IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ALLIANCE FOR NATURAL HEALTH US, et al.,	)	
Plaintiffs,	)	
v.	)	**Case No. 1:09-cv-01470-ESH**
KATHLEEN SEBELIUS, et al.,	)	
Defendants.	)	

MEMORANDUM IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT

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I. INTRODUCTION

Plaintiffs Alliance for Natural Health US ("ANH"); Durk Pearson and Sandy Shaw ("Pearson and Shaw"); and the Coalition to End FDA and FTC Censorship ("CEC") move for a declaration that the June 20, 2009 Food and Drug Administration ("FDA") final order, FDA Docket No. FDA-2008-Q-0323-0015 (hereinafter "Order"), SMF ¶ 14, violates Plaintiffs' First Amendment rights to use on labels and in labeling the claims specified herein with "short, succinct, and accurate" disclaimers and the constitutional mandates of the United States Court of Appeals in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999) ("*Pearson I*") and of this Court in *Whitaker v. Thompson*, 248 F. Supp. 2d 1 (D.D.C. 2002), appeal dismissed, 2003 U.S. App. LEXIS 18288 (D.C. Cir. 2003) ("*Whitaker I*"). They also move for an injunction blocking FDA from taking any action to prevent their use of the claims specified herein with reasonable "short, succinct, and accurate" disclaimers prescribed by the agency.

The FDA's Order banned five qualified health claims for selenium-containing dietary supplements that associate this anti-carcinogenic nutrient with a reduction in the risk of certain cancers. The claims are supported by over 200 peer-reviewed scientific studies (including 30 placebo controlled clinical trials; 105 case control studies; 12 animal studies; and 11 in vitro studies). SMF ¶ 17. FDA's Order reversed a decision it reached in 2003 (based on a smaller quantity of supportive scientific evidence) to allow two of the claims (Claims I and II *infra*), a decision that came on the heels of *Whitaker I*, 248 F. Supp. 2d 1 (D.D.C. 2002), condemning FDA's recalcitrant, unconstitutional refusal to permit qualified health claims backed by credible science. SMF ¶ 16.

The agency's actions, reversing the constitutional order of disclosure over suppression, are in contumacious disregard of the First Amendment and the precise teachings of our Court of Appeals and this Court. Indeed, those actions (coming after four federal court decisions prohibiting the same kind of censorship) rest on the supposition that this agency is not bound by the constitutional decisions of the federal courts and may function independent of the rule of law, as a law unto itself. Having repeatedly been given clear instruction on the constitutional standard from our Court of Appeals in *Pearson I,* 164 F.3d at 655-660, and this Court in *Whitaker I,* 248 F. Supp. 2d at 27-29; *Pearson v. Shalala*, 130 F.Supp. 2d 105, 112-113, 118-119 (D.D.C. 2001) ("Pearson II"), and *Pearson v. Thompson*, 141 F.Supp. 2d 105, 112 (D.D.C. 2001) ("*Pearson III*"), FDA did not recite, let alone apply, the very First Amendment standard the Court ordered it to apply in its evaluation of qualified health claims. In addition, FDA undertook no analysis to determine whether the claims presented could be rendered nonmisleading through the addition of reasonable disclaimers such as those recommended by the Court in *Pearson I* and *Whitaker I*. Moreover, before suppressing the claims FDA neither adduced nor analyzed any empirical evidence, as required by the Court in *Pearson I* and *Whitaker I,* that consumers would be hopelessly bewildered by the qualified claims. *See Pearson I*, 164 F.3d at 659-660; *Whitaker I,* 248 F. Supp. 2d 10. In short, FDA contumaciously continues to favor suppression as its operative rule and disclosure as the rare exception, flouting the First Amendment mandates in *Pearson I and Whitaker I*. FDA's speech police are thus rogue agents who view their power to censor unanswerable to the law--beyond the reach of the First Amendment and this Court.

II. BACKGROUND: FDA'S LEGACY OF SUPPRESSION

A. QUALIFIED HEALTH CLAIMS

Qualified health claims are a court mandated constitutional exception to FDA's statutory health claims approval process. *See generally Pearson I*, 164 F.3d 650. The Nutrition Labeling and Education Act ("NLEA") required FDA to create rules for approval of health claims on dietary supplements. SMF ¶ 1. FDA adopted regulations interpreting its statutory authority to limit FDA "approved" claims to those it deemed backed by conclusive proof. *Pearson I,* 164 F.3d at 660-661 (holding FDA's failure to define a clear approval standard arbitrary and capricious agency action under 5 U.S.C. § 706(2)(A)).

In *Pearson I*, the Plaintiffs argued that FDA's health claim approval process violated the First Amendment because it censored from the marketplace all truthful representations of nutrient-disease relationships except those which it subjectively deigned backed by conclusive proof. *Id.* at 654. Plaintiffs further argued the FDA was required to "employ a less draconian method - - use of disclaimers - - to serve the governments interests" of eliminating potential misleadingness. *Id*. The Court agreed, *Id*. at 655-660, ruling that the First Amendment forbad FDA from censoring accurate representations of inconclusive science. The Court held truthful claims based on inconclusive science had to be allowed with reasonable disclaimers that reveal the inconclusiveness, such as "The evidence in support of this claim is inconclusive" or "The FDA does not approve this claim." *Id*. at 658-659 (quoting *Board of Trustees of the State University of New York v. Fox*, 492 U.S. 469, 480, 109 S.Ct. 3028 (1989) (stating, "It is clear, then, that when government chooses a policy of suppression over disclosure-at least

where there is no showing that disclosure would not suffice to cure misleadingness-government disregards a 'far less restrictive' means").

The Court prohibited FDA from censoring claims that were only potentially misleading, ordering the agency to rely on qualifications (disclaimers) as a less speech restrictive alternative to outright suppression. *Id*. at 655 (quoting *In re R.M.J.*, 455 U.S. 191, 203, 102 S.Ct. 929, 71 L.Ed.2d 64 (1982)) ("But the States may not place an absolute prohibition on ... potentially misleading information ... if the information also may be presented in a way that is not deceptive"). The Court mandated the qualified health claim regime as an exception to FDA's statutory health claim approval process to ensure that truthful information would not be banned by FDA because FDA deemed the science supporting the claim less than conclusive. *Pearson I*, 164 F.3d at 659-660.

B. THE FIRST AMENDMENT STANDARD: DISCLOSURE OVER SUPPRESSION

In *Pearson I*, our Court of Appeals established a First Amendment standard for constitutional review of qualified health claims, i.e., claims not "approved" by FDA. *See Pearson I*, 164 F.3d 650 (D.C. Cir. 1999). The Plaintiffs challenged the FDA's censorship of four scientifically supported health claims (folic acid/neural tube defect risk reduction; antioxidant vitamins/cancer risk reduction; fiber/colorectal cancer risk reduction; and fish oil/heart disease risk reduction) (hereinafter "The Four Claims")). *See id*. The FDA censored every claim, finding the evidence for each "inconclusive for one reason or another." *Id*. at 653. The Court in a 3-0 decision overturned FDA's speech ban, finding the claims backed by credible scientific evidence, albeit evidence FDA deemed inconclusive. *See id*. The Court held that under *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 100 S. Ct. 2343 (1980), the proposed health

claims were protected speech because they were, at worst, only *potentially* misleading. *Pearson I*, 164 F.3d at 655-56 (calling FDA's arguments for suppression "almost frivolous"). The *Pearson I* Court then ordered FDA to use claim qualification in lieu of outright suppression as a less restrictive means to eliminate potential misleadingness. *See id*. at 655-60.

When post-*Pearson I* FDA refused to permit use of any of the claims our Court of Appeals had held unconstitutionally censored, this court condemned FDA's recalcitrance in response to an appeal challenging the suppression of one of those claims and explained in unmistakable terms the First Amendment limits on FDA's speech suppressive powers (*See Whitaker I*, 248 F. Supp. 2d 1 (D.D.C. 2002), *appeal dismissed*, 2003 U.S. App. LEXIS 18288 (D.C. Cir. 2003):

> Specifically, *Pearson I* identified two situations in which a complete ban would be reasonable. First, when the 'FDA has determined that *no* evidence supports [a health] claim,' it may ban the claim completely. *Id*., 164 F.3d at 659-660 (emphasis in original). Second, when the FDA determines that 'evidence in support of the claim is qualitatively weaker than evidence against the claim--for example, where the claim rests on *only one or two old studies*,' it may impose an outright ban. *Id.*, 164 F.3d at 659 n.10 (emphasis added). Even in these two situations, a complete ban would only be appropriate when the government could demonstrate with empirical evidence that disclaimers similar to the ones [the Court] suggested above ["The evidence in support of this claim is inconclusive" or "The FDA does not approve this claim"] would bewilder consumers and fail to correct for deceptiveness.

Id. at 10 (quoting *Pearson I*, 164 F.3d at 659-660) (emphasis in original). Disclosure is thus the constitutional rule; suppression, the rare exception. FDA bears a high burden of proof:

> The First Amendment places the burden on the government to prove that its method of regulating speech is the least restrictive means of achieving its goals. The First Amendment does not allow the FDA to simply assert that Plaintiff's Claim is misleading in order to supplant [its] burden to demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.

Id. at 9 (internal citations omitted).

FDA cannot meet its burden based speculative assertions that the evidence presented is inconclusive or unacceptable for one reason or another. To meet its burden, FDA must establish (1) that there is "no [scientific] evidence" in support of the claims or (2) that the "evidence in support of the health claim is qualitatively weaker than the evidence against the claim." *Id*. In *Pearson III*, 141 F.Supp. 2d 105 (citing *Pearson I*, 164 at 660), this Court explained that the "mere absence of significant affirmative evidence in support of a particular claim … [is not] negative evidence 'against' it." Even if (1) or (2) is met, FDA may not suppress a claim unless it also proves with "empirical evidence" that disclaimers "would bewilder consumers and fail to correct for deceptiveness." *Whitaker I*, 248 F. Supp. 2d at 10. Without satisfying each of those elements, FDA lacks legal authority to ban a health claim.

