

**Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

In re: Food Labeling; Dietary Supplement Health Claims; Public Meeting Concerning Implementation of Pearