina A, Figueiras A, Freire-Garabal M, Barros-Dios JM. Antioxidant vitamins and risk of lung cancer. *Curr Pharm Des* 2006;12:599-613.
45. Holick CN, De Vivo I, Feskanich D, Giovannucci E, Stampfer M, Michaud DS. Intake of fruits and vegetables, carotenoids, folate, and vitamins A, C, E and risk of bladder cancer among women (United States). *Cancer Causes Control* 2005;16:1135-45.
46. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. *J Clin Oncol* 2005;23:8152-60.
47. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *Jama* 2002;287:3116-26.
48. Stanner SA, Hughes J, Kelly CN, Buttriss J. A review of the epidemiological evidence for the 'antioxidant hypothesis'. *Public Health Nutr* 2004;7:407-22.
49. Ames BN. Micronutrients prevent cancer and delay aging. *Toxicol Lett* 1998;102-103:5-18.
50. Patterson RE, White E, Kristal AR, Neuhaus ML, Potter JD. Vitamin supplements and cancer risk: the epidemiologic evidence. *Cancer Causes Control* 1997;8:786-802.
51. Kang D, Lee KM, Park SK, et al. Functional variant of manganese superoxide dismutase (SOD2 V16A) polymorphism is associated with prostate cancer risk in the prostate, lung,

- colorectal, and ovarian cancer study. *Cancer Epidemiol Biomarkers Prev* 2007;16:1581-6.
52. Weinstein SJ, Wright ME, Lawson KA, et al. Serum and dietary vitamin E in relation to prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2007;16:1253-9.
 53. Wright ME, Weinstein SJ, Lawson KA, et al. Supplemental and dietary vitamin E intakes and risk of prostate cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev* 2007;16:1128-35.
 54. Joniau S, Goeman L, Roskams T, Lerut E, Oyen R, Van Poppel H. Effect of nutritional supplement challenge in patients with isolated high-grade prostatic intraepithelial neoplasia. *Urology* 2007;69:1102-6.
 55. Kirsh VA, Hayes RB, Mayne ST, et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst* 2006;98:245-54.
 56. Meyer F, Galan P, Douville P, et al. Antioxidant vitamin and mineral supplementation and prostate cancer prevention in the SU.VI.MAX trial. *Int J Cancer* 2005;116:182-6.
 57. Dagnelie PC, Schuurman AG, Goldbohm RA, Van den Brandt PA. Diet, anthropometric measures and prostate cancer risk: a review of prospective cohort and intervention studies. *BJU Int* 2004;93:1139-50.
 58. Shekelle P, Coulter I, Hardy M, et al. Effect of the Supplemental Use of Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cancer. Evidence Report/Technology Assessment No. 75. Prepared by Southern California Evidence-based Practice Center. Rockville, MD: Agency for Healthcare Research and Quality, 2003.
 59. Lippman SM, Goodman PJ, Klein EA, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Natl Cancer Inst* 2005;97:94-102.
 60. Navarro Silvera SA, Rohan TE. Trace elements and cancer risk: a review of the epidemiologic evidence. *Cancer Causes Control* 2007;18:7-27.
 61. Brinkman M, Buntinx F, Muls E, Zeegers MP. Use of selenium in chemoprevention of bladder cancer. *Lancet Oncol* 2006;7:766-74.
 62. Brinkman M, Reulen RC, Kellen E, Buntinx F, Zeegers MP. Are men with low selenium levels at increased risk of prostate cancer? *Eur J Cancer* 2006;42:2463-71.
 63. Etminan M, FitzGerald JM, Gleave M, Chambers K. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. *Cancer Causes Control* 2005;16:1125-31.
 64. Zhuo H, Smith AH, Steinmaus C. Selenium and lung cancer: a quantitative analysis of heterogeneity in the current epidemiological literature. *Cancer Epidemiol Biomarkers Prev* 2004;13:771-8.
 65. Klein EA. Selenium: epidemiology and basic science. *J Urol* 2004;171:S50-3; discussion S53.
 66. Sabichi AL, Lee JJ, Taylor RJ, et al. Selenium accumulation in prostate tissue during a randomized, controlled short-term trial of l-selenomethionine: a Southwest Oncology Group Study. *Clin Cancer Res* 2006;12:2178-84.
 67. Karunasinghe N, Ferguson LR, Tuckey J, Masters J. Hemolysate thioredoxin reductase and glutathione peroxidase activities correlate with serum selenium in a group of New Zealand men at high prostate cancer risk. *J Nutr* 2006;136:2232-5.