C. FDA HAS NEVER APPLIED, LET ALONE CITED, THE FIRST AMENDMENT STANDARD IN ANY HEALTH CLAIM DECISION

FDA refuses to cite and implement the First Amendment standard that this Court required in *Whitaker I*. *Id.*, 248 F. Supp. 2d at 10. In 1995, after FDA adopted the rules governing health claim review, it denied approval of The Four Claims. SMF ¶ 4. Plaintiffs Pearson and Shaw along with other co-petitioners including the American Preventive Medical Association ("APMA") (predecessor to ANH) filed comments explaining that FDA could not constitutionally ban the claims because scientific evidence supported them. *Id.* FDA rejected the comments, deeming each claim backed by inconclusive evidence and banning them all. *Id*.

In 1999, Plaintiffs' challenge to this act of censorship reached our Court of Appeals where, in a landmark ruling, that court held FDA's speech ban unconstitutional and ordered FDA to allow use of qualified claims when it deemed science supporting the

claims inconclusive for one reason or another. SMF ¶ 6; *see also Pearson I,* at 655-60. When FDA received the Court of Appeals' mandate, it did not allow the claims to be made with reasonable disclaimers. Instead, it contumaciously ordered the claims censored until it completed a new rulemaking concerning them. SMF ¶ 7. For 7 years, the claims were censored. In the rulemaking, FDA received additional science supportive of the claims. Then in 2000, FDA issued its order, contumaciously banning anew all 4 claims our Court of Appeals held unconstitutionally suppressed. The Plaintiffs, 2 years after *Pearson I,* returned to this court on the same claims. SMF ¶ 7. Plaintiffs sought declaratory and injunctive relief. *See Pearson v. Shalala*, 130 F.Supp. 2d 105 (D.D.C. 2001) ("*Pearson II*"). In *Pearson II*, this Court held FDA's censorship unconstitutional and demanded that FDA implement *Pearson I*, explaining that FDA had "failed to adequately consider the teachings of *Pearson* [*I*]." *Pearson II*, 130 F.Supp. 2d at 119; 130 ("The agency appears to have at best, misunderstood, and at worst, deliberately ignored . . . the Court of Appeals opinion"). The Court demanded that FDA allow the claims with "one or more short, succinct, and accurate alternative disclaimers, which may be chosen by Plaintiffs to accompany [the proposed claims]." *See id*. at 120. Instead of complying with this order, FDA filed a motion for reconsideration. SMF ¶ 8; *see also Pearson v. Thompson*, 141 F.Supp. 2d 105 (D.D.C. 2001) ("*Pearson III*"). Swiftly dispatching the motion, this Court held FDA's repeated attempts to avoid its constitutional duties inexcusable and ordered immediate agency compliance. *Pearson III*, 141 F.Supp 2d at 108.

Several months following *Pearson III*, Plaintiffs were again forced to file an action seeking enforcement of the *Pearson I* decision (after FDA denied yet another

science backed claim at issue in *Pearson I*). *Whitaker I*, 248 F.Supp. 2d 1; *see also* SMF ¶ 9. This Court again ordered FDA to follow the *Pearson* decisions (*I, II, III*) without delay, concluding that "FDA has failed to comply with the Court of Appeals decision in Pearson I," *id*. at 8, and "[t]here is no question that the agency has acted with less than reasonable speed in this case." *Id*. at 17 n.20.

In this case, FDA again demonstrates its contumacious refusal to follow the rule of law, revealing hubris, for the fourth time, by insisting that it not be bound by the First Amendment and the decisions of our Court of Appeals and this Court. The actions may no longer be ascribed to misunderstanding but must be seen for what they are: deliberate, willful, disobedient, contumacious, and lawless abdications of FDA's duty under the Constitution. These are acts imposed by executive officers who view themselves and FDA as above the law, unaccountable to this Court, and not beholden to the oaths they swore to uphold the Constitution and the laws. *See Pearson III*, 141 F.Supp.2d at 108, 112 ("In its motion for reconsideration, the FDA has again refused to accept the reality and finality of that conclusion by the Court of Appeals").

D. FDA'S PRIOR APPROVAL OF TWO QUALIFIED SELENIUM CLAIMS

Two months after *Whitaker I* FDA approved two qualified claims for selenium and cancer risk reduction. SMF ¶ 10.[1] The claims read:

> 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.

[1] *See also* FDA 2003 Order Approving Selenium Health Claims, Docket No. FDA-02P-0457, *available at*, http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm072786.htm, (last visited October 2, 2009).

> 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.

SMF ¶ 10(a) and (b). The FDA's allowance of the selenium qualified health claims was based primarily on three intervention,[2] and four observational studies.[3] The FDA allowed the claims with qualifications.[4] In its 2009 Order censoring Plaintiffs' selenium qualified health claims, FDA abruptly reversed its decision to allow the two previously permitted selenium claims, again censoring every claim associating selenium with cancer risk reduction. SMF ¶¶ 16, 48.[5]

E. FDA'S RETURN TO A PRE-PEARSON I, DE FACTO STANDARD OF NEAR CONCLUSIVE PROOF AND TO SUPPRESSION OVER DISCLOSURE

In January 2009 the FDA revised its industry guidance entitled "Evidence-Based Review System for the Scientific Evaluation of Health Claims" ("EBRS"). SMF ¶ 48.[6] In the revision, FDA reverted to its pre-*Pearson I* exclusive reliance on its statutory claim approval process (under the "Significant Scientific Agreement" standard, 21 USC 343(r)(5)(D), in contumacious disregard of *Pearson I* and *Whitaker I,* writing:

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[2] SMF ¶ 11 (citing 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)).

[3] SMF ¶ 11 (citing Brooks et al., 2001, Willet et al. (92), Yoshizawa et al. (97), and Hardell et al., 1995).

[4] In particular, FDA adheres to the legally erroneous view that the claims are unlawful but that it is exercising "enforcement discretion" to avoid prosecuting the speakers for using them. SMF ¶ 16 (citing FDA Final Order asserting "enforcement discretion"). As *Pearson I* and *Whitaker I* make clear, the claims are constitutionally protected speech that FDA has no lawful power to censor. Thus, it is not that FDA is exercising discretion which avoids enforcement. FDA has no lawful power and thus, no "discretion" to act otherwise.

[5] *See* Jenna Greeene, *A Bitter Pill: 15-Year Battle Over Vitamin Health Claims Is Back In Court*, The National Law Journal, 21, 24, 26 (Sept. 28 2009) (quoting the FDA Chief Counsel Sheldon Bradshaw who presided over the present health claim review as saying that "even he was puzzled by the re-evaluation, adding that it struck him as a 'misguided use of agency resources'").

[6] Available at http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm, (last visited, October 2, 2009).

> . . . the components of the scientific review process for an SSA health claim and qualified health claim are very similar. Because of the similarity . . . *FDA intends to use the approach set out in this guidance for evaluating the scientific evidence in petitions that are submitted for an SSA health claim or qualified health claim.*

Id. Under EBRS, FDA demands conclusive proof before it recognizes science as "credible." *Id.* Under EBRS, the FDA culls from the evidence those studies which are intervention or observational, then rejects the remainder as not "credible." SMF ¶ 48. After completing this step, FDA then reviews the intervention and observational studies for possible source of inconclusiveness. *Id*. If FDA finds an irregularity, it dismisses the study in toto, concluding that no scientific conclusions can be drawn from it. *Id*. If there is a lack of conclusive proof, only then does FDA turn to the qualified health claim analysis *but bases its qualified claim analysis on this artificially limited (severely limited) universe of science*. *Id*. FDA's prescribed review is thus not a review of the totality of the scientific evidence but of a narrow subset of it.

EBRS, as applied, guts *Pearson I* and *Whitaker I,* returning the regulation of claims to a de facto pre-*Pearson I* standard. Significantly, FDA does not cite the First Amendment standard of review in the EBRS, SMF ¶ 48, and EBRS does not require FDA to adduce empirical data to prove disclaimers incapable of curing misleadingness before permitting outright bans on claims, again flouting *Pearson I* and *Whitaker I*. *Id*.

F. PLAINTIFFS' SCIENCE-BACKED CLAIMS

The qualified claims at issue in this case are:

> 1. Selenium may reduce the risk of certain cancers. Scientific evidence supporting this claim is convincing but not yet conclusive. ("Claim I")[7]

[7] FDA allowed this substantive claim by letter dated February 21, 2003. SMF ¶ 10. It revoked that allowance by letter dated June 20, 2009. SMF ¶ 16.

> 2. Selenium may produce anticarcinogenic effects in the body. Scientific evidence supporting this claim is convincing but not yet conclusive. ("Claim II")[8]
>
> 3. Selenium may reduce the risk of prostate cancer. Scientific evidence supporting this claim is convincing but not yet conclusive. ("Claim III")
>
> 4. Selenium may reduce the risk of lung and respiratory tract cancers. Scientific evidence supporting this claim is convincing but not yet conclusive. ("Claim IV")
>
> 5. Selenium may reduce the risk of colon and digestive tract cancers. Scientific evidence supporting this claim is convincing but not yet conclusive. ("Claim V")

SMF ¶ 15. Each claim is backed by credible scientific evidence, including original peer-reviewed research and the reports of two leading selenium research scientists, Dr. Richard A. Passwater and Dr. Gerhard Norbert Schrauzer. SMF ¶ 18.

