UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

JULIAN M. WHITAKER, MD., et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	**Civil Case No. 1:01CV01539 (GK)**
	)	
TOMMY G. THOMPSON,	)	
SECRETARY et al.,	)	
	)	
Defendants.	)	

MEMORANDUM OF POINTS AND AUTHORITIES
IN SUPPORT OF APPLICATION FOR PRELIMINARY INJUNCTION

Plaintiffs Julian M. Whitaker, M.D.; Pure Encapsulations, Inc.; Wellness Lifestyles, Inc. d/b/a American Longevity; Durk Pearson and Sandy Shaw; and the American Preventive Medical Association (APMA), by counsel and pursuant to LCvR 65.1(c) and (d) and Fed.R.Civ.P. 65, hereby submit this Memorandum of Points and Authorities, attached affidavits, and attached documentary evidence in support of their Application for Preliminary Injunction.

The Plaintiffs seek a preliminary injunction barring the Food and Drug Administration (FDA) from taking any action to prohibit them from including on the

labels and in the labeling[1] of their dietary supplements[2] that contain antioxidant vitamins (vitamins C and E)[3] the following truthful and nonmisleading statement:

> **"Consumption of antioxidant vitamins may reduce the risk of certain kinds of cancers"** (hereinafter "Antioxidant Vitamin Health Claim").

The Plaintiffs ask that the injunction remain in place until this Court has issued its final decision on all causes of action brought by Plaintiffs against the Defendants. The Plaintiffs have been, and continue to be, willing to accept any reasonable disclaimer for use with the Antioxidant Vitamin Health Claim, see Exh. 1, including the disclaimer recommended for the Antioxidant Vitamin Health Claim by the United States Court of Appeals in Pearson I:

> **The evidence is inconclusive because existing studies have been performed with *foods* containing antioxidant vitamins, and the effect of those foods on reducing the risk of cancer may result from other components in those foods.**

In violation of the Pearson I remand order and this Court's orders on construction contained in Pearson v. Shalala, 130 F.Supp.2d 105 (D.D.C. 2001) (hereinafter "Pearson

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[1] As explained in Pearson v. Shalala, 164 F.3d 650, 653 (D.C.Cir. 1999) *reh'g denied en banc*, 172 F.3d 72 (D.C.Cir. 1999) (hereinafter "Pearson I"), a "label" is "a display of written, printed, or graphic matter upon the immediate container of any article." 21 U.S.C. § 321(k)(1994). "Labeling" is defined as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Id. § 321(m).

[2] A "dietary supplement" is a "product (other than tobacco) intended to supplement the diet" that contains one or more of certain dietary ingredients, including a vitamin . . .," 21 U.S.C. § 321(ff)(1)(A)-(D) (Supp. 1998), "is not represented for use as a conventional food or as a sole item of a meal or the diet," id. § 321(ff)(2)(B), and "is labeled as a dietary supplement." Id. § 321(ff)(2)(c).

[3] Thirteen multi-vitamin dietary supplements in which Dr. Whitaker has a direct financial interest each contain antioxidant vitamin C (60-1,500 mg) and antioxidant vitamin E (50-800 iu). Eight of the multi-vitamin dietary supplement products manufactured, distributed, and sold by Pure each contain antioxidant vitamin C (100-1,000 mg) and antioxidant natural vitamin E (100-400 iu). Seven of the multi-vitamin dietary supplement products manufactured, distributed, and sold by AL each contain antioxidant vitamin C (10-1,000 mg) and antioxidant vitamin E (10-300 iu). Pearson and Shaw license for sale two multivitamin dietary supplements that each contain antioxidant vitamin C (900-1,076 mg) and antioxidant synthetic vitamin E (200-330 iu). Several APMA physicians, including many of its over 450 physician members and several of its 19 physician board members, sell multivitamin dietary supplements that each contain antioxidant vitamin C and antioxidant vitamin E. The foregoing amounts are below the "safe upper limits" established by the Institute of Medicine's Food and Nutrition Board. See FOOD AND NUTRITION BOARD, INSTITUTE OF MEDICINE, DIETARY REFERENCE INTAKES FOR VITAMIN C, VITAMIN E, SELENIUM, AND CAROTENOIDS 162, 258 (2000).

II"), FDA has again denied a health claim outright without evaluating use of disclaimers as a less restrictive alternative to speech suppression. See Exh. 2 (FDA Letter Ruling on Remand Denying Antioxidant Vitamin Health Claim (hereinafter "Letter Ruling")). The obvious hubris shown by that action in the face of plainly controlling Court orders (Pearson I, Pearson II, and Pearson v. Thompson, 141 F. Supp. 2d 105 (D.D.C. 2001) (hereinafter "Pearson III")) begs the question whether an agency of this government shall be permitted to disobey the constitutional orders of the federal courts and not be held accountable. Plaintiffs urge the Court to take prompt and decisive action to end FDA's law violations and hold it accountable.

I. THE FACTS AND THE LAW SUPPORT ISSUANCE OF THE REQUESTED PRELIMINARY INJUNCTION

In Pearson I our Court of Appeals held FDA's prohibition of the Antioxidant Vitamin Health Claim a violation of the First Amendment. See Pearson I at 657. The Court held the claim not "inherently misleading" but backed by scientific evidence. The Court held the claim, at worst, potentially misleading, and—consistent with an unbroken line of First Amendment cases from In re R.M.J., 455 U.S. 191, 203 (1982) to 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996) (see id. at 657-658)—ordered FDA to evaluate the use of a disclaimer as a less restrictive alternative to outright claim suppression. The Court ruled that FDA may not ban outright any dietary supplement health claim unless it establishes that the claim is "inherently misleading" (meaning incapable of being rendered nonmisleading through the addition of a disclaimer). See Pearson I at 655 and 659. For claims that are, at worst, only potentially misleading, the Pearson I Court found the constitutional remedy more disclosure, not less, i.e., allowance

of the claim when accompanied by such disclaimer as is, or such disclaimers as are, reasonably necessary to avoid misleadingness. See id. at 659-660.

In particular, the Court recommended FDA consider use of the following disclaimer with the Antioxidant Vitamin Health Claim: "The evidence is inconclusive because existing studies have been performed with *foods* containing antioxidant vitamins, and the effect of those foods on reducing the risk of cancer may result from other components in those foods." Id. at 658. On remand, FDA disobeyed the Court of Appeals' order. It did not evaluate disclaimers for use with the Antioxidant Vitamin Health Claim. Instead, FDA opened a new rulemaking proceeding, called for more scientific evidence, hired a panel to give it more evidence, and then spent in excess of two years before issuing a decision letter that again denied the health claim without evaluating a single disclaimer (the Court of Appeals' recommended disclaimer included). See 64 Fed. Reg. 48841 (September 8, 1999); 64 Fed. Reg. 67289 (December 1, 1999); 64 Fed. Reg. 71794 (December 22, 1999); 65 Fed. Reg. 14219 (March 16, 2000); 65 Fed. Reg. 59855 (October 6, 2000).

On February 1, 2001, this Court granted Plaintiffs' post Pearson I application for a preliminary injunction concerning a folic acid/neural tube defect claim, holding FDA's outright suppression of that claim, ".8 mg of folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form," a violation of the First Amendment and of the Court of Appeals' Pearson I remand order. Pearson II, 130 F.Supp. 2d at 120. In its injunction, the Court compelled FDA to adopt a "short, succinct and accurate" disclaimer, which the agency eventually did do but only after unsuccessfully seeking reconsideration of the original

order. Pearson III at 108. FDA did not appeal the order and it is thus final and binding law.

In Pearson II, this Court made its determination that FDA had failed to comply with the Pearson I remand order unmistakably clear, writing: ". . . the FDA simply failed to comply with the constitutional guidelines outlined in Pearson [I];" "the agency appears to have at best, misunderstood, and at worst, deliberately ignored, highly relevant portions of the Court of Appeals Opinion;" and ". . . "FDA has continually refused to authorize the disclaimers suggested by the Court of Appeals—or any disclaimer, for that matter . . ." Pearson II at 112, 114. The Court at length instructed FDA on the meaning of the Court of Appeals' decision and directed that FDA follow that decision. Pearson II at 114-115, 118. Indeed, it did so a second time in Pearson III at 110-112. Despite those teachings, FDA has utterly refused to follow the Court's orders; in the face of them, it has refused again to evaluate a disclaimer for use with another Pearson I claim, the Antioxidant Vitamin Health Claim. It continues to disobey the constitutional requirement of disclosure with disclaimer as a less restrictive alternative to outright suppression.

The First Amendment violations present in Pearson I and Pearson II have thus been repeated by FDA in its present denial of the remanded Antioxidant Vitamin Health Claim. As confirmed by the attached documentation, a preliminary injunction should issue forthwith. In Pearson II, this Court explained the elements that must be satisfied for a preliminary injunction to issue:

> To obtain a preliminary injunction, Plaintiffs must show (1) a substantial likelihood of success on the merits; (2) a substantial threat that they will suffer irreparable injury if the injunction is not granted; (3) that the threatened irreparable injury outweighs the threatened harm that the injunction would cause Defendants and third parties; and (4) that granting the preliminary injunction would be in the public interest. See Mova Pharm. Corp. v. Shalala, 140 F.3d

1060, 1066 (D.C. Cir. 1998); Washington Metro. Area Transit Comm'n v. Holiday Tours, Inc., 559 F.2d 841 (D.C. Cir. 1977).

130 F.Supp.2d at 112. Plaintiffs satisfy each of those elements, as explained below.

A. IRREPARABLE INJURY

Plaintiffs' Antioxidant Vitamin Health Claim is commercial and scientific speech protected by the First Amendment (Pearson I at 655). The Supreme Court has held violation of a First Amendment right, even for a very short period of time, an irreparable injury without proof of more. See Elrod v. Burns, 427 U.S. 347, 373 (1976) (plurality opinion) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury") *quoted in* Jackson v. City of Columbus, 194 F.3d 737, 747 (6th Cir. 1999); Iowa Right to Life Comm., Inc. v. Williams, 187 F.3d 963, 969 (8th Cir. 1999); Brownsburg Area Patrons Affecting Change v. Baldwin, 137 F.3d 503, 507 (7th Cir. 1998); New York Magazine v. Metropolitan Transportation Authority, 136 F.3d 123, 127 (2nd Cir. 1998); see also Lakewood v. Plain Dealer Publishing Co., 486 U.S. 750, 758 (1988); Washington Free Community v. Wilson, 426 F.2d 1213, 1218 (D.C. Cir. 1969). When government violates First Amendment rights, delay in eliminating the rights violation is unconstitutional: "Speakers . . . cannot be made to wait for years before being able to speak with a measure of security." Riley v. National Federation of the Blind, 784 U.S. 781, 793-94 (1988) (internal quotes omitted). See Pearson II, 130 F. Supp. 2d at 119 (holding FDA health claim suppression irreparable injury).

Plaintiffs have been forced to wait ***2784 days*** to date—well over ***seven years***—to place their nonmisleading and constitutionally protected scientific and commercial speech on their dietary supplement products. That extraordinarily long period of speech

suppression unquestionably constitutes irreparable harm. Not only have Plaintiffs suffered loss of vital First Amendment rights, but consumers seeking better health have been denied access to relevant scientific information at the point of sale.[4]

B. SUBSTANTIAL LIKELIHOOD OF SUCCESS

1. The Governing Law

In Pearson I, the United States Court of Appeals for the D.C. Circuit held that FDA violated the First Amendment "by declining to employ," in lieu of outright claim suppression, the "less draconian method [of] disclaimers." Id. at 654. The Court required that FDA's speech suppression be evaluated under the First Amendment commecial speech standard, rejecting FDA's call for deference to its scientific assessment.[5] The Court thus applied to FDA's suppression of the claims the three-part test articulated in Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n, 447 U.S. 557, 566 (1980) (as modified by its progeny). It found FDA's ban on the four claims there in issue to "encounter[] difficulty" with the second and third prongs of the Central Hudson test (the direct advancement and the means-ends portions of the test). In particular, the Court held that FDA's choice of suppression, over disclosure with disclaimers, violated the third prong of Central Hudson because suppression was "substantially excessive, disregarding far less restrictive and more precise means," *citing*

[4] As the Court of Appeals recognized, a claim made directly on the label of a dietary supplement is more effective than alternative channels of communication because the claim is more effective in reaching consumers and imposes lower search costs on them, citing John E. Calfee & Janis K. Pappalardo, *How Should Health Claims for Foods Be Regulated?* 26-27 (Bureau of Economics, Federal Trade Commission, 1989). Pearson I at 658, n7.

[5] The FDA argued to the Court that its suppression of health claims should not be subjected to First Amendment scrutiny, but to a more deferential review (e.g., the APA "substantial evidence" test). The Court soundly rejected that contention. At the outset, the Court held that Plaintiffs' First Amendment cause of action "requested [a] remedy [that] stands apart from appellants' request under the APA," Id. at 654. It then evaluated FDA's acts of suppression under the First Amendment commercial speech standard. In addition, the Court held that FDA's speech suppression warranted First Amendment review and refused to

Shapero, 486 U.S. at 476. The Pearson I Court stated: "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." Id. at 657.

From the Supreme Court's commercial speech precedent, the Pearson Court found a strong constitutional presumption favoring disclosure over suppression (rejecting "the government's position that there is no general First Amendment preference for disclosure over suppression," Id. at 658; finding "the preferred remedy . . . more disclosure, rather than less," Id. at 657, *citing* Bates v. State Bar of Arizona, 433 U.S. 350, 376 (1977); and explaining that the Supreme Court "has reaffirmed this principle, repeatedly pointing to disclaimers as constitutionally preferable to outright suppression," *citing*, *inter alia*, Peel v. Attorney Registration and Disciplinary Comm'n of Illinois, 496 U.S. 91, 110 (1990); In re R.M.J., 455 U.S. at 206 n.20).[6]

The Court found the disclosure presumption unrebuttable except upon proof both (1) that the speech in issue was inherently misleading (Id. at 655, *citing* In re R.M.J., 455 U.S. 191, 203 (1982); see also Peel v. Attorney Registration and Disciplinary Comm'n of Illinois, 496 U.S. 91, 110 (1990) (". . . State may not . . . completely ban statements that are not actually or inherently misleading")) and (2) that no disclaimer could correct for misleadingness ("we cannot allow rote invocation of the words 'potentially misleading' to supplant the [government's] 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 659, *citing*

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adopt FDA's call for "a more deferential review of government regulations on potentially misleading commercial speech." Id. at 658.

Ibanez, 512 U.S. at 146, and ". . . we are skeptical that the government could demonstrate *with empirical evidence* that disclaimers . . . would bewilder consumers and fail to correct for deceptiveness . . ." Id. at 659) (*emphasis added*).

In addition the Court found "almost frivolous" and "reject[ed]" the FDA's argument that health claims not satisfying its "significant scientific agreement" standard of review were by that fact "inherently misleading" and suppressible outright, writing: "As best we understand the government, its first argument runs along the following lines: that health claims lacking 'significant scientific agreement' are inherently misleading… We think this contention almost frivolous . . . We reject it." Id. at 655. Indeed, the Court agreed that when scientific evidence in support of a claim has not been proven to a conclusive degree (i.e., when it is inconclusive), that status (inconclusiveness) does not warrant claim suppression; it justifies a disclaimer to that effect. Pearson I at 658-659.

As the Court of Appeals and this Court have made manifest in Pearson I, II, and III, FDA may not suppress a health claim except upon meeting a very high burden of proof. Pearson II at 118 ("[T]he agency must shoulder a very heavy burden if it seeks to totally ban a particular health claim"). As a condition precedent to suppression, FDA must prove that the claim is incapable of being rendered nonmisleading through the addition of a disclaimer and is, therefore, "inherently misleading." See Pearson I at 655, *citing* In re R.M.J., 455 U.S. 191, 203 (1982); Ibanez v. Florida Dep't of Business and Prof'l Regulation, 512 U.S. 136, 144-46 (1994); Peel v. Attorney Registration and Disciplinary Comm'n of Illinois, 496 U.S. 91, 99-111 (1990). In its Letter Ruling denying Plaintiffs' Antioxidant Vitamin Health Claim, FDA not only failed to satisfy that

[6] See also Ibanez, 512 U.S. at 145, citing Peel, 496 U.S. at 111 n.10: "Concern about the possibility of deception in hypothetical cases is not sufficient to rebut the constitutional presumption favoring disclosure

burden, it entirely omitted the required constitutional analysis. See Exh. 2; compare orders in Pearson I at 656-657; II at 110-111. FDA has thus shirked its constitutional obligations as mandated by the Pearson Courts and has violated Plaintiff's First Amendment rights yet again.

Under the First Amendment, government bears a heavy burden to justify speech suppression. See Ibanez v. Florida Dep't. of Business and Prof'l Regulation, 512 U.S. 136, 143 (1994) ("The State's burden is not slight; the 'free flow' of commercial information is valuable enough to justify imposing on would-be regulators the costs of distinguishing the truthful from the false, the helpful from the misleading, and the harmless from the harmful," *citing* Zauderer v. Office of Disciplinary Counsel of Supreme Court of Ohio, 471 U.S. 626, 646 (1985)); Lorillard Tobacco Company v. Reilly, 121 S.Ct. 2404, 2422, 2425, 2428, 2001 U.S. LEXIS 4911, at 53, 64, 74 (2001) ("a governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree," citing Greater New Orlans Broadcasting Assn., Inc. v. United States, 527 U.S. 173, 184 (1999); it must "carefully calculate the costs and benefits associated with the burden on speech imposed," citing Cincinnati v. Discovery Network, Inc., 507 U.S. 410, 417 (1993); and it must be mindful of the admonition that "there is no *de minimis* exception for a speech restriction that lacks sufficient tailoring or justification"); Bartnicki v.Vopper, 121 S.Ct. 1753, 1764n.18; 2001 U.S. LEXIS 3815, at 31n.18 (2001) (noting that "the burden of justifying restrictions on commercial speech requires more than 'mere speculation or conjecture'"); see also Pearson I, 164 F.3d at 659, *citing* Ibanez, 512 U.S. at 146 ("If the protections afforded commercial speech are to

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over suppression."

retain their force, we cannot allow rote invocation of the words 'potentially misleading' to supplant the [government's] burden to demonstate that the harms it recites are real and that its restriction will in fact alleviate them to a *material* degree") (*emphasis added*) and citing Edenfield v. Fane, 507 U.S. 761, 771 (1993).

As a condition precedent to commercial speech suppression, then, it is incumbent upon FDA, like every other government agency, to prove that (1) it has a substantial state interest; (2) that its regulation directly advances that interest; and (3) that the fit between the means chosen and the ends is reasonable. See Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of New York, 447 U.S. 557 (1980). In particular, "to supplant the [government's] burden," it must "demonstrate that the harms it recites are *real* and that its restriction will in fact alleviate [the harms] to a *material* degree." Edenfield, 507 U.S. at 771 (1993) (*emphasis added*); Ibanez, 512 U.S. at 146. In short, the government must prove the existence of actual harm to consumers and it must show that its chosen remedy, here outright suppression, is not overbroad, is not more extensive than necessary to address those harms, but is a reasonable fit between its means and ends. See Lorillard Tobacco Company, 2001 U.S. LEXIS 4911, at 64 (condemning regulations that sweep too broadly and unnecessarily suppress protected speech and requiring careful calculation of the costs of speech regulation); Edenfield, 507 U.S. at 770, 771; Zauderer, 471 U.S. at 648-649; Ibanez, 512 U.S. at 142; Pearson, 164 F.3d at 659 (FDA "must still meet its burden of justifying a restriction on speech—here the FDA's conclusory assertion falls far short," *citing* Ibanez, 512 U.S. at 146; Edenfield, 507 U.S. at 771). See also Pearson I, 164 F.3d at 659-660 ("while we are skeptical that the government could demonstrate *with empirical evidence* that disclaimers . . . would bewilder consumers and fail to correct

for deceptiveness, we do not rule out that possibility"). FDA has suppressed the Antioxidant Vitamin Health Claim without proving that the claim misleads consumers or that the less restrictive alternative of a disclaimer would not suffice to cure any proven misleadingness. FDA did not analyze its speech suppressive action under any part of the Central Hudson test the Pearson I and II Courts held applicable to health claims, electing on remand to disobey those orders.

In Pearson II, this Court found that FDA had disregarded the constitutional teachings of Pearson I (". . . it is clear that the FDA simply failed to comply with the constitutional guidelines outlined in Pearson. Indeed, the agency appears to have at best, misunderstood, and at worst, deliberately ignored, highly relevant portions of the Court of Appeals Opinion," Pearson II, 130 F. Supp. 2d at 112; ". . . FDA has continually refused to authorize the disclaimers suggested by the Court of Appeals—or any disclaimer, for that matter," Id. at 114; and "the FDA has failed to comply with the Court of Appeals decision in Pearson," Id.). The Pearson II Court found that, post-Pearson I, FDA had continued to violate the Pearson plaintiffs First Amendment rights, failing to authorize with disclaimers a claim that the Pearson II court found backed by "credible evidence" ("The Court finds, as a matter of law, that Plaintiffs' Folic Acid Claim is not 'inherently misleading,' and the FDA therefore erred in not drafting disclaimers to accompany the Claim," Id.) and thus the Pearson II Court held FDA's suppression of the claim unconstitutional and ordered the agency to come up with "one or more short, succinct, and accurate alternative disclaimers which may be chosen by Plaintiffs to accompany their Folic Acid Claim." Id. at 120. In the facts of Pearson II, the FDA evaluated the folic acid health claim under its review standard, deemed it "inherently

misleading" without even mentioning, let alone applying, the Central Hudson three part test prescribed in Pearson I, and suppressed it in its entirety without resort to disclaimers (precisely as it has done again in the case at bar). See id. at 111-112. The Pearson II Court found FDA's seemingly endless protestations about the comparative strength of the scientific evidence reinforcement of the need for a disclaimer and not justification for suppressing the health claim altogether. See id. at 118.

"[A]s the Pearson opinion strongly suggests, the FDA may not ban [a claim] simply because the scientific literature is inconclusive . . . ," this Court instructed FDA, rather, ". . . even if the FDA's criticism of the [claim] is valid, [the] criticism does not make the Claim inherently misleading; it instead suggests the need for a well-drafted disclaimer, which the FDA has steadfastly thus far refused to even consider." Id. at 118.[7]

Despite the clear teachings of Pearson I and Pearson II (and in the advent of both decisions) FDA has again suppressed a health claim remanded from Pearson I without even attempting to satisfy the three parts of the Central Hudson test and without employing, let alone evaluating, any of the numerous accurate and succinct potential disclaimers that could have been appended to the Antioxidant Vitamin Health Claim as a remedy for potential misleadingness. In short, by violating the constitutional orders of our Court of Appeals and this Court, FDA has established a substantial likelihood of Plaintiffs' success on the merits under the preliminary injunction standard.