68. Kranse R, Dagnelie PC, van Kemenade MC, et al. Dietary intervention in prostate cancer patients: PSA response in a randomized double-blind placebo-controlled study. *Int J Cancer* 2005;113:835-40.
69. Gianduzzo TR, Holmes EG, Tinggi U, Shahin M, Mactaggart P, Nicol D. Prostatic and peripheral blood selenium levels after oral supplementation. *J Urol* 2003;170:870-3.
70. Vogt TM, Ziegler RG, Graubard BI, et al. Serum selenium and risk of prostate cancer in U.S. blacks and whites. *Int J Cancer* 2003;103:664-70.
71. Duffield-Lillico AJ, Dalkin BL, Reid ME, 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;91:608-12.
72. Cai L, You NC, Lu H, et al. Dietary selenium intake, aldehyde dehydrogenase-2 and X-ray repair cross-complementing 1 genetic polymorphisms, and the risk of esophageal squamous cell carcinoma. *Cancer* 2006;106:2345-54.
73. Lu H, Cai L, Mu LN, et al. Dietary mineral and trace element intake and squamous cell carcinoma of the esophagus in a Chinese population. *Nutr Cancer* 2006;55:63-70.
74. Li H, Li HQ, Wang Y, et al. An intervention study to prevent gastric cancer by micro-selenium and large dose of allitridum. *Chin Med J (Engl)* 2004;117:1155-60.
75. Reid ME, Duffield-Lillico AJ, Sunga A, Fakih M, Alberts DS, Marshall JR. Selenium supplementation and colorectal adenomas: an analysis of the nutritional prevention of cancer trial. *Int J Cancer* 2006;118:1777-81.
76. Peters U, Chatterjee N, Church TR, et al. High serum selenium and reduced risk of advanced colorectal adenoma in a colorectal cancer early detection program. *Cancer Epidemiol Biomarkers Prev* 2006;15:315-20.
77. Jacobs ET, Jiang R, Alberts DS, et al. Selenium and colorectal adenoma: results of a pooled analysis. *J Natl Cancer Inst* 2004;96:1669-75.
78. Wright ME, Mayne ST, Stolzenberg-Solomon RZ, et al. Development of a comprehensive dietary antioxidant index and application to lung cancer risk in a cohort of male smokers. *Am J Epidemiol* 2004;160:68-76.
79. Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004;164:2335-42.
80. Qu CX, Kamangar F, Fan JH, et al. Chemoprevention of primary liver cancer: a randomized, double-blind trial in Linxian, China. *J Natl Cancer Inst* 2007;99:1240-7.
81. You WC, Brown LM, Zhang L, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 2006;98:974-83.
82. Hoenjet KM, Dagnelie PC, Delaere KP, Wijckmans NE, Zambon JV, Oosterhof GO. Effect of a nutritional supplement containing vitamin E, selenium, vitamin c and coenzyme Q10 on serum PSA in patients with hormonally untreated carcinoma of the prostate: a randomised placebo-controlled study. *Eur Urol* 2005;47:433-9; discussion 439-40.
83. Hercberg S, Ezzedine K, Guinot C, et al. Antioxidant supplementation increases the risk of skin cancers in women but not in men. *J Nutr* 2007;137:2098-105.
84. Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981;290:201-8.

85. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. The ATBC Cancer Prevention Study Group. *Ann Epidemiol* 1994;4:1-10.
86. Albanes D, Heinonen OP, Taylor PR, et al. Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst* 1996;88:1560-70.
87. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *Jama* 2005;294:56-65.
88. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
89. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *Jama* 2007;297:842-57.
90. Miller ER, 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37-46.