This Extensive data includes, thirty placebo controlled clinical trials, 105 case control studies, 12 animal studies, and 11 in vitro studies support the claims. SMF ¶ 17. In addition, Plaintiffs submitted to FDA 40 peer-reviewed review articles, book chapters, and meta-analyses, documenting wide scientific acceptance of selenium's anticarcinogenic effects. *Id*. There is, thus, credible (indeed, convincing) scientific evidence supporting selenium's role in reducing cancer risk. SMF ¶¶ 26-35, 37-46. As stated by Dr. Richard Passwater, a leading selenium and cancer researcher:

> Even though initial events (such as radiation, carcinogens, etc.) may differ, often the common route of cancer cause . . . involves free radical pathology (including damage initiated by free radicals, reactive species and oxidants) to damage cell membranes and DNA, which in turn is the direct cause of the mutations that become cancers. The cause per se of these cancers is not various initiating events, but free-radical pathology per se, which is a single (common) cause that can be blocked by certain antioxidant nutrients including selenium-containing compounds.

[8] FDA allowed this substantive claim by letter dated February 21, 2003. SMF ¶ 10. It revoked that allowance by letter dated June 20, 2009. SMF ¶ 16.

SMF ¶ 29.

In support of Claim III, Plaintiffs submitted 3 double blind placebo controlled intervention studies[9] and 6 nested case-controlled observational studies.[10] SMF ¶ 30-35. Each provides scientific support for selenium's prostate cancer risk reducing effects. *Id*. In addition, Plaintiffs cited the AHRQ report, which cites an interim reanalysis of 843 male patients with prostate specific antigen levels less than 4 ng/ml, taking into account a 2-year treatment lag, and finding that the selenium group had a "significant reduction in prostate cancer." SMF ¶ 31.

In support of Claim IV Plaintiffs submitted 1 placebo controlled intervention study,[11] 2 nested case-controlled observational studies,[12] and 1 meta-analysis.[13] SMF ¶ 37-40. As with the aforementioned studies, each provides credible scientific evidence of selenium's prostate cancer risk reducing effects.

In support of claim V Plaintiffs submitted 1 nested case controlled intervention study,[14] 1 cross-sectional observational study,[15] 1 ecological study,[16] 2 prospective studies, [17] and 3 nested-case control observational studies.[18] SMF ¶ 40-46. In addition, Plaintiffs cited a 2007 peer-reviewed review article on the chemopreventive effect of selenium on colorectal cancer authored by Das, et al., 2007. The scientists there explained, "selenium compounds have . . . been shown to inhibit the development of

[9] Duffield-Lillico et al., 2003a, Duffield-Lillico et al., 2003b, Clark et. al., 1998. SMF ¶ 30-35.
[10] Li, et al., 2004; Yoshizawa, et al., 1998; Helzlsouer, et al., 2000; Nomura et al., 2000; Van den Brandt, et al., 2003; Brooks et al., 2001. *Id*.
[11] Hercberg, et al., 2004. SMF ¶ 39.
[12] Van den Brandt, et. al., 1993; Knekt, et al., 1998. SMF ¶ 37-40.
[13] Zhuo, et al., 2004. SMF ¶ 39.
[14] Wei, et al., 2004. SMF ¶ 44.
[15] Clark, et al., 1993. SMF ¶ 40.
[16] Schrauzer, et al., 1977. SMF ¶ 45.
[17] Garland, et al., 1995; Peters, et al., 2006. SMF ¶¶ 41 46.
[18] Ghadirian, et al., 2000; Fernandez-Banares, et al., 2002; Jaskiewicz, et al., 1988. SMF ¶¶ 41, 43.

adenocarcinomas in animal models of colorectal carcinogenesis, and there is evidence from epidemiological studies showing an inverse relation between [human] cancer mortality and selenium content in diet." SMF ¶ 41.

G. FDA'S ORDER REVERSING PREVIOUSLY ALLOWED CLAIMS AND CENSORING ALL NEW SELENIUM CLAIMS IN VIOLATION OF *PEARSON I* AND *WHITAKER I*

On December 21, 2007, FDA published a Federal Register notice stating its intention to reevaluate the scientific data available for two previously allowed selenium qualified health claims. SMF ¶ 12.[19] FDA identified the "new scientific evidence" as a May 2006 AHRQ report (which it commissioned), and described the report as stating that the evidence for the selenium /cancer risk reduction association was "low." SMF ¶ 13. That is false. The AHRQ report actually stated the supportive evidence was "moderate." SMF ¶ 28.

On February 19, 2008, petitioners Pearson, Shaw, Youngevity (not a Plaintiff here), and CEC filed comments in opposition to FDA's proposed re-evaluation. SMF ¶ 14. In addition, on April 24, 2008, those petitioners submitted a new health claim petition pursuant to 21 U.S.C. § 343(r)(3)(B)(i) seeking FDA allowance of ten qualified health claims (five of which are presented here) for selenium and reduction in cancer risk, two of which were restatements of the two previously FDA allowed selenium claims (Claims I and II). *Id*. On June 20, 2009, the FDA issued its Order suppressing seven of the ten claims. SMF ¶ 16.

Although the FDA allowed use of three site specific health claims, it saddled each with misleading and lengthy disclaimers, violating the applicable requirement that

[19] Note that this same approach, a rulemaking to reconsider the science , was used by FDA post-*Pearson I* to create new justification to ban claims the *Pearson I* court held unconstitutionally suppressed.

disclaimers be reasonable, "short, succinct and accurate" from this Court, the Court of Appeals, and the Supreme Court. *Whitaker I*, 248 F. Supp. 2d at 10 (quoting *Pearson I*, 164 F.3d at 659-660 (and cases cited therein)) (requiring "short, succinct, and accurate disclaimer[s]").

Since the 2003 approval of two selenium qualified health claims, scientific support has grown appreciably. SMF ¶¶ 10, 17.[20] Plaintiffs submitted over 150 peer reviewed scientific publications on the cancer risk-reducing effects of selenium. SMF ¶ 17. The FDA reviewed an additional 77 for a total of 233. *Id*.

In rejecting Claims I and II FDA failed to review any specific scientific studies that supported the claims (including evidence previously relied on by the agency when allowing the claims in 2003). *Id*. (rejecting the 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) each of which were relied on by FDA to permit the claims); *see also* SMF ¶ 27. FDA banned the claims previously allowed deeming them "too broad and general to be accurate." SMF ¶ 16. It also held that it made a mistake in deeming the term "anticarcinogenic" appropriate for use in a health claim, announcing that the term exclusively referred to disease treatment, not disease risk reduction. *Id.*

In its analysis of Claim III, FDA found that of fifteen studies that discussed selenium's prostate cancer risk reduction effects, it would draw conclusions from only nine. Of those nine, FDA found only two supportive. In coming to this conclusion, FDA

[20] In 2003 FD reviewed only 101 publications supporting the selenium cancer relationship compared to 233 in 2009.

dismissed 3 intervention [21] and 3 nested case-control observational studies.[22] In addition, FDA erroneously found "no significant difference in plasma selenium levels between the cancer-free controls … and prostate cancer cases" in the 2004 Harvard Physicians Study (Li, et al., 2004), a nested case-control observational study, wherein by contrast the researchers themselves stated, "We found a statistically significant inverse association between pre-diagnostic plasma selenium levels and subsequent risk of advanced prostate cancer among men enrolled in the Physician's Health Study. The association was statistically significant during the post-PSA era, even after 8 years of follow-up." SMF ¶ 32. Moreover, FDA did not consider the 2004 Li study *at all*. *Id.* The FDA severely qualified the health claim, SMF ¶ 16, requiring the following inaccurate and false qualification:

> Two weak studies suggest that selenium intake may reduce the risk of prostate cancer. However, four stronger studies and three weak studies showed no reduction in risk. Based on these studies, FDA concludes that it is highly unlikely that selenium supplements reduce the risk of prostate cancer.

Id.

There were nine studies, not two, supporting the selenium prostate cancer risk reduction effects. The studies not revealing an effect, Lippman et al., (2009); Criqui et al., (1991); Goodman et al., (2001); Peters et al., (2007); Peters et al., (2008); Willett et al., (1983), were not "against" (as *Peasron II* defined the term) those showing an effect, Duffield-Lillico et al., (2003 a); Duffield-Lillico et al., (2003b); Clark et. al., (1998); Li, et al., (2004); Yoshizawa, et al., (1998); Helzlsouer, et al., (2000); Nomura et al., (2000); Van den Brandt, et al., (2003); Brooks et al., (2001). SMF ¶ 30-36. FDA did not attempt

[21] Duffield-Lillico et al., 2003a, Duffield-Lillico et al., 2003b, Clark et. al., 1998. SMF ¶ 30-35. Rejecting NPC trial follow-up studies because they were reviewing results for secondary endpoints rather than the primary endpoints thus, the results may be inconclusive due to a possible bias of preexisting cancers in the treatment and placebo groups. SMF ¶ 25.

[22] Yoshizawa, et al., 1998; Helzlsouer, et al., 2000; Van den Brandt, et al., 2003. *Id*.

to determine whether differences in dosage or selenium form affected outcomes and, thus, failed to perceive that the form and dose Plaintiffs use (sodium selenite/200 µg per day or selenium-enriched yeast/200 µg per day) was consistently shown to produce significant risk reduction in the science. *Id*.

FDA found that no scientific conclusions could be drawn from any evidence submitted in support of claim IV. The FDA dismissed a placebo controlled intervention study,[23] 2 nested case-controlled observational studies,[24] and 1 meta-analysis study[25] deeming each inconclusive for one reason or another. FDA thus suppressed Claim IV. SMF ¶ 15-16.

FDA found no scientific conclusions derivable from the scientific evidence submitted in support of Claim V. The FDA dismissed 1 nested case controlled intervention study,[26] 1 cross-sectional observational study,[27] 1 ecological study,[28] 2 prospective studies, [29] and 3 nested-case control observational studies.[30] SMF ¶ 40-46.