2. The Relevant Facts

a. Procedural History

[7] To be sure, a claim backed by no scientific evidence or one that cannot be rendered nonmisleading through the addition of a disclaimer may be banned outright. See Pearson I, 164 F.3d at 659. That circumstance did not exist with Plaintiffs' folic acid claim, and it certainly does not exist with the Antioxidant Vitamin Health Claim. Each claim is backed by substantial scientific evidence.

FDA has repeatedly and deliberately refused to analyze health claims under the constitutional framework prescribed in Pearson I and II. As a result, Plaintiffs have been denied their First Amendment right to freedom of speech for over ***31 months*** since Pearson I was decided and for over ***seven years*** since they first requested that FDA approve the Antioxidant Vitamin Health Claim.

For ***18 months*** after Pearson I FDA refused to set a "date certain" by which the agency would implement the constitutional mandate of Pearson I. Counsel for Plaintiffs repeatedly requested (by letters dated July 19, 1999; January 19, 2000; February 18, 2000; and March 3, 2000) that FDA commit to a date by which it would evaluate the Antioxidant Vitamin Health Claim under Pearson I. FDA repeatedly responded (by letters dated September 17, 1999; February 17, 2000; February 28, 2000; and March 2, 2000) that it would not commit to a date by which it would comply with the Court's Order.

On July 6, 2000, FDA finally committed to October 10, 2000, as its "date certain" for issuing a decision regarding the Antioxidant Vitamin Health Claim—***633 days*** after the Court of Appeals remanded the case. Despite that generous review period of almost two years, FDA failed to issue its decision by the October 10, 2000 deadline. Instead FDA wrote to counsel for Plaintiffs extending the "date certain" until October 24, 2000. FDA continued to postpone the "date certain" six more times (those deadlines were November 30, 2000; December 22, 2000; February 23, 2001; March 30, 2001; April 20, 2001; and May 4, 2001). Finally on May 4, 2001, FDA finally issued a decision letter denying the Antioxidant Vitamin Health Claim outright—***206 days*** after its initial

deadline, ***972 days*** after the Pearson I decision, and ***2890 days*** after the Plaintiffs first requested approval of the claim.

FDA has denied Plaintiffs their constitutionally protected right to freedom of speech for a total of ***972 days*** past the Pearson I remand. FDA has **never** performed the Central Hudson review required of it by the Court of Appeals and by this Court in Pearson II and has **never** evaluated disclaimers as less restrictive alternatives to outright claim suppression consistent with the Court of Appeals and this Court's orders.

b. The Scientific Evidence

To meet its high burden of proof to justify health claim suppression, FDA must establish both (1) that no credible scientific evidence supports the claim and (2) that use of a disclaimer would not suffice to cure any potential to mislead conveyed by the claim. Pearson I at 659-660; Pearson II at 118-119. If credible evidence exists, even if that evidence is inconclusive, FDA cannot constitutionally suppress the claim. Rather, a disclaimer revealing the inconclusiveness is, as the Court of Appeals found, the constitutional corrective mechanism, fully consistent with the First Amendment presumption favoring disclosure over suppression. As the evidence attached to this application confirms, the weight of the available credible and reliable scientific evidence supports the Antioxidant Vitamin Health Claim. In addition, Plaintiffs have consistently been willing to accept any reasonable disclaimer to avoid misleadingness.

Significantly, health agencies of the federal government other than FDA have published that antioxidant vitamins may reduce the risk of certain kinds of cancers. The National Institutes of Health, Office of Dietary Supplements publishes the following:

> Antioxidants such as vitamin E help protect against the damaging effects of free radicals, which may contribute to the development of chronic diseases such as

> cancer. Vitamin E may also block the formation of nitrosamines, which are carcinogens formed in the stomach from nitrites consumed in the diet. It also may protect against the development of cancers by enhancing immune function.

NIH, Office of Dietary Supplements, Facts About Dietary Supplements, Facts About Vitamin E, http://www.cc.nih.gov/ccc/supplements/vite.html Exh. 3.

The United States Department of Agriculture, Agricultural Research Service, includes in its Quarterly Report for the 4th Quarter of 1996, the following: "Antioxidants are thought to help prevent heart attack, stroke, and cancer." Exh. 4. The United Sates Department of Agriculture and the Department of Health and Human Services include in Nutrition and Your Health: Dietary Guidelines for Americans, fourth edition, 1995, the following: "The antioxidant nutrients found in plant foods (e.g. vitamin C, carotenoids, vitamin E, and certain minerals) are presently of great interest to scientists and the public because of their potentially beneficial role in reducing the risk of cancer and certain other chronic diseases." Exh. 5 at 13. Tim Byers and Geraldine Perry of the United States Centers for Disease Control, Epidemiology Branch, Division of Nutrition, write in the Annual Review of Nutrition at 139-159 (1992) the following: "Antioxidant micronutrients, especially carotenes, vitamin C, and vitamin E, appear to play many important roles in protecting the body against cancer. They block the formation of chemical carcinogens in the stomach, protect DNA and lipid membranes from oxidative damage, and enhance immune function." Exh 6.

No fewer than twenty-five of the nation's leading scientists who study the relationship between antioxidant vitamins and cancer have openly urged FDA to allow the claim, concluding that the weight of the scientific evidence supports it. Sixteen of those scientists presented that opinion in comments responding to FDA's initial denial of the claim. Exh.7. One of them, Gladys Block, Ph.D., and another extremely well-

respected scientist, Adrienne Bendich, Ph.D., have since published their criticisms of the decision, reciting substantial and credible scientific evidence in support of the claim. Exh. 8 and Exh. 9. Nine more scientists who have evaluated FDA's recent Letter Ruling have come to the same conclusion, i.e., that the Plaintiffs' claim is supported by the weight of the available credible and reliable scientific evidence. Exh. 10.

The evidence of record reveals that through the neutralization of oxidants and other free radicals, the blocking of carcinogenic N-nitrosamines, and the stimulation of immune system function, antioxidant vitamins C and E deactivate carcinogens, block nitrosation, and stimulate immune function—all mechanisms responsible for reducing the risk of initiation of certain cancers in healthy individuals. Exh. 10 at 5-6. Those mechanisms are critical to reduce the initiation stage of certain cancers of the stomach, prostate, bladder, breast, cervix, colorectum, lung, oral cavity, pharynx, esophagus, pancreas, and skin where free radicals, oxidants, or N-nitrosamines are implicated in cellular damage linked to cancer initiation. Exh. 10 at 8-14.

Cancer is recognized as having three primary phases: initiation, promotion, and progression. See, e.g., Pryor, W., "Cigarette Smoke Radicals and the Role of Free Radicals in Chemical Carcinogenicity," 105 *Environmental Health Perspectives*, S4, 875-882, 875 (June 1997) (Exh. 12); Garewal, H., "Antioxidants in oral cancer prevention," *Am. J. Clin. Nutr.*, 1995;62(suppl) 1410S-6S, 1411S (Exh. 17). Oxidants, other free radicals, and N-nitrosamines (all reduced or blocked by antioxidants) are implicated in the initiation of certain cancers. E.g., Exh. 10 at 5. While there is some evidence that antioxidants also interfere with the promotion phase of certain kinds of cancer, the claim here in issue is based on reduction of cancer risk in the healthy, not treatment of cancer in

people in whom cancer initiation, promotion, or progression has already occurred.[8] Plaintiffs make no claim that antioxidant vitamins are effective in the treatment of cancer, only that they may reduce the risk of certain kinds of cancers.

One of the primary flaws in the FDA Letter Ruling is its purposeful obfuscation of the scientific distinction between cancer risk reduction in healthy populations and cancer treatment. FDA's analysis is hopelessly arbitrary and capricious because it declares antioxidants C and E ineffectual in reducing cancer risk based on scientific evidence that fails to find efficacy of antioxidants in the treatment of patients who have precancerous polyps or lesions or who have active cancers (thus involving people in whom cancer is in an advanced stage of promotion or progression). FDA erroneously demands proof that antioxidants C and E are effective in these "treatment" studies as a condition precedent for allowing Plaintiffs' "risk reduction" claim. Those demands are not only inappropriate for a risk reduction claim but are also arbitrary and capricious deviations from FDA's stated position that it considers disease treatment claims approvable only via new drug applications, not via health claim petitions. See Exh. 11.