Appendix A.

August 29, 2007

RE: Docket No. 2007D-0125, CFSAN 200710. Draft Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims; Availability

The Council for Responsible Nutrition (CRN) appreciates the opportunity to provide FDA with comments regarding the recently issued *Draft Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims*. CRN recognizes that this guidance is intended not to provide any new information or to announce any change in FDA's views toward the health claim and qualified health claim review process, but rather to be a comprehensive overview of the Agency's evidence-based review (EBR) system for evaluation of health claims and qualified health claim petitions.

CRN applauds FDA for its recognition of the importance of health claims and qualified health claims for nutritional products. We are further encouraged by the Agency's view that these can translate into significant public health benefits by helping consumers make informed choices when purchasing such products.

However, we do have several concerns with the draft guidance as currently presented, including but not limited to some aspects of FDA's characterization of the "evidence base" and the over-reliance on the randomized, controlled trial (RCT) as the "gold standard" for assessing the effects of nutrients. We believe that the final guidance should provide a better balance between the importance and need for properly evaluated health claims and limitations inherent in all forms of research. We will, in these comments, provide some suggestions that in our opinion, will lead to an improved guidance document.

All research approaches and indeed all studies are accompanied by inherent limitations, and in general, we agree with the Agency's "ranking" of relevant data, from *in vitro* and animal studies being least relevant and human studies being most relevant. We also agree, in principle, with the criteria the Agency uses to assess the quality of the various types of observational and intervention studies. By and large, these criteria are practical in nature and would or should be considered by any well-trained scientist when evaluating research.

However, we take exception to FDA's characterization of observational studies as solely "hypothesis generating" studies, while RCTs are considered "confirmatory". The very title of Section F of the draft guidance, "Evaluation of the Totality of the Evidence", is directly contradicted by the dismissive tone taken towards observational studies in favor of RCTs. Instead, we suggest the Agency should point out that all studies, including RCTs possess inherent limitations, which may or may not allow them to "trump" data gathered by other means. Because the type, quality and quantity of data vary greatly for any proposed substance-disease relationship, FDA should evaluate the totality of the evidence on a case-by-case basis, and not make sweeping conclusions about one study type "trumping" another.

We further disagree with the Agency's characterization of the RCT as the "gold standard" for evaluating substance-disease relationships, and believe the well known limitations of RCTs vis-à-vis the study of the effects of nutrients in humans should be acknowledged. As eloquently addressed recently by Heaney (1), "The randomized controlled trial (RCT), which has become the gold standard for establishing the efficacy of pharmacologic agents, is poorly suited to the evaluation of nutritional effects" (Attachment A). Essentially, FDA in this draft guidance, is proposing to evaluate nutrients like drugs. Heaney correctly surmises that nutrients, unlike drugs, are present in the

body at background levels and the body responds to targeted drugs very differently than it does to nutrients, which affect multiple organ systems within the body. The classic drug-based RCT model, when used to test the effects of nutrients, requires comparison of a “replete” or “supplemented” group vs. a “deficient” group presenting both ethical and practical dilemmas that often times cannot be resolved (e.g. the Women’s Health Initiative (2, 3)). While these factors should not lessen the importance of the RCT in establishing causality, they should be recognized and acknowledged by the Agency as limitations to this approach.

Another limitation of RCTs is cost. The Agency is no doubt well aware of the costs associated with demonstrating the effects of nutrient(s) on reduction of disease risk. Prospective RCTs examining the effect of a substance on chronic disease risk (the very subject of health claims) are so costly they are rarely conducted. When such studies are conducted, they are faced with a litany of limitations, some of which were described above, all of which reduce the reliability and applicability of the study outcome. Take for example, the multivitamin, the regular daily use of which has been associated with a reduction in the risk of a variety of chronic diseases (4). Under FDA’s presently described EBR system, in order for a health claim or qualified health claim to be approved for this substance-disease relationship, a prospective RCT would need to be conducted and the results would have to show statistically significant differences in relevant outcome measures for an “active” vs. placebo group. This is similar to the stance taken by a panel of “experts” convened by NIH in 2006 to assess the effectiveness of multivitamins for the prevention of chronic disease (5). Under these circumstances, among other obstacles, such a study would require up to hundreds of thousands of subjects, would need to last decades, and thus is completely cost-prohibitive. These and other limitations to relying solely on the RCT to study the disease modifying effects of multivitamins were recently highlighted in a Letter to the Editor by Ames et al. (6) (Attachment B). Nonetheless the Agency, like NIH has chosen to ignore this critical fact in the draft guidance. The cost limitation alone should prompt the Agency to adjust its EBR system to be more inclusive of other types of studies, recognizing the limitations of all studies, lest the public be left devoid of the critical information they need to make informed and healthful choices.