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[23] Hercberg, et al., 2004. SMF ¶ 39.
[24] Dismissing the Van den Brandt, et. al., 1993, and Knekt, et al., 1998 studies because data was observed from a population with selenium deficiencies. SMF ¶ 37-38.
[25] As with other meta-analyses and book chapters FDA chose to ignore the conclusions reached in the Zhuo, et al., 2004 study. SMF ¶ 39.
[26] FDA rejected 2004 Wei, et al., study because it tested selenium-deficient populations in China. SMF ¶ 44.
[27] FDA rejected 1993 Clark, et al., categorizing it as a "[r]etrospective observational stud[y] that measured a post-diagnostic biomarker of selenium intake in subjects with cancer" and thus the FDA found the evidence inconclusive. SMF ¶ 40.
[28]FDA rejected 1977 Schrauzer, et al. because they were peer-reviewed review articles or meta-analyses and not original research. SMF ¶ 45.
[29] FDA eliminated from consideration 1995 Garland, et al., article because it "did not adequately adjust for confounders of risk of the specific type of cancer being studied." SMF ¶ 41. FDA found 2006 Peters, et al. of "high methodological quality," SMF ¶ 46, but, without detailed explanation, concluded that "this study does not provide any evidence for a relationship between selenium and reduced risk of colorectal cancer," citing a lack of "significant difference in the overall incidence of adenomous colorectal polyps … " The researchers' findings in the study contradict FDA's conclusion. *Id*.
[30] FDA rejected 2000 Ghadirian, et al., 1988 Jaskiewicz, et al., and 2002 Fernandez-Banares, et al.,outright because they were retrospective post-diagnostic studies. SMF ¶¶ 41, 43.

FDA thus ordered outright suppression of yet another claim, deeming supportive evidence inconclusive. SMF ¶ 15-16.

In all, of the 233 scientific articles supporting the proposed claims, FDA found only 20 met its EBRS evidence standard. *Id*. In its Order, FDA relied on 1 intervention study out of 30 and 19 observational studies out of 105. *Id*. In addition, the FDA failed to credit the same evidence it previously credited in support of Claims I and II. *Id*. (rejecting the 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)); see also SMF ¶ 27. FDA gave no weight to 23 animal and in vitro studies. *Id*. The Order did not identify any evidence specifically "against" the science supporting the proposed claims, nor did the FDA produce any empirical data that consumers would be mislead by the claims if "short, succinct, and accurate" qualifications were employed in lieu of outright suppression. SMF ¶ 17.

III. ARGUMENT

A. SUMMARY JUDGMENT STANDARD

Under Federal Rule of Civil Procedure (FRCP) 56, summary judgment should be granted when "there is no genuine issue as to any material fact" and "the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). "Disputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment." *Anderson v. Liberty Lobby, Inc*., 477 U.S. 242, 247-48 (1986). Although the Court must view all evidence in the light most favorable to the non-moving party, the non-movant must present more than a "metaphysical doubt as

to the material facts" to survive summary judgment. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986).

B. THE FIRST AMENDMENT STANDARD

In *Pearson I* our Court of Appeals established a First Amendment standard for FDA review of qualified health claims. *See Pearson I*, 164 F.3d 650 (D.C. Cir. 1999). The challenge Plaintiffs bring is exclusively constitutional, not dependent on administrative law. Consequently, the higher law applies, and not the deferential *Chevron U.S.A., Inc. v. Natural Resources Defense Council,* 467 U.S. 837 (1984) or Administrative Procedures Act, 5 U.S.C. § 501 et al., standards.

Pearson I held that the First Amendment requires FDA to "allow" claims it does not approve unless it satisfies a strict First Amendment burden of proof for claim suppression. *See Id*. at 656-. *Pearson I* determined that FDA cannot constitutionally censor claims it does not "approve" unless it can establish *with empirical evidence* that the claims are inherently misleading (i.e., incapable of being rendered non-misleading through the addition of reasonable disclaimers). *See id*. at 655.

FDA was ordered to accept disclaimers as its lawful resort, but they had to be "short, succinct, and accurate." *Pearson I* and *Whitaker I* made clear that this indeed was the First Amendment requirement, explaining that the Constitution compelled FDA to adopt disclosure as the rule and suppression as the rare exception. *See Pearson I*, 164 F.3d at 657 (citing *Bates v. State Bar of Arizona*, 433 U.S. 350, 376, 97 S.Ct. 2691, (1977)); *Whitaker I*, 248 F.Supp.2d at 14.

In short, *Pearson I* upholds as a matter of First Amendment law that the FDA may not prohibit speech based on its subjective dislike of the science or its view that the

science is inconclusive. Rather, FDA's power to censor is limited to those rare instances where it can prove, with empirical evidence, that qualifications cannot cure misleadingness but "hopelessly bewilder consumers." *Id.* at 659-660. The First Amendment squarely plants the burden of proof on FDA. *Whitaker I*, 248 F.Supp. 2d at 9. As a condition precedent to censorship, FDA's speech police must prove that the evidence it has been presented is incapable of being conveyed accurately because empirical evidence proves no potential qualification sufficient to save consumers from bewilderment and confusion. That it has never done. *See Bates*, 433 U.S. at 374-375 ("[I]t seems peculiar to deny the consumer, on the ground that the information is incomplete, at least some of the relevant information needed to reach an informed decision. The alternative the prohibition of advertising serves only to restrict the information that flows to consumers").

In *Whitaker I* this court explained the high First Amendment standard applicable to FDA claims review:

> Specifically, *Pearson I* identified two situations in which a complete ban would be reasonable. First, when the 'FDA has determined that *no* evidence supports [a health] claim,' it may ban the claim completely. *Id*., 164 F.3d at 659-660 (emphasis in original). Second, when the FDA determines that 'evidence in support of the claim is qualitatively weaker than evidence against the claim--for example, where the claim rests on *only one or two old studies*,' it may impose an outright ban. *Id.*, 164 F.3d at 659 n.10 (emphasis added). Even in these two situations, a complete ban would only be appropriate when the government could demonstrate with empirical evidence that disclaimers similar to the ones [the Court] suggested above ["The evidence in support of this claim is inconclusive" or "The FDA does not approve this claim"] would bewilder consumers and fail to correct for deceptiveness.

Whitaker I, 248 F.Supp. 2d at 10 (quoting *Pearson I*, 164 F.3d at 659-660) (emphasis in original). The burden is FDA's alone:

> The First Amendment places the burden on the government to prove that its method of regulating speech is the least restrictive means of achieving its goals. The First Amendment does not allow the FDA to simply assert that Plaintiff's Claim is

> misleading in order to supplant [its] burden to demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.

Id. at 9 (internal citations omitted).

Despite this Court's command that FDA apply the First Amendment standard when reviewing health claims, it has never done so. FDA has never even recited, let alone applied, the standard. In the present case, FDA again fails to cite and apply the standard, contumaciously refusing to abide by the higher law. Moreover, it refuses to limit its censorship to those instances where it can prove with empirical evidence that reasonable disclaimers fail to correct for deceptiveness and bewilder consumers. Instead, it has imposed a Kafkaesque review to achieve the same degree of suppression that pre-existed *Pearson I*, categorically culling from the science all it deems for one reason or another inconclusive and then rendering its opinion on the remainder with an essential onus favoring suppression guiding its hand. In this case it unscientifically declared all treatment studies (probative of the mechanism by which selenium reduces cancer risk); all animal studies and in vitro studies; and all review articles excluded. It thus reduced a total of 233 peer-reviewed scientific publications supporting the claims to a subset of 20 and then attacked those remaining on subjective grounds deeming inconclusiveness a sufficient basis for censorship, a position directly contrary to the pro-disclosure First Amendment standard required by *Pearson I* and *Whitaker I*.

The agency's review does not ask whether science is credible and how best to ensure through qualification that the science is accurately presented. Rather, the agency's review asks whether FDA is persuaded by the science, a subjective assessment of conclusiveness, precisely what the *Pearson I* court forbad when FDA performs a qualified claims review. FDA's present review is a de facto reassertion of FDA's pre-

Pearson I standard wherein the agency asks the question of whether the science is conclusive, rather than whether science supporting the claim exists. The agency rejects the rule of law. The consequence is a resurrection of the prior unconstitutional schema in which suppression is the rule and disclosure the exception, contrary to the constitutional mandate of *Pearson I* and *Whitaker I*.

The *Pearson I* Court required that FDA use claim qualification in lieu of outright suppression as a less speech restrictive means to eliminate potential misleadingness. *See Pearson I*, 164 F.3d at 655-60. It did so based on an unbroken line of Supreme Court precedent from *In re R.M.J.*, 455 U.S. 191, 206 n. 20102 S.Ct. 929 (1982) to *Ibanez v. Florida Dep't of Business and Prof'l Regulation*, 512 U.S. 136, 144-46, 114 S.Ct. 2084 (1994), holding government censorship of truthful commercial information unconstitutional under *Central Hudson*'s final, less speech restrictive alternative, prong and directing government to rely on reasonable claim qualification as the constitutionally required less restrictive means. *See Bates v. State Bar of Arizona*, 433 U.S. 350, 376, 97 S.Ct. 2691 (1977) ("the preferred remedy is more disclosure, rather than less"); *see also In re R.M.J.*, 455 U.S. 191, 206 n. 20102 S.Ct. 929 (1982); *Peel v. Attorney Registration and Disciplinary Comm'n of Illinois*, 496 U.S. 91, 99-111, 110 S.Ct. 2281 (1990) (stating that "disclosure of truthful, relevant information is more likely to make a positive contribution to decision making than is concealment of such information"); *Ibanez v. Florida Dep't of Business and Prof'l Regulation*, 512 U.S. 136, 144-46, 114 S.Ct. 2084 (1994). Instead of accepting disclosure as the rule, FDA maintains a regime of suppression, repeatedly preferring suppression of scientific information to its release in the market, regardless of what this Court holds.

FDA's pre-*Pearson I* review, wherein it asked whether FDA was persuaded by the science, a subjective assessment of conclusiveness, is precisely the same kind of review it performs presently. On appeal from FDA's censorship of the folic acid-neural tube defect and antioxidant claims, this Court again declared FDA's censorship unconstitutional, chastening the agency for its flip refusal to follow *Pearson I*'s constitutional mandate and giving FDA a specific standard to follow in reviewing future claims. See *Pearson II*, 130 F. Supp. at 114-115; *See also Pearson III*, 141 F.Supp. 2d at 108; *Whitaker I*, 248 F.Supp. 2d at 10. FDA has never cited to, nor applied, that standard. Without meeting its heavy constitutional burden, FDA's speech police cannot lawfully censor Plaintiffs' protected speech.