As explained in detail below, and corroborated in the scientific evidence appended hereto, potentially carcinogenic oxidants and other free radical molecules are produced in the body trillions of times per second (Synderman et al., "Reactive Oxygen Metabolites, Antioxidants and Head and Neck Cancer," 21 Head Neck 467, 471-472(1999)) by mechanisms of action that are well-accepted: the damaging of cellular

[8] FDA tacitly recognizes that, because the agency has taken the position that disease treatment claims may not be made as health claims and that petitions seeking to make such claims will not be reviewed. See Exh. 11 (May 26, 2000 Letter by Joseph A. Levitt, CFSAN, FDA, denying Plaintiff's health claim concerning saw palmetto). That matter is a subject in other litigation before this Court. See Whitaker v. Thompson, 99-3247 (GK), U.S. District Court for the District of Columbia. Thus, even were vitamin C and E actually effective in treating cancer, FDA would presumably not review such a claim or approve it if submitted in a

DNA, cellular proteins, and cellular fatty acids. "The carcinogenic role of oxidative processes and free radicals is well established," writes Block in "The Data Support a Role for Antioxidants in Reducing Cancer Risk," 50 Nutrition Reviews 207, 207 (1992)(Exh. 8); see also Synderman et al., *supra* at 18, 468-469 ("there are many factors involved in the initial sequences leading to mutation and ultimately cancer. One such factor is the free oxygen radical . . . or reactive oxygen metabolite"); Exh. 12 at 17; Slaga, T. "Inhibition of the Induction of Cancer by Antioxidants, Nutrition and Biotechnology in Heart Disease and Cancer," p. 167-174, 167 (J.B. Longenecker Eds. Plenum Press, NY 1995)(Exh. 13); Schorah, P.J., "Micronutrients, Antioxidants and Risk of Cancer," The Scientific Basis for Vitamin Intake in Human Nutrition, Bibl. Nutr. Dieta. Basel, Karger 1995, No. 52, p. 92-107 (Walter, P. Eds.)(Exh. 14); Block, G., 1992, Exh. 8.

In addition, N-nitrosamines produced from consumption of foods are known carcinogens. Exh. 8. at 208; Rokkas, T. et al., "Helicobacter pylori infection and gastric juice vitamin C levels," 40 *Digestive Diseases and Sciences*, 3: 615-621,616 (March 1995)(Exh. 20). Antioxidants neutralize oxidants and free radicals and block nitrosation reactions that produce carcinogenic nitrosamines, thereby reducing the risk of cancer initiation. Zhang, Z. et al., "The relation between gastric vitamin C concentrations, mucosal histology, and CagA seropositivity in the human stomach," *Gut* 1998; 43:322-326 (Exh. 15). Ames, B., "Dietary Carcinogens and anticarcinogens," 221 *Science* 1256-1264 (Sept. 23 1983) (Exh. 16).

Compromised immune system function is also an important factor enhancing cancer risk. E.g. Pappalardo, G. et al., "Antioxidant agents and colorectal carcinogenesis:

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health claim petition. Plaintiffs have challenged that incorrect interpretation of the law in another case pending before this Court. See Id.

Role of β-carotene, vitamin E and vitamin C," Tumori, 82: 6-11, 1996 (Exh. 23). Antioxidants have been shown to stimulate immune function and thereby reduce cancer risk. Exh. 23 at 7-8, Patterson, R, et al., "Vitamin supplements and cancer risk: the epidemiologic evidence," *Cancer Causes and Control*, 1997, 8, 786-802 (Exh. 22).

Truth be told, FDA has earlier accepted these mechanisms of action in its rulemaking that culminated in allowance of a food antioxidant/cancer risk reduction claim. The agency there wrote:

> Vitamins C and E . . . are vitamins that function as antioxidants . . . . Vitamin C . . . serves as an effective free-radical scavenger to protect cells from damage by oxidants. It is in this capacity that vitamin C may provide protection against adverse effects of potential carcinogens. Vitamin C plays roles in maintaining the integrity of intracellular matrices, enhances the immune system, and is necessary for several types of biochemical reactions . . . . The basic biological function of vitamin E in animal tissues is an antioxidant where it acts as a defense against potentially harmful reactions with oxygen . . . . The antioxidant vitamins are interactive in that they complement each other during situations of biological stress. Vitamin C, most of which is located in the aqueous portion of the cell, spares vitamin E until the vitamin C reserve is depleted. Vitamin E is located in the lipid portions of all membranes, and it deactivates free radicals . . . . Beta-carotene, vitamin C and vitamin E all inhibit damage by oxidative chemicals, including carcinogens. More specifically, beta-cartoene traps reactive oxygen molecules, vitamin E and beta-carotene remove free radicals, and vitamin C inhibits oxidative reactions and also removes free radicals. . . . A major effect of vitamin C that could be the basis of protection against cancer is its ability to inhibit nitrosamine formation. Nitrosamines (N-nitroso amines and N-nitroso amides) are types of carcinogens which occur in foods and are produced within the body by the reaction of nitrite with other dietary or endogenous amines and amides. Some nitrite occurs in food, but more is produced from reduction of nitrate by bacteria in the mouth and small intestine. Nitrate occurs in food, and some is produced in the body from L-arginine. The nitrosation reactions occur rapidly in the acid environment of the stomach and upper duodenum. Most nitrosamines tested in experimental animals are carcinogenic, and some are very potent carcinogens affecting multiple sites . . . . [V]itamin C blocks the formation of carcinogenic nitrosamines from nitrates and nitrites in the digestive tract. The combination of evidence from epidemiological studies and evidence from several types of studies with animals which involved administration of carcinogens and carcinogen precursors provides a strong basis on which to postulate that vitamin C reduces the risk of cancer in humans . . . . Animal studies have demonstrated an inhibitory effect of vitamin E on cancers induced by ultraviolet light and certain

> chemicals. These studies date back to the earliest days of vitamin E chemistry. More recently, the implications of reactive oxygen molecules in cancer development provide a theoretical basis for the involvement of vitamin E (a strong antioxidant) in the development of cancer, because carcinogens are activated by oxidative processes and oxidation of cell components may contribute to cancer development.

56 Fed. Reg. 60624, 60627-60628 (Nov. 27, 1991).

It is well-accepted that "oxidative damage to DNA, lipids and proteins in the human body is generally considered to be an important factor in carcinogenesis." Peter Greenwald of the Division of Cancer Prevention, National Cancer Institute, and Sharon S. McDonald, "Antioxidants and the Prevention of Cancer" in Antioxidants in Human Health and Disease 217 (1999). See also A. Bendich et al., "the Health Effects of Vitamin C Supplementation: A Review," 14 Journal of the American College of Nutrition 124, 125 (1995) ("Free radicals and oxidative processes are involved in both cancer initiation and tumor promotion"); Cerutti, 1985, Exh. 10, Att. 25; Cross, 1987, Exh. 10, Att. 33; Beckman et al., 1997, Exh. 10, Att. 9. Cross, C., et al., "Oxygen Radicals and Human Disease," *Annals of Internal Medicine*, 1987; 107: 526-545, 538 (Exh. 18); Schorah, C.J., "Ascorbic Acid Metabolism and Cancer in the human stomach," *Acta Gastro-Enterologica Belgica*, Vol. LX, July-Setp 1997, 217-219, 217 (Exh. 19); Romney, S.L., "Nutrient Antioxidants in the Pathogenesis and Prevention of Cervical Dysplasias and cancer," *J of Cellular Biochem*., 23S: 96-103,101 (1995)(Exh. 21). Oxidants (including superoxide radicals, nitric oxide, and hydroxyl radicals) and other free radical molecules responsible for this damage are "by-products of normal energy metabolism." Bruce N. Ames, "Micronutrients Prevent Cancer and Delay Aging," 102-103 Toxicology Letters 9-10 (1998)(Exh. 24); Cerutti, 1985, Exh. 10, Att. 25; Cerutti et al., 1994, Exh. 10, Att. 26. "[B]ursts of oxidants, and consequent inflammation, from

phagocytic cells . . . ([producing] a mixture of reactive nitrogen oxides) [also] contributes to . . . . cancer." Id. at 9-10. In addition, radiation and pollutants from the environment as well as injuries to the body induce the production of oxidants and other free radicals. E.g. Carroll, 1987, Exh. 18 at 528, 537.