Perhaps the most concerning portion of the draft guidance is FDA’s continued reference to inconsistencies between observational studies and RCTs as a rationale for why the former cannot be relied on solely when evaluating a health claim. The repeated mention in the draft guidance of RCTs “invalidating” results from observational studies involving antioxidant nutrients is misdirected and out of context. This reflects either an intrinsic bias within and/or a lack of fundamental understanding of research methods on the part of the Agency. There are multiple references to the Lichtenstein and Russell review (7), which questions the benefit and safety of supplemental nutrients based on a series of negative RCTs, involving vitamin E and beta-carotene in particular, which followed very positive observational studies. What FDA (and others) fail to acknowledge is that the observational studies showing an inverse relationship between antioxidant consumption (or serum levels) and disease risk and the RCTs examining the effect of antioxidant supplementation on disease risk were asking and answering very different questions. Briefly, the former asked whether exposure to antioxidants over a significant period of time (decades) reduced the risk of disease in a healthy baseline population, while the latter asked whether treatment with high doses of antioxidants over relatively short periods of time (months to years) can prevent the reoccurrence of events associated with disease in those already with the disease (and on multiple medications).

These are completely different questions and the results from one cannot be used to completely refute or confirm the other. The Agency contradicts itself by, on the one hand stating that results from studies conducted with diseased patients are generally not applicable to the general healthy population (for which health claims are intended), while on the other hand using results from RCTs conducted in diseased patients showing no benefit or even harm to refute the results of observational studies showing benefit. The fact is, with few exceptions, prospective RCTs examining the effect of supplemental nutrients on disease risk reduction in a healthy baseline population are extremely rare for pragmatic reasons. While FDA characterizes the RCT as the most reliable type of study for determining a cause-and effect relationship, running such studies in healthy individuals, as the FDA generally proposes, is inherently problematic because of the difficulty in showing any effect from the nutrient in healthy individuals in the typical time course of an intervention study, especially a statistically significant effect in comparison to a group of healthy individuals treatment with a placebo. One exception is the Women's Health Study (8), the largest and longest prospective RCT examining the effect of vitamin E supplementation on chronic disease risk in a healthy population. This study showed beneficial effects of vitamin E supplementation on several secondary outcome measures related to cardiovascular disease, yet it is conspicuously absent from both the Lichtenstein and Russell review and FDA's draft guidance. While the emphasis on RCTs testing the effect of a proposed new drug on a subject population suffering from the disease or condition to be treated by the proposed new drug makes eminent sense in that context, the same emphasis on RCTs in healthy individuals to show an effect of the proposed nutritional ingredient in preventing a disease or health condition in such healthy individuals is misplaced. While FDA allows the use of such "healthy subject" data if the available scientific evidence demonstrates that (a) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanisms for risk reduction effects in non-diseased populations and (b) the substance affects these mechanisms in the same way in both diseased and healthy people, these limitations, as a practical matter, significantly limit a petitioner's ability to rely on RCTs in the same diseased or at risk population that the petitioner seeks to benefit with its nutrient.

The Agency standard of not using data from research performed on one population to establish policy for a different population is generally acceptable, even practical. But this standard should be applied consistently, to avoid the appearance of subjectivity and bias. Therefore, we strongly recommend the removal from the guidance document the use of examples that compare results from RCTs conducted on diseased patients using multiple concomitant medications to results from observational studies derived from healthy populations. Or we request that FDA apply its standards fairly, consistently and in a more balanced manner.