C. FDA'S ORDER VIOLATES THE FIRST AMENDMENT, *PEARSON I* AND *WHITAKER I*

There are two rare instances when FDA may ban a claim outright: (1) "when the 'FDA has determined that no evidence supports [a health] claim,' it may ban the claim completely," *Whitaker I,* 248 F. Supp. 2d 10 (quoting *Pearson I*, 164 F.3d at 659-660); and (2) "when . . . FDA determines that 'evidence in support of the claim is qualitatively weaker than evidence against the claim--for example, where the claim rests on *only one or two old studies*,' it may impose an outright ban." *Id*. But even in those rare instances (3) FDA censorship is stayed unless it can "demonstrate with empirical evidence that disclaimers . . . would bewilder consumers and fail to correct for deceptiveness." *Id*. FDA has utterly failed to meet any element of its three fold burden of proof.

In this case, like in *Pearson II, III*, and *Whitaker I*, "[t]he FDA has simply failed to adequately consider the teachings of *Pearson* [*I*]: that the agency must shoulder a *very heavy burden* if it seeks to totally ban a particular health claim." *Pearson II*, 130 F.Supp.

2d 119 (emphasis added). It has deliberately refused to abide by the governing law. In its Order, FDA could not establish that there was no evidence in support of Claims I, II, IV, and V or that the evidence not showing an effect was specifically "against" the evidence showing an effect, nor did the FDA even attempt to demonstrate with empirical evidence that reasonable disclaimers would hopelessly bewilder consumers. Thus, FDA's Order fails the First Amendment standard, violates Plaintiff's First Amendment rights, and violates the rule of law in *Pearson I* and *Whitaker I*. If the rule of law has meaning, FDA's contumacious disregard of it must be declared unconstitutional.

Under the First Amendment, FDA may only ban a scientifically-backed health claim if it can prove that the evidence in support of the claim is qualitatively weaker than the evidence "against" it. This Court has explained exactly what is meant by evidence "against": The "mere absence of significant affirmative evidence in support of a particular claim … does not translate into negative evidence 'against' it." *Pearson III*, 141 F.Supp. 2d 105 (citing *Pearson I*, 164 at 660); *Pearson II*, 130 F.Supp. 2d at 115. Rather, evidence "against" a claim must be both qualitatively superior and directly contrary to the supportive evidence. FDA lacks both.

In its Order FDA cites the SELECT trial (Lipmann et. al., 2009) as the only intervention study from which scientific conclusions could be drawn and attempts to use SELECT as evidence "against" the selenium prostate cancer risk reduction relationship. SMF ¶ 36. The SELECT trial was a large study of vitamin E and selenomethionine prematurely halted in October 2008. The SELECT trial has been criticized for using the wrong form of selenium (selenomethionine instead of selenium yeast like that used in the NPC trial (Clark et al., 1996)) and of being halted before the selenomethionine had the

opportunity to demonstrate its effect. *Id*. Selenomethionine is diverted into non-cancer fighting pathways and thus is a less "potent" form of selenium than methylselenocysteine, taking longer to demonstrate its beneficial effects. As the SELECT trial investigators who halted the study stated (in the official publication describing the study), "[p]otential limitations of SELECT include that it did not test different formulations or doses of selenium and vitamin E and that it did not definitively assess results in subgroups of men who may have responded differently than did the overall population." *Id*. In an editorial, Dr. Alan R. Kristal, one of the SELECT researchers, said, "[t]he possibility remains that the decisions of SELECT on dose and formulation were wrong." *Id*. In addition, selenium scientists at the Karolinska Institute stressed in their recent article that "[s]elenium has a clear role in the regulation of normal and malignant cell growth.. . . . [R]esults from the SELECT trial must not lead to the depreciation of all positive and interesting data generated over the past decades. The reported cancer preventive effects in several studies are extraordinary for selenium… In the near future selenium may thus be used by the public as a cancer preventive dietary factor but also be used by the medical profession in the treatment of cancers." *Id*. SELECT thus by its own investigators and researchers' admission does not translate into negative evidence "against" any of the supportive evidence presented by Plaintiffs.

In short, it is not enough that a study fails to confirm an entire body of science supportive of the claim. That one study must be proven both qualitatively superior to the other studies and to be directly "against" the other supportive studies. *See Pearson III*, 141 F.Supp. 2d at 112 (citing *Pearson I*, 164 at 660) (critically explaining that the "mere absence of significant affirmative evidence in support of a particular claim … [is not]

negative evidence 'against' it"). An interpretive gloss on the meaning of a study is not the same as scientific proof that prior evidence is false.

The science-backed claims here in issue are thus not inherently misleading but, at worst, only potentially misleading. Consequently, under the First Amendment the FDA was forbidden from banning them. FDA violated the First Amendment when it chose outright suppression over disclosure with "reasonable" "short, succinct, and accurate disclaimers."

Two of the claims FDA now bans anew it previously allowed Claims I and II). SMF ¶ 10. Claim I was allowed in 2003 after a thorough review of the scientific evidence. In that review FDA considered seven supportive scientific studies and credited each one. SMF ¶ 11. That same science remains in FDA's files and is complemented by the new science in Plaintiffs' present petition. SMF ¶ 17. The earlier science revealed site specific cancer risk reductions in the prostate, lung, and colorectum. SMF ¶ 11. FDA does not explain why that evidence is no longer credible or why the complementary evidence that has come to light since is not credible. Claim II, which FDA allowed, it now *sua sponte* deems exclusively a disease treatment claim (the latter being prohibited for supplements, *see Whitaker v. Thompson*, 239 F.Supp.2d 43(D.D.C. 2002)). FDA argues that it made a mistake in understanding the term's meaning before and now believes "anticarcinogenic" exclusively connotes cancer treatment, not cancer prevention. SMF ¶ 16.

FDA's gratuitous redefinition of the term, however, contradicts the meaning ascribed to it by FDA's more knowledgeable sister agency, the National Cancer Institute ("NCI"). NCI is "the Federal Government's principal agency for cancer research and

training." *See* NCI mission statement, available at, http://www.cancer.gov/aboutnci/overview/mission (last visited October 5, 2009); *see also* Pub. L. No. 244, 75th Cong., 50 Stat. 559 (Aug. 5, 1937). NCI defines "anticarcinogenic" as "having to do with preventing or delaying the development of cancer." NCI Dictionary of Cancer Terms, available at, http://www.cancer.gov/dictionary/?CdrID=44272, (last visited, October 2, 2009). NCI thus defines the term as one concerning risk reduction, not disease treatment. In any event, given the NCI definition, it is reasonable to construe the term to mean risk reduction as NCI does and begs for a claim qualification as a less speech restrictive alternative to an outright ban. What then does the First Amendment require of the agency? Under First Amendment, the Supreme Court has explained that a truthful claim may not be censored on the basis that more information germane to it could have been supplied or may be supplied in the future. *See Bates*, 433 U.S. at 374-375 ("[I]t seems peculiar to deny the consumer, on the ground that the information is incomplete, at least some of the relevant information needed to reach an informed decision. The alternative the prohibition of advertising serves only to restrict the information that flows to consumers"). Rather, as *Pearson I, II, and III* and *Whitaker I* require, a "short, succinct, and accurate" disclaimer must be employed.

The solution, as explained in *Pearson I* and as required by the final prong of *Central Hudson*, is more information, not less. Thus, when FDA gratuitously ascribed to the term, "anticarcinogenic," a disease treatment connotation, it was required next to determine if the term had a non-disease treatment meaning. It does, as the National Cancer Institute makes clear. Therefore, rather than ban the claim, it was incumbent

upon FDA to rely on the less speech restrictive alternative of a reasonable qualification. Thus, FDA could have required that the claim be qualified with the following: "Anticarcinogenic' refers to cancer risk reduction, not cancer treatment." The heavy hand of FDA's speech police would be stayed in favor of disclosure. The Plaintiffs would accept this or any other reasonable and succinct qualification of the term to avoid what they do not intend to claim in any event, i.e., that selenium is a treatment for cancer rather than a dietary means to reduce cancer risk.[31]

In its petition, Plaintiffs' submitted two exhaustive reports written by leading experts in selenium and cancer documenting the current state of peer-reviewed scientific evidence supporting the risk reduction relationship between selenium and cancer generally and selenium and site specific cancers. SMF ¶ 19-21.[32] Plaintiffs submitted the following peer-reviewed scientific evidence in support of the claims:

1. Scientific Evidence Supporting Selenium's Anticarcinogenic Effects (Claims I and II)

FDA's Order erroneously reversed agency allowance of Claims I and II because it found that use of the terms "certain kinds of cancer" and "anticarcinogenic" were "too broad to be accurate."[33] SMF ¶ 16. The FDA refused to accept, as it had in the past, that selenium has antioxidant and other properties that produce system-wide anticarcinogenic

[31] Indeed, the Plaintiffs will accept any reasonable short, succinct, and accurate disclaimer for association with all of the claims here in issue as substitutes for the qualifications they proposed. The elucidation of appropriate qualifications is FDA's First Amendment obligation under *Pearson I* as the First Amendment burden remains inexorably FDA's.

[32] Plaintiffs do not reference in the body of this memorandum all articles submitted (which are included in the Administrative Record and include the entire submissions made to FDA). Those identified in this memorandum are a representative subset of the total science provided to the agency.