Naturally occurring within each cell are certain antioxidant defenses in the form of catalase, superoxide dismutase, glutathione, glutathione peroxidase, and associated enzymes. Maria Dusinska et al., "Indicators of Oxidative Stress, Antioxidants and Human Health," in Antioxidants in Human Health and Disease 411-422 (1999). Unfortunately, the intracellular defenses are imperfect and falter, particularly with age. Bruce N. Ames, "Micronutrients Prevent Cancer and Delay Aging," 102-103 Toxicology Letters 9-10 (1998) ("antioxidant defenses [within the body], though numerous, are not perfect")(Exh. 24); Evstigneeva et al., "Vitamin E as a Universal Antioxidant and Stabilizer of Biological Membranes," 12 Membrane Cell Biology 151, 157 (1998); Hughes, "Effects of dietary antioxidants on the immune function of middle-aged adults, " 58 Proceedings of the Nutrition Society 79-84 (1999). As a consequence, antioxidants are required to complement intracellular antioxidant defenses in the fight against cancer initiation:

> Many intrinsic enzyme systems protect cells from oxidative damage. These include SOD [superoxide dismutase], glutathione peroxidase, the glutathione transferase, and catalase. Additionally, a variety of small molecules in the human diet are required for antioxidant mechanisms. Vitamin E (tocopherol) is an excellent example and functions to trap radicals in lipid membranes and has been used clinically in a variety of oxidative stress-induced diseases. This vitamin attenuates . . . the carcinogenicity of quinones, adriamycin, and duanomycin, which are mutagenic, carcinogenic, and cardiotoxic because of free radical generation . . . Vitamin E is also known to decrease the formation of PGE2 in several different tissues. PGE2 is established to suppress the production of cytokine such as interleukin-2(IL-2), mitogen-and antigen-induced lymphocyte proliferation, antibody production, and the activity of cytolytic T cells.

* * * *

> Vitamin C, another known antioxidant nutrient, has also been shown to protect from cancer risk and may operate by inhibiting nitrosamine formation, preventing the activation of various other carcinogens, enhancing the immune system, and inhibiting the promotion phase of carcinogenesis."

Synderman et al., "Reactive Oxygen Metaolites, Antioxidants and Head and Neck Cancer," 21 *Head Neck* 467-479 (1999).

Indeed, "[o]xidative damage to DNA and other macromolecules appears to have a major role in aging and degenerative diseases associated with aging, such as cancer" due in no small measure to imperfect intracellular defense against free radicals and inadequate dietary intake of antioxidant vitamins. Ames at 9-10. Aging humans experience a reduction in the presence of the intracellular antioxidants superoxide dismutase, catalase, and glutathione peroxidase (Synderman et al., at 471-472) and thus appear to require more antioxidants from external sources like foods and dietary supplements. As NCI's Peter Greenwald [Division of Cancer Prevention] writes:

> Oxidative damage to DNA, lipids and proteins in the human body is generally considered to be an important factor in carcinogenesis. Reactive oxygen species such as superoxide, nitric oxide and hydroxyl radicals, formed continuously as a result of biochemical reactions, can cause significant oxidative damage. Also, environmental carcinogens from various sources—for instance, tobacco smoke and industrial pollution – and food contaminants such as heterocyclic aromatic amines (HAAs) contribute to an individual's total burden of oxidative stress (Jacob and Burri, 1996; Loft and Poulsen, 1996). Antioxidant defenses – for example, enzymes that continually repair DNA damage – frequently cannot counteract all of the oxidative attack, and the resulting damage may lead to genetic mutations that could contribute to carcinogenesis. Dietary antioxidants, ubiquitous in plant foods where they have evolved to protect the plants against oxidative assault, may be protective to humans, in terns of reducing cancer risk.

Greenwald at 217.

The antioxidative effects of Vitamins C and E reduce the risk of cancer by complementing the role of intracellular antioxidants in neutralizing the harmful effects of oxidant and free radical damage:

> . . . . [V]itamins C [and] E . . . are potent antioxidants and free radical scavengers and may have a preventive role in cancer pathogenesis. These compounds appear to neutralize metabolic products, interfere with the activation of procarcinogens, prevent the binding of carcinogens to the DNA molecule, suppress the action of cancer promoters, and may even lead to regression of precancerous lesions such as leukoplakia and erythroplakia.

Synderman at 475. Vitamin E is the major trap for free radicals in lipid membranes and ameliorates the carcinogenicity of agents that generate reactive oxygen species. Ames, 1983. "Dietary Carcinogens and Anticarcinogens," *Science*, Vol. 221, 1256-1264 (Sept. 23 1983). Vitamin C and vitamin E scavenge nitrites and the nitroso radical, thereby inhibiting synthesis of N-nitrosamines in the human stomach. Mackerness et al., 1989, Exh. 10, Att. 89; Ohshima et al., 1981, Exh. 10, Att. 102.

In addition to the above evidence, study after study documents the cancer risk reducing effect of antioxidants. The evidence for Vitamin C and reduced risk of stomach cancer is particularly strong, including a well-designed retrospective case-control study that reported a statistically significant decrease in risk for stomach cancer with increased vitamin C intake. Deneo-Pellegrini et al., 1999, Exh. 10, Att. 36. Likewise, the evidence for reduced risk of prostate cancer is particularly strong; a double-blind placebo controlled clinical trial involving 29,133 participants (the ATBC Study) found vitamin E to have a statistically significant protective effect on prostate cancer incidence and mortality (Heinonen et al, 1998, Exh. 10, Att. 60) and a retrospective case-control study reported a statistically significant inverse association between vitamin E intake and prostate cancer risk (Tzonou et al., 1999, Exh. 10, Att. 129).

Numerous well-designed studies associate consumption of vitamins C and E with statistically significant reductions in the risk of cancer at various sites. Among them from the record below are the following: (1) reduced risk of bladder cancer with vitamin C supplementation (prospective cohort study, Shibata et al., 1992, Exh. 10, Att. 119); (2) reduced risk of breast cancer with vitamin C supplementation (a prospective cohort study, Zhang et al., 1999, Exh. 10, Att. 151; four retrospective case-control studies, Zaridze et al, 1991, Exh. 10, Att. 149; Landa et al, 1994, Exh. 10, Att. 79; Yuan et al., 1995, Exh. 10, Att. 148; and Ronco et al., 1999, Exh. 10, Att. 112; and a meta-analysis of retrospective case-control studies, Howe et al., 1990, Exh. 10, Att. 64); (3) reduced risk of breast cancer with vitamin E supplementation (a prospective cohort study, Zhang et al., 1999, Exh. 10, Att. 151, and four retrospective case-control studies, Torun et al., 1995, Exh. 10, Att. 128; Favero et al., 1998, Exh. 10, Att. 41; Mezzetti et al., 1998, Exh. 10, Att. 95; Mannisto et al., 1999, Exh. 10, Att. 92); (4) reduced risk of cervical cancer with vitamin E supplementation (three retrospective case-control studies, Cuzick, et al., 1990, Exh. 10, Att. 34; Ho et al., 1998, Exh. 10, Att. 63; Verrault et al., 1989, Exh. 10, Att. 136); (5) reduced risk of colorectal cancer with vitamin C and E supplementation (adenomatous polyp prevention intervention trial controlled with a "no treatment" group instead of placebo, Roncucci et al., 1993, Exh. 10, Att. 113; a prospective cohort study, Shibata et al., 1992, Exh. 10, Att. 119; and four retrospective case-control studies, La Vecchia et al., 1988, Exh. 10, Att. 80; Freudenheim et al., 1990, Exh. 10, Att.50; Ferraroni et al., 1994, Exh. 10, Att.44; La Vecchia et al., 1997,Exh. 10, Att. 82); (6) reduced risk of colorectal cancer with vitamin E supplementation (a prospective cohort study, Bostick et al., 1993, Exh. 10, Att.18; a retrospective case-control study, La