While not critical for mention in the guidance, FDA should recognize that many public health policy decisions are based on observational data alone. For example, anti-cigarette smoking policy has been established solely on the basis of observational studies – no RCT has been conducted to show that cigarette smoking causes lung cancer. In addition, the recommendations in the USDA dietary guidelines, "science-based advice to promote health and to reduce risk for major chronic diseases through diet and physical activity" (9), are also based on observational studies showing an inverse relation between, for example, fruit and vegetable consumption and the risk for certain cancers. We agree that results from studies examining the effects of whole foods cannot be directly extrapolated to individual nutrients. However, we also believe that there is sufficient and credible precedent for the reliance on

observational data to support public health policy, i.e. health claims. This does not in any way diminish the importance of the RCT, but instead places it on more equal ground with observational studies.

The final, but by no means less important comment we have related to the draft guidance is on the topic of “validated” surrogate endpoints or biomarkers. The list of only four surrogate endpoints is discouragingly few, since these are the key to the future of disease risk reduction research (and therefore future health claims). Relying on them as outcome measures for disease can significantly reduce costs associated with clinical trials. The Agency claims to derive their list from those “accepted by NIH and/or CDER”; left off this list are cognitive function for Alzheimer’s disease (which has been mentioned as a surrogate marker at several public presentations CFSAN staff have conducted over the past few years), homocysteine levels for cardiovascular disease, joint space narrowing for osteoarthritis, prostate specific antigen levels for prostate cancer, levels of inflammatory factors for cardiovascular disease (such as C reactive protein), serum 25(OH)D levels for various cancers and macular pigment density for age-related macular degeneration. Granted, the data for many on this list are still emerging or are somewhat conflicting, but the Agency should agree to openly recognize and appreciate new markers as the data confirm their reliability and rely on other qualified groups or agencies to help identify such surrogate markers. For example, medical conditions that can be diagnosed using medical devices approved by FDA’s CDRH should be eligible surrogate endpoints. Surrogate endpoints identified by those authoritative agencies recognized by FDA under FDAMA should also be acceptable markers or surrogate endpoints.

Therefore, we request that cognitive function be added to the list of validated surrogate endpoints, and although it might be outside the scope of this guidance document, we ask that the Agency include more language stressing the importance of and future reliance on surrogate endpoints for assessing disease risk.

Once again, CRN appreciates the opportunity to comment on this valuable draft guidance. We hope the Agency finds these comments both supportive and constructive and that they will be given ample consideration in the drafting of the final guidance.

1. Heaney RP. Nutrition, chronic disease, and the problem of proof. *Am J Clin Nutr* 2006;84:471-2. <http://www.ajcn.org/cgi/content/full/84/3/471>
2. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
3. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684-96.
4. Dickinson A, Shao A. Multivitamins and other dietary supplements for better health http://www.crnusa.org/pdfs/CRN_PostitionPaper_MULTIVITAMIN.pdf. Washington, DC: Council for Responsible Nutrition, 2006.
5. NIH State-of-the-Science Conference: Multivitamin/Mineral Supplements and Chronic Disease Prevention, May 15-17, 2006, Bethesda, Maryland, USA. *Am J Clin Nutr* 2007;85:251S-327S.
6. Ames BN, McCann JC, Stampfer MJ, Willett WC. Evidence-based decision making on micronutrients and chronic disease: long-term randomized controlled trials are not enough. *Am J Clin Nutr* 2007;86:522-525. <http://www.ajcn.org/cgi/content/full/86/2/522>
7. Lichtenstein AH, Russell RM. Essential nutrients: food or supplements? Where should the emphasis be? *Jama* 2005;294:351-8.
8. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *Jama* 2005;294:56-65.
9. Dietary Guidelines for Americans. Sixth ed. U.S. Department of Agriculture. U.S. Department of Health and Human Services <http://www.health.gov/dietaryguidelines/dga2005/recommendations.htm>, 2005.