[33] Note well that FDA did not find there was no evidence supporting the claims instead making the argument that Claim I and II were too broad and thus inaccurate without addressing the possibility of clarifying disclaimers or producing any type of empirical data demonstrating that appropriate disclaimers would fail to correct for misleadingness as required under *Pearson I* and *Whitaker I*. *See Pearson I*, 164 F.3d at 659-660; *Whitaker I*, 248 F. Supp. 2d at 10.

effects. SMF ¶ 29. In their petition, Plaintiffs' expert explained in an uncontroverted passage:

> [the] position that each form of cancer is a unique disease based on organ site, risk factors, treatment options and mortality risk is not relevant to simply preventing cancer by reducing the common cellular membrane and DNA damage that is involved in most cancers. Even though initial events (such as radiation, carcinogens, etc.) may differ, often the common route of cancer cause then involves free radical pathology (including damage initiated by free radicals, reactive species and oxidants) to damage cell membranes and DNA, which in turn is the direct cause of the mutations that become cancers. The cause per se of these cancers is not various initiating events, but free-radical pathology per se, which is a single (common) cause that can be blocked by certain antioxidant nutrients including selenium-containing compounds.

SMF ¶ 29 (Dr. Richard A. Passwater). In addition, a 1998 peer-reviewed article published in the Journal of Nutrition explained that selenium-containing compounds cause "tumor inhibition . . . in mammary gland, liver, skin, pancreas, esophagus, colon and a few other sites." *Id*. The FDA summarily refused to credit these system-wide anticarcinogenic effects. *Id*.

Selenium exhibits anticarcinogenic properties, at least in part, because of its antioxidant and immune-enhancing activity. SMF ¶ 20. Selenium-containing nutrients exert their anti-cancer effects by protecting cell membranes and DNA, but also by regulating nuclear factor activities including nuclear factor kappa-B and p53. *Id.* The mechanisms include antioxidant effects of selenium mediated through glutathione peroxidase, modification of carcinogen metabolism, effects on the immune system and endocrine functions, production of cytotoxic metabolites, inhibition of protein synthesis and enzymes that catalyze cell proliferation, and induction of apoptosis. *Id.*

Selenium's antioxidant activity is also attributed to its role in selenium-dependent thioredoxin reductases. SMF ¶ 21. Much of the biological function of thioredoxin reductase (TR) is attributed to its role as a reductant of the protein thioredoxin (TRx). *Id.*

Both TR and TRx are critical for redox control at the cellular level; together they participate in several biologic processes including antioxidant defense, cell proliferation, and inhibition of apoptosis. *Id.*

Dr. Gerhard Schrauzer has identified six selenium anti-cancer mechanisms of action (stimulation of immune response; protection against radicals, oxidants and radiation; detoxification of environmental mutagens or carcinogens, liver protection; maintenance of cellular respiration and additional nonspecific effects). SMF ¶ 23(a).[34] A 1997 animal study found that selenium compounds can raise the levels of cytochrome P450 and mixed function oxidases responsible for the detoxification of carcinogens. SMF ¶ 23(b).[35]

An article published in 2001 lists five mechanisms for the carcinostatic properties of selenium, explaining that catalytic redox selenium metabolites are formed by selenium metabolism which modulates the mitochondrial redox equilibrium and induces apoptosis in cancer cells which have lost this regulating ability. SMF ¶ 23(c).[36]

In 2000, an in vitro study conducted by Zou, et al., demonstrated that selenium arrests growth of cancer cells and induces apoptosis (programmed cell death). SMF ¶ 23(d).[37] As discussed in a peer-reviewed book excerpt from 2006 (explaining the significance of apoptosis), "[t]he controlling factor for the induction of cellular apoptosis

[34] FDA chose not to review this evidence because it was a chapter in a peer-reviewed book and not original research. *Id.*
[35] FDA rejected the researchers' findings because the study was conducted using rats, *id*., but FDA has no proof that the mechanism of action studied in the rats, identical to that in humans, is not indicative of the effects of the substance in humans. Its view is entirely speculative. Under the First Amendment FDA bears the burden of proof. *See Whitaker I*, 248 F. Supp. 2d at 9.
[36] FDA provided no discussion of the article in its Order and erroneously rejected this publication and the scientific evaluation therein because it consisted of a review article. *Id*. Yet the AHRQ report was a review article and it was accepted.
[37] FDA rejected this study outright because it was an in vitro study. *Id.*

is the mitochondrion . . . Selenium compounds are known to cause mitochondrial swelling, a precursor event to apoptosis." SMF ¶ 23(e).[38]

In a 1998 review by Combs et al., these scientists endorsed selenium's anticarcinogenic properties stating, "it is clear from a fair body of epidemiological studies and a large number of experimental animal tumor model studies that it is plausible to consider Se compounds as potential chemopreventative agents. The results of recent clinical trials, despite their specific limitations, add considerably to that plausibility …" SMF ¶ 23(f).[39]

In 1983, Willet et al. reported a case-control observational study of 10,000 American men and women. SMF ¶ 23(g). The researchers analyzed blood samples from all participants for selenium content. *Id.* The authors discovered a significantly greater than expected cancer incidence in the lower blood selenium group. *Id.* The increased risk of cancer in the lower quintile of baseline was twice that in the highest quintile. *Id.*[40]

In addition, Plaintiffs submitted numerous studies demonstrating that selenium inhibits the genesis of MMTV-induced mammary tumors in C3H mice. SMF ¶ 23(h). Subsequent studies demonstrated that selenium at sub-toxic levels significantly prevented the genesis of tumors without side-effects. *Id.*[41]

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[38] FDA eliminated this publication from consideration because it was part of a peer-reviewed book chapter. *Id*.

[39] FDA's Final Order did not consider the merits of the Combs article because it was a peer-reviewed meta-analysis. *Id.*

[40] FDA found the 1983 Willet study was of moderate methodological quality, but the FDA only considered the study in support of certain site-specific cancers and ignored the article's support of general anti-carcinogenic mechanisms, *id.* (citing case-study in reference to breast cancer, colon and digestive tract cancers, lung cancer and prostate cancer). FDA did not consider the remaining findings of the 1983 Willet et al., study in support of selenium's general anticarcinogenic effect. *Id.*

[41] FDA eliminated all animal studies from its review of the "credible" science because the effects may be different in humans, yet FDA requires both animal and human studies for new drug approval. *Id*. Plaintiffs' expert credibly discussed the relevance of the various studies in his report (i.e. relevance of Se-Cr interactions in human cancer and relation between studies conducted on mice and human breast cancers) but FDA ignored this explanation. *Id*.

Plaintiffs also submitted a 1997 article written by one of its experts which analyzed an ecological study that compared serum selenium levels in healthy individuals with cancer mortality, the results revealed a "statistically highly significant" inverse relationship for total cancer mortalities "as well as for cancers of the colon, rectum, prostate, breast, ovary leukemia, pancreas, bladder, skin, buccal cavity and pharynx." SMF ¶ 24.[42]

In 1996 the Journal of the American Medical Association published the Nutritional Prevention of Cancer Trial (NPC), explaining the results of a double-blind, randomized intervention trial. SMF ¶ 25. The original data published in the NPC trial found that daily supplementation of diets with 200 micrograms of selenium reduced cancer mortality 50 percent. *Id.* Total cancer incidence was reduced 37 percent and total carcinoma incidence was reduced 45 percent. *Id.* More recent reviews of the full data provide an average of 7.9 years of follow-up per patient (which allows greater statistical precision than was available for the original analyses when only 6.4 years of follow-up per patient had been achieved). *Id.* The analyses of the complete data support the strongest protective effects previously detected, *to wit*, selenium supplementation was associated with reduced risks of total cancer incidence and incidences of carcinomas in the prostate, colon, and rectum. *Id.* Plaintiffs submitted seven reports to FDA concerning the NPC trial (Clark et al., 1996; Clark et al., 1998; Duffield-Lillico et al., 2002; Duffield-Lillico et al., 2003a, 2003b; Reid et al., 2002; Reid et al., 2006). *Id.* Despite FDA's previous reliance on NPC trial post-hoc studies to allow Claims I and II, finding that "the observational studies provide limited and inconclusive evidence to

[42] FDA made no findings on the 1977 Schrauzer articles nor the ecological study analyzed in the articles because they consisted of review articles and meta-analyses. *Id.*

suggest a possible relationship between selenium intake and reduced risk of cancer,"[43] in its 2009 Order FDA did not consider any of the seven post-hoc analyses of the NPC trial to be credible. SMF ¶ 17. FDA did not follow the First Amendment standard. Had it done so, this evidence would have to be accepted as credible even if FDA deemed it inconclusive, and the claim would have to be allowed with a "short, succinct, and accurate" disclaimer.

In 2004, a French intervention trial named the "Supplementation en Vitamines et Mineraux Antioxydants" (SU.VI.MAX) affirmed the results of the NPC trial. SMF ¶ 26. The SU.VI.MAX trial found that selenium supplementation significantly lowered total cancer incidence in men by 31 percent, but not in women. *Id*[44]. The significant reductions in cancer incidence were widespread in cancer type and included thyroid, urinary tract, skin, respiratory tract, digestive tract, and oral cavity cancers. *Id.* Plaintiffs submitted three reports based on the SU.VI.MAX trial that found anticarcinogenic effects from selenium consumption. *Id.*[45] A subsequent French study entitled the Etude du Vieillissement Arteriel (EVA), reported in 2005, found yet again a significant association between cancer-related mortality and low plasma selenium concentrations. SMF ¶ 27.[46]

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[43] *See* SMF ¶ 17; *see also supra* pg. 10-12 (discussing FDA's reliance upon NPC trial in 2003 acceptance of selenium qualified health claims).

[44] The results in women is most likely a product of the women being younger than men in this trial, and generally had a healthier lifestyle as evident by higher serum β-carotene and vitamin C and fewer smokers. SMF ¶ 26 Fn. 4.

[45] FDA rejected all studies involving the SU.VI.MAX trial and stated that, "Because the SU.VI.MAX study did not confirm that all subjects were free of the cancers of interest prior to the intervention, the study may have involved subjects who had the site-specific cancers evaluated in the two SU.VI.MAX reports, and consequently the results with respect to effects on the risk of those cancers may be biased." *Id*.