Vecchia et al., 1997,Exh. 10, Att. 82; and a retrospective case-control study, Whelan et al., 1999,Exh. 10, Att. 140); (7) reduced risk of lung cancer with vitamin C supplementation (five prospective cohort studies and two retrospective case-control studies reporting inverse association between vitamin C intake and lung cancer incidence, Knekt et al., 1991, Exh. 10, Att. 74; Bandera et al., 1997, Exh. 10, Att. 7; Ocke et al., 1997, Exh. 10, Att. 101; Yong et al., 1997,Exh. 10, Att. 145; Voorrips et al., 2000, Exh. 10, Att.137; Fontham et al., 1988,Exh. 10, Att. 46; LeMarchand et al., 1989, Exh. 10, Att. 85, and one prospective cohort study finding low concentrations of vitamin C and E associated with statistically significant increases in lung cancer mortality, Eicholzer et al., 1996, Exh. 10, Att. 39); (8) reduced risk of lung cancer with vitamin E supplementation (two prospective cohort studies, two prospective nested case-control studies, and two retrospective case-control studies, Knekt et al., 1991, Exh. 10, Att. 74; Yong et al., 1997,Exh. 10, Att. 145; Knekt et al., 1993, Exh. 10, Att. 76; Woodson et al., 1999, Exh. 10, Att. 142; LeGardeur et al., 1990, Exh. 10, Att. 84; Harris et al., 1991, Exh. 10, Att. 58, finding inverse association between plasma vitamin E concentrations and lung cancer risk, and a prospective cohort study, Eicholzer et al., 1996, Exh. 10, Att. 39, finding low concentrations of vitamin C and E associated with statistically significant increases in lung cancer risk); (9) reduced risk of oral cavity, pharynx and esophagus cancer with vitamin C supplementation (three retrospecive case-control studies reporting inverse associations between dietary vitamin C intake and risk of cancers of the upper digestive tract, McLaughlin et al., 1988, Exh. 10, Att. 94; DeStefani et al., 1999, Exh. 10, Att. 37; and Negri et al., 2000, Exh. 10, Att. 100); (10) reduced risk of oral cavity, pharynx and esophagus cancer with vitamin E supplementation (two retrospective case-control studies

reporting inverse association of vitamin E intake and risk of oral cavity cancer, Barone et al., 1992, Exh. 10, Att. 8 and Gridley et al, 1992, Exh. 10, Att. 56; a retrospective case-control study finding inverse association of vitamin E intake with risk of oral cavity cancer, Negri et al., 2000, Exh. 10, Att. 100; and two prospective nested case-control studies reporting inverse association of vitamin E concentrations and upper digestive tract cancer risk, Knekt et al., 1988, Exh. 10, Att. 72 and Zheng et al., 1993, Exh. 10, Att. 152); (11) reduced risk of pancreatic cancer with vitamin C supplementation (a prospective cohort study, Eicholzer et al., 1996, Exh. 10, Att. 39); (12) reduced risk of skin cancer with vitamin E supplementation (a retrospective case-control study, Stryker et al., 1990, Exh. 10, Att. 126, and a prospective nested case-control study, Knekt et al., 1991, Exh. 10, Att. 74); and (13) reduced risk of stomach cancer with vitamin E supplementation (a randomized, placebo-controlled General Population Trial, Blot et al., 1993; two retrospective case-control studies, Buiatti et al., 1990, Exh. 10, Att. 23; Charpiot et al., 1999, Exh. 10, Att. 27; and a prospective nested case-control analysis of mortality data, Knekt et al., 1988, Exh. 10, Att. 72; Knekt et al., 1991, Exh. 10, Att. 74, 75).

Thus, in addition to general acceptance of the mechanisms of action for cancer risk reduction associated with antioxidation, blocking nitrosation, and stimulating immune function, there is substantial and credible scientific evidence in support of the health claim in the scientific literature concerning risk reduction at specific sites.

Dissected in detail, FDA's Letter Ruling is riddled with profound and basic errors of science, making it a virtual "guidance" on how not to conduct unbiased scientific reviews. Among those errors documented in a comprehensive scientific evaluation of the

Letter Ruling endorsed by nine scientific experts (attached) are the following. (1) FDA has misrepresented the findings of several of the published scientific reports that it used to justify its denial of the claim. See Exh. 10 at 14 - 18. (2) FDA violated fundamental principles of statistical theory and statistical inference in its interpretation of scientific evidence. See Exh. 10 at 18 - 21. (3) FDA ignored the results of statistical analysis when the results contradicted its conclusions. See Exh. 10 at 21. (4) FDA has required evidence in support of the claim and evidence failing to support the claim to satisfy different standards of scientific quality and rigor, to justify its conclusions. See Exh. 10 at 21 - 22. (5) FDA has misconstrued the meaning of the phrase "risk reduction" and has misapplied experimental models of cancer treatment and secondary prevention efficacy to the issue of primary prevention of cancer. See Exh. 10 at 28 - 33. (6) FDA is inconsistent in its use of the results of statistical analysis. See Exh. 10 at 34 - 35. (7) FDA is inconsistent in the application of its own hierarchy of persuasiveness of evidence. See Exh. 10 at 35 - 36. (8) FDA violated its own "Schema for Assessing Strength and Consistency of Scientific Evidence Leading to Significant Scientific Agreement." See Exh. 10 at 36 – 37. (9) FDA either selectively accepted or glibly ignored statements by other government agencies that contradicted its Letter Ruling conclusions. See Exh. 10 at 37 - 38. Exhibit 10 hereto provides a detailed scientific critique of each error at the pages listed. Thus, the violation of the remand order and the instructions of this Court are contumacious, arbitrary and capricious. The Letter Ruling itself, to the trained eye, is a deliberate misrepresentation of data and an inconsistent application of scientific standards in an all too obvious attempt to justify a biased, negative conclusion.

The FDA is in error to conclude that the "evidence in support of the claim is outweighed by evidence against the claim," that the claim is "incurable by a disclaimer," or that the evidence rests on the basis of "only one or two old studies." Indeed, on the record, the Antioxidant Vitamin Health Claim is supported by the weight of the available substantial and credible scientific evidence.

c. Analysis

FDA has utterly failed to comply with the constitutional remand order of the Court of Appeals in Pearson I and with this Court's instructions on evaluating health claims in Pearson II and III. It has utterly failed to address, let alone satisfy, its high burden of proof for suppressing protected scientific and commercial speech. The record reveals an abundance of credible and reliable evidence that antioxidant vitamins may reduce the risk of certain kinds of cancer, evidence so strong that it has led leading scientists in this field to endorse the claim in comments to the agency, in publications, and in the attached review of the Letter Ruling. Indeed, the evidence is so strong that characteristically conservative health agencies of the federal government other than the FDA have seen fit to publish to the public statements associating antioxidant vitamins C and E with cancer risk reduction.

As our Court of Appeals and this Court have made very clear, even if the evidence in support of a health claim is inconclusive, FDA cannot suppress the claim unless it proves the absence of credible supporting evidence. FDA has not proved the absence of such evidence nor has it established that the less restrictive alternative of a disclaimer would not suffice to correct for any perceived misleadingness. Because a disclaimer, such as that recommended by our Court of Appeals, can suffice to eliminate

any provable misleading connotation, allowance of the claim with such a disclaimer is constitutionally required.

Under the three-part Central Hudson test, FDA has failed to satisfy its First Amendment burden. The first prong of Central Hudson asks whether the state's interest in regulating the Plaintiffs' speech is substantial. Without question FDA's interest in protecting public health and preventing consumer fraud is a substantial one. As the Court in Pearson I at 656 previously stated, "At this level of generality, . . . a substantial governmental interest is undeniable."

The second prong of Central Hudson, 447 U.S. at 566, asks "whether the regulation *directly* advances the governmental interest asserted." In this evaluation, FDA must show that its "speech restriction directly and materially advance[s its] asserted governmental interest." Lorillard Tobacco Company, 2001 U.S. LEXIS 4911, at 53. FDA must show that the harms it recites are real and that its restriction will in fact alleviate those harms to a material degree. Lorillard Tobacco Company, at 53. The prohibition on Plaintiffs' Statement neither directly advances FDA's interest in protecting public health nor directly advances FDA's interest in preventing consumer fraud.

As a preliminary matter, the substances here in issue at the dose levels contained in Plaintiffs' multi-vitamins are, contrary to FDA's unsubstantiated charges in the Letter Ruling, recognized as safe by the Food and Nutrition Board of the Institute of Medicine. See Exh. 25: DIETARY REFERENCE INTAKES FOR VITAMIN C, VITAMIN E, SELENIUM, AND CAROTENOIDS, Institute for Medicine, National Academy Press (2000)(Vitamin C at 155-161, Vitamin E at 249-260, Selenium at 311-318, and Carotenoids at 366-371). Secondarily, the claim here in issue does not reach beyond the scientific evidence but

conforms to it, conveying accurately the state of scientific knowledge. The common understanding of the term "may" in the claim reveals that the proof, while credible and strong, is not conclusive. The term "reduce the risk of" pertains to reduction in the risk of cancer, not treatment of cancer. As explained above, the evidence amply supports the risk reduction claim. Finally, no claim is being made that antioxidants may reduce the risk of every kind of cancer, only "certain kinds of cancers," namely those for which oxidants and free radicals; nitrosation; and weakened immune system function are antagonistic factors linked to cancer initiation. The Antioxidant Vitamin Health Claim is thus not in any fashion a threat to consumer health and safety (to the contrary, ignorance of it—borne from a lack of truthful information—denies informed choice and threatens consumer health and safety). Allegations to the contrary lack credible scientific evidence to support them. The antioxidant vitamins in question are routinely sold across the United States in multivitamin supplements and have been for over fifty years without a single instance of FDA declaring multivitamins "adulterated" or unsafe merely because they contain antioxidant vitamins.

The restriction on Plaintiff's claim does not alleviate the alleged harms to a material degree. Aside from the fact that FDA charges of harm to public health have not been proven real and are, in fact, contradicted by the weight of the scientific evidence and that FDA charges of consumer deception are wholly unsubstantiated, the FDA's chosen speech restriction (outright suppression of the claim) actually reduces public health and increases lack of awareness about legally marketed multi-vitamins containing antioxidant Vitamins C and E. Denying the consumer at the point of sale access to accurate information on the potential of antioxidant vitamins to reduce the risk of certain kinds of

cancers redounds to the detriment of public health. Suppression of the potential health benefits of antioxidant vitamins robs consumers of a meaningful opportunity to exercise informed choice in their efforts to improve health and reduce risk of disease. It thereby harms consumers. Moreover, the absence of accurate information at the point of sale increases the likelihood that consumers will rely on misinformation or fraudulent representations. It thereby increases their risk of being defrauded. It is thus the case that FDA's suppression of the claim violates the direct advancement prong of the commercial speech test.

The third prong of Central Hudson, 447 U.S. at 566, asks whether there is a "reasonable 'fit between the . . . ends and the means chosen to accomplish those ends, . . . a means narrowly tailored to achieve the desired objective.'" Lorillard Tobacco Company, 2001 U.S. LEXIS 4911, at 54. As in Pearson I and II, so too here, the means-ends fit is not reasonable because there is an obvious and less restrictive alternative to outright suppression that is consistent with the First Amendment presumption in favor of disclosure: use of a short, concise, and accurate disclaimer that corrects for misleadingness. Outright suppression is not the kind of careful calculation of costs and benefits that the First Amendment requires of regulators. Indeed, Pearson I, II, and III order FDA to rely on reasonable disclaimers as the appropriate means to qualify a scientifically credible claim. Pearson I at 659; Pearson II at 113; Pearson III at 110. It is thus the case that FDA's suppression of the claim violates the means-ends fit prong of the commercial speech test.

Under Pearson I and II, FDA had a constitutional obligation to permit Plaintiffs' Statement and to rely on a disclaimer added to that statement as its corrective remedy.

FDA shirked its constitutional duty even in the face of three federal court orders. Yet again, under the third prong of Central Hudson, FDA has violated the First Amendment in its continuing suppression of the Antioxidant Vitamin Health Claim—committing the very same civil rights violation that produced the holdings in Pearson I, II, and III. Accordingly, Plaintiffs have demonstrated a substantial likelihood of success on the merits.

C. NO SUBSTANTIAL INJURY TO DEFENDANTS OR OTHERS

The Defendants will in no way be injured by Plaintiffs' Antioxidant Vitamin Health Claim. To the contrary, a central objective of the Defendants' public mission, to improve the health of Americans, will be promoted if more consumers become aware that the antioxidant vitamins contained in Plaintiffs' dietary supplements may reduce the risk of certain kinds of cancer.

D. AN INJUNCTION WILL SERVE THE PUBLIC INTEREST

There can be no doubt that cancer is a public health consequence of profound national significance. In light of the overwhelming prevalence of cancer, and its ever present threat of lethality (particularly in a rapidly aging population[9]), its extraordinary financial cost to patients and the nation, and its devastating physical and emotional cost to all who contract it, there is a profound national need for healthy Americans to learn of reasonable means throughout life to reduce their risks of cancer initiation. FDA's decision to prohibit the Antioxidant Vitamin Health Claim denies the public access to credible and strong scientific evidence on the potential benefits of a simple, inexpensive, and health enhancing means for reducing the risk of initiation of

[9] Bishop, M.J et. al (Eds.), SCIENTIFIC AMERICAN MOLECULAR ONCOLOGY, 1996, 179-181, 180 ("The risk of contracting most cancers increases steeply with age.")

certain kinds of cancer. It is thus in the public interest that the injunction issue forthwith so that the Plaintiffs can communicate, and consumers can receive, the important health information conveyed by the claim.

II. RELIEF REQUESTED

For the foregoing reasons and based upon the affidavits and documentary support appended hereto, the Plaintiffs respectfully request that this Honorable Court issue an immediate preliminary injunction barring FDA from taking any action to prohibit them from including on the labels and in the labeling of their dietary supplements that contain antioxidant vitamins the following truthful and nonmisleading statement: "**Consumption of antioxidant vitamins may reduce the risk of certain kinds of cancers.**" Plaintiffs stand willing to accept any reasonable short, succinct, and accurate disclaimer to guard against potential misleadingness. The Plaintiffs stand willing to accept any reasonable short, succinct and accurate disclaimer to guard against misleadingness. Plaintiffs ask that the injunction remain in place until such time as this Court has issued its final decision on all claims brought by Plaintiffs against the Defendants.

Respectfully submitted,

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