[46] FDA provided no specific discussion concerning the EVA study, except to categorize the study as one "that reported no data on the relationship between selenium intake and risk of cancers for which the petition requested qualified health claims." *Id.* However the EVA study discusses plasma selenium and causes of death stating that, "bivariate Cox models showed a significant association between cancer-related mortality and low plasma selenium concentrations." *Id*.

Finally, Plaintiffs cited the report authored by the Agency for Healthcare Research and Quality (AHRQ). SMF ¶ 28. The report was based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the AHRQ. *Id*. The report was funded by the National Institutes of Health Office of Medical Applications of Research. *Id.* The data sources used in the AHRQ report were said to be all articles published through February 28, 2006, on MEDLINE®, EMBASE®, and the Cochrane databases. *Id.* In its 2007 Notice expressing an intent to reevaluate the science supporting the 2003 Selenium health claims, FDA stated that it was undertaking a reevaluation of the scientific basis for these qualified health claims because of new scientific evidence that has emerged for these substance-disease relationships. *Id*.; *see also* 72 Fed. Reg. 72738 (Dec. 21, 2007). FDA referred to their Reference 5, the 2006 AHRQ report, as the only newly emerged scientific study of selenium and cancer. *Id.* Tellingly, the FDA misrepresented the AHRQ in its decision stating, "[t]he report concluded that the overall strength of the evidence for … selenium supplements on cancer risk is … low." SMF ¶ 13. Not so. The actual AHRQ report concludes, "Taking into consideration the quantity, quality, and consistency of evidence on the efficacy of selenium in preventing chronic disease [including, but not limited to, cancer], we concluded that the overall strength of evidence is 'moderate.'" SMF ¶ 28. The AHRQ report identified six articles that met stringent criteria and provided evidence on the efficacy of selenium supplements in the prevention of cancer. *Id.* The Order addresses several of the studies identified in the AHRQ report, fails to credit them as credible, and never addresses the AHRQ report itself or its conclusions. *Id.*

Throughout the Order FDA asked not whether any credible science existed to support the claims (clearly credible evidence does exist, as the above representative subset from Plaintiffs' FDA petition reveals). Rather, FDA asked whether it was persuaded by the science, a subjective assessment of conclusiveness, precisely what the *Pearson I* court forbad FDA to do in qualified claims review under the First Amendment. FDA's Order is thus a contumacious rejection of *Pearson I* and *Whitaker I* reassertion of FDA's pre-*Pearson I.*

2. Scientific Evidence Supports Selenium's Lung and Respiratory Tract Cancer Risk Reduction Effects (Claim IV)[47]

Plaintiffs submitted a 1993 cohort study (Van den Brandt, et. al., 1993) involving 120,852 Dutch men and women aged 55-69 demonstrating a 50 percent risk of lung cancer associated with above baseline selenium concentrations. SMF ¶ 37. The authors observed, "The results of this study support an inverse association between selenium status and lung cancer." *Id*. The authors stated that, "The rate ratio of lung cancer for subjects in the highest compared to the lowest quintile . . . after controlling for age, gender, smoking, and education, was 0.50% (95% confidence interval)…" *Id.*[48]

In a 1998 nested case-control study (Knekt, et al., 1998) involving 9,000 Finns researchers observed that "the relative risk of lung cancer between the highest and lowest tertiles of serum selenium, adjusted for smoking, serum alpha-tocopherol, serum cholesterol, serum copper, serum orosomucoid, and body mass index, was 0.41" SMF ¶

[47] Plaintiffs do not recite a comprehensive list of articles submitted in support of the petitioned lung and respiratory cancer health claims. *See* Administrative Record for the articles provided to the FDA in their entirety.
The summary of scientific evidence serves as a representative subset of the total science provided to FDA.
[48] FDA found the study findings inconclusive because it thought the study's findings concerning Chinese, Finnish, and Dutch men not applicable to Americans and, thus, drew no scientific conclusions because of differences it presumed existed in serum and toenail selenium levels in Chinese, Finnish, or Dutch subjects compared to Americans. *Id*.

38. The researchers concluded that "the findings suggest that very low selenium status may contribute to the risk of lung cancer." *Id.*[49]

In addition, a meta-analysis (Zhuo, et al., 2004) from 2004 analyzed 16 separate studies and found a significant decreased risk of lung cancer with increased selenium intake or status. SMF ¶ 39. The authors concluded that, "Overall, these results suggest that selenium may have some protective effect against lung cancer in populations where average selenium levels are low." *Id.*[50]

Finally, Plaintiffs submitted evidence from the SU.VI.MAX Intervention trial (Hercberg, et al., 2004) (which included lung cancers under the broader category of "respiratory tract cancers"). SMF ¶ 39. The SU.VI.MAX authors discovered that in men, the incidence of respiratory cancers was reduced from 88 per 100,000 for the control to 37 per 100,000 for the supplemented group. *Id.* In women, who had better diets and may have a higher expression of selenoproteins due to estrogenic effects, the incidence of respiratory tract cancers was reduced from 21 per 100,000 in the control to only 12 per 100,000 in the supplemented group. *Id.* FDA rejected that study because it involved a post-hoc analysis of secondary cancers. *Id.* FDA's findings are incorrect; the authors of the SU.VI.MAX study explained that participants were routinely given physicals and observed for signs of "cancer of any kind." *Id.*

Throughout the Order, FDA asked not whether credible science existed to support Claim IV (credible evidence clearly exists, as the above representative subset from

[49] FDA found the 1998 Knekt study inconclusive because like the Van den Brandt study, *surpa* n.20, the data was observed from an area with selenium-deficient populations. *Id.* However, according to federal government statistics, recited in the petition, 50% of Americans do not ingest the recommended level of selenium to produce anticarcinogenic effects. SMF ¶ 47.

[50] As with other meta-analysis and book chapters FDA chose to ignore any theories or conclusions reached in the Zhuo meta-analysis. *Id.*

Plaintiffs' FDA petition reveals) but whether it was persuaded by the science, a subjective assessment of conclusiveness, precisely what the *Pearson I* court forbad in qualified claims review under the First Amendment.

3. Scientific Evidence Supports Selenium's Colon and Digestive Tract Cancer Risk Reduction Effects (Claim V)[51]

Plaintiffs submitted a 1993 cross-sectional observational study (Clark, et al., 1993) of 48 individuals in the United States that found an almost 4-fold increased risk of colorectal cancer for plasma selenium concentrations below 128 mcg/L versus those above 128 mcg/L. SMF ¶ 40. The authors concluded, "[t]he results . . . are consistent with the experimental animal studies, geographic mortality studies, and prospective cohort studies of selenium and colorectal cancer." *Id.*[52]

Plaintiffs submitted two observational studies from 2000 (Ghadirian, et al., 2000) and 2002 (Fernandez-Banares, et al., 2002) that reported a statistically significant inverse association between toenail levels of selenium and colorectal cancer. SMF ¶ 41.[53] A similar 1988 observational study (Jaskiewicz, et al., 1988) determined that mean selenium levels of subjects with premalignant or malignant esophageal cytological changes were significantly lower than those of subjects without such lesions. SMF ¶ 43.[54]

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[51] The studies recited in this memorandum are but a representative subset of all germane studies presented to the FDA in Plaintiffs' petition. *See* Administrative Record for the articles provided to the FDA in their entirety.

[52] FDA rejected the 1993 Clark study, categorizing the study as a "[r]etrospective observational stud[y] that measured a post-diagnostic biomarker of selenium intake in subjects with cancer" and thus the FDA deemed the evidence inconclusive drawing no conclusions from it. *Id.*

[53] FDA rejected the 2000 Ghadirian article outright because it was a retrospective post-diagnostic study. *Id.*

[54] FDA erroneously rejected the Jaskiewicz study without discussion because it involved a retrospective observational study measuring post-diagnostic biomarkers of selenium intake and thus gave no weight to the study whatsoever. *Id.*

A 2007 review article by Das, et al., 2007, explained that "selenium compounds have . . . been shown to inhibit the development of adenocarcinomas in animal models of colorectal carcinogenesis, and there is evidence from epidemiological studies showing an inverse relation between cancer mortality and selenium content in [the] diet." SMF ¶ 42. Dr. Das et al., discussed a pooled analysis of data from 3 randomized trials that tested the effects of various nutritional interventions for colorectal adenoma prevention in subjects that had recently undergone adenoma removal. *Id*. They demonstrated that the subjects with serum or plasma selenium in the highest quartile, when compared with those in the lowest quartile, had a significantly lower risk of adenoma recurrence. *Id.*[55] In addition, Plaintiffs provided FDA with an ecological study (Schrauzer, et al., 1977) that produced statistically significant inverse associations between the estimated dietary selenium intakes and the mortalities from cancer of the large intestine of men and women. SMF ¶ 45.[56]

In a 2004 nested intervention study (Wei, et al., 2004) from the Nutrition Intervention Trial in Linxian, China researchers found that when the subjects were classified by quartile of selenium, those in the highest quartile had a 65 percent reduction in the risk of death from esophageal squamous cell carcinoma and a 69 percent reduction in the risk of death from gastric-cardia cancer when compared with subjects in the lowest quartile. SMF ¶ 44.[57]

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[55] FDA failed to account for any of the theories or analysis in the 2007 Das article in its order and did not consider the publication in its review of credible science because the Das piece was a review article. *Id*. Yet the AHRQ report was a review article and it was accepted.
[56] FDA rejected the Schrauzer ecological studies because they were review articles or meta-analyses. *Id*.
[57] FDA rejected the 2004 Wei study because it tested selenium-deficient populations in China stating that conclusions could not be extrapolated to the United States population based on selenium-deficient Chinese population. *Id*.

Finally, the authors of a 2006 prospective study (Peters, et al., 2006) involving 758 cases of advanced colorectal adenoma, a cancer precursor and 767 sex- and race-matched controls concluded that, "Selenium may reduce the risk of developing advanced colorectal adenoma, particularly among the high-risk group of recent smokers." *Id.* The authors observed that, "[a] large body of experimental data, including animal models for colon cancer, supports a role for selenium in cancer prevention, potentially acting through multiple pathways. Selenium, particularly methylated forms, directly affects cell cycle control and apoptosis. In cell lines, selenomethionine activates p53, with related increases in p53-dependent DNA repair. Selenium may also interact with the folate/ homocysteine pathway, potentially altering DNA methylation patterns, as an early step in colorectal development." *Id.* The authors also concluded, that the "higher selenium levels were associated with reduced risk of advanced colorectal adenoma…" *Id.* In its Final Order, FDA found that the 2006 Peters study was of "high methodological quality" but rejected it by quibbling over methodological details not shown to affect the study outcome. *Id*.

Throughout the Order, FDA asked not whether any credible science existed to support the claims (credible evidence did) but whether it was persuaded by the science, a subjective assessment of conclusiveness, precisely what the *Pearson I* court forbad in qualified claims review under the First Amendment.

In its Order completely suppressing Plaintiffs' Claims I, II, IV, and V, FDA failed to provide any empirical evidence that use of disclaimers would fail to cure potential deceptiveness. *Whitaker I,* 248 F. Supp. 2d 10 (quoting *Pearson I*, 164 F.3d at 659-660). Instead, FDA summarily concluded that disclaimers would not suffice. SMF ¶ 49.

D. IN ITS ORDER, FDA CONTUMACIOUSLY REFUSES TO RELY ON REASONABLE "SHORT, SUCCINCT AND ACCURATE" DISCLAIMERS (Claim III)

Under the First Amendment standard, claim qualifications must be "reasonable," *Fox*, 492 U.S. at 480, 109 S.Ct. 3028(discussing *Central Hudson*, 447 U.S. at 564-66, 100 S.Ct. 2343); *Bates*, (citing *Virginia Pharmacy Board v. Virginia Consumer Council*, 425 U.S. 748, 771, 96 S.Ct., 1817, 1830 (1976)), which our Court of Appeals and this Court have determined to mean in the health claims context that they be "***short, succinct, and accurate***." *Whitaker I*, 248 F. Supp 2d at 10 (emphasis added); *see also Pearson I*, 164 F.3d at 659. Our Court of Appeals and this Court gave FDA precise examples of such claims, either one or both of which the Plaintiffs would readily accept: "The evidence in support of this claim is inconclusive" and "The FDA does not approve this claim." *Pearson I*, 164 F.3d at 659. FDA's disclaimer ("Two weak studies suggest that selenium intake may reduce the risk of prostate cancer. However, four stronger studies and three weak studies showed no reduction in risk. Based on these studies, FDA concludes that it is highly unlikely that selenium supplements reduce the risk of prostate cancer") is lengthy and, critically, false. SMF ¶ 16(b)(i). FDA offers no explanation (or empirical evidence) as to why the Court's recommended disclaimers would not suffice.

Here is how FDA arrived at its qualification. Of fifteen studies supporting the claim, FDA rejected all but nine. Of those, it found only two adequately supportive. Its disclaimer thus falsely states the number of supportive studies: There are not merely two, but a total of nine.

Plaintiffs submitted several articles discussing the NPC trial, which demonstrated that selenium supplementation was associated with a 65 percent reduction in prostate

cancer risk.[58] SMF ¶ 30. Plaintiffs submitted a 1998 study review by Clark et al., which examined data from the NPC trial and reported a 63 percent decreased risk of prostate cancer for those receiving 200 mcg of selenium per day versus placebo after 4.5 years of treatment and 6.5 years of follow up. *Id.* FDA gave no weight to any of the articles discussing the findings in the NPC trial on prostate cancer. *Id.* FDA excluded completely from its disclaimer any reference to the findings in the NPC trial. *Id*. The FDA eliminated the follow-up studies because they were reviewing results for "secondary endpoints." *Id*. The NPC trial nonetheless presented credible evidence of a significant reduction in prostate cancer. *Id*.

Plaintiffs submitted a 2004 Harvard Physicians Study (Li, et al., 2004) wherein a Harvard group examined the records of physician volunteers. SMF ¶ 32. Researchers found that, "[t]he inverse association between baseline plasma selenium levels and risk of advanced prostate cancer, even among men diagnosed during the post-PSA era, suggests that higher levels of selenium may slow prostate cancer tumor progression." *Id*. Specifically, the authors stated, "[w]e found a statistically significant inverse association between pre-diagnostic plasma selenium levels and subsequent risk of advanced prostate cancer among men enrolled in the Physician's Health Study. The association was statistically significant during the post-PSA era, even after 8 years of follow-up." *Id.* FDA's conclusion directly rejected the study author's and did not consider the 2004 Li study as supporting the selenium-prostate claim. *Id.* The FDA proposed disclaimer thus erroneously includes the Li study as evidence *against* a selenium prostate cancer risk reduction relationship. *Id*.

[58] Duffield-Lillico et al., 2003a, Duffield-Lillico et al., 2003b, Clark et. al., 1998. SMF ¶ 30-35.

In a 1998 nested case-control study (Yoshizawa, et al., 1998), the Harvard researchers concluded that, "[o]ur results support earlier findings that higher selenium intakes may reduce the risk of prostate cancer." SMF ¶ 33. Despite the thorough nature of the Yoshizawa study, FDA completely eliminated the study from consideration.

In another observational study (Helzlsouer, et al., 2000) that FDA rejected, researchers analyzed over 10,000 Maryland men finding that higher levels of selenium were associated with a lower risk for developing prostate cancer when the levels of vitamin E were also high. SMF ¶ 34. The study included controls for medical histories including medications used, smoking history, height and weight, and age. *Id*.

Finally, Plaintiffs submitted a 2003 observational study (Van den Brandt, et al., 2003) that reported after 6.3 years of follow-up, an inverse association between selenium levels and prostate cancer risk. SMF ¶ 35. According to the researchers, "These results confirm the hypothesis that higher selenium intake may reduce prostate cancer risk." *Id.* FDA rejected the Van den Brandt study out of hand because it deemed the results "not applicable to the general U.S. population." *Id*.

Thus, FDA falsely represents that there are only "[t]wo weak studies" supporting the claim when in fact there are a total of nine studies supporting it, studies scientists who cite them in Plaintiffs' submissions do not deprecate with the adjective "weak."[59] It has characterized the science not as our Court of Appeals and this Court allow, as "inconclusive" without a value judgment, but rather as "weak," which view is contradicted by other scientific opinion, such as that of the two renowned experts whose reports accompany Plaintiff's submission (and even of the AHRQ commissioned by FDA

[59] *See* SMF ¶ 30-36 (discussing Duffield-Lillico et al., (2003 a); Duffield-Lillico et al., (2003b); Clark et. al., (1998); Li, et al., (2004); Yoshizawa, et al., (1998); Helzlsouer, et al., (2000); Nomura et al., (2000); Van den Brandt, et al., (2003); Brooks et al., (2001)).

that found the scientific support "moderate" not "low" as FDA falsely states). Moreover, the disclaimer FDA requires is four times longer than the disclaimer recommended by our Court of Appeals and this Court. It is not, as required, "short, succinct, and accurate."

In *Pearson I* and *Whitaker I*, the FDA was given a mandate to "draft and submit one or more such appropriately ***short, succinct, and accurate*** disclaimers." *Whitaker I*, 248 F. Supp 2d at 10 (emphasis added); *see also Pearson I*, 164 F.3d at 659. In its Final Order, FDA failed that requirement. It has required use of an extremely long, negatively value-laden, inaccurate disclaimer, and false disclaimer contrary to the governing law.

IV. CONCLUSION

For the above stated reasons, Plaintiffs respectfully request that this Honorable Court:

Declare in accordance with 28 U.S.C. § 2201 (the Declaratory Judgment Act) that the FDA's June 19, 2009 final order (Docket No. FDA-2008-Q-0323-0015) denying Plaintiff's petition for qualified health claims is unconstitutional:

(a) that the FDA's June 19, 2009 final order (Docket No. FDA-2008-Q-0323-0015) violates the free speech clause of the First Amendment to the United States Constitution by censoring Claims I, II, IV, and V;

(b) that the FDA has contumaciously failed to follow the required court mandated analysis in *Pearson I*, *Pearson II*, *Pearson III* and *Whitaker I* in its censorship of Claims I, II, IV, and V and in its qualification of Claim III; and

(c) that the FDA's proposed misleading qualification for Plaintiffs' Claim III concerning selenium reducing the risk of prostate cancer violates the First

Amendment by mandating use of a false and lengthy qualification on Plaintiff's speech contrary to the requirements of *Pearson I* and *Whitaker I*.

Order FDA to refrain from taking any action that would preclude the Plaintiffs from placing the following health claims on the labels and in the labeling of their dietary supplements with suggested doses of 170-300 µg of selenium per day with the disclaimers present in the second sentence of the following proposed claims or with such reasonable short, succinct, and accurate disclaimers as the FDA may prescribe:

1. Selenium may reduce the risk of certain cancers. Scientific evidence supporting this claim is convincing but not yet conclusive.

2. Selenium may produce anticarcinogenic effects in the body. Scientific evidence supporting this claim is convincing but not yet conclusive.

3. Selenium may reduce the risk of prostate cancer. Scientific evidence supporting this claim is convincing but not yet conclusive.

4. Selenium may reduce the risk of lung and respiratory tract cancers. Scientific evidence supporting this claim is convincing but not yet conclusive.

5. Selenium may reduce the risk of colon and digestive tract cancers. Scientific evidence supporting this claim is convincing but not yet conclusive.

Enjoin through a permanent injunction FDA from taking any action that would preclude the Plaintiffs from placing the foregoing five health claims on the labels and in the labeling of their dietary supplements with suggested doses of 170-300 µg of selenium per day bearing either the disclaimers present in the second sentence of the claims or reasonable short, succinct, and accurate disclaimers as the FDA may prescribe.

Respectfully submitted,

____/s/_____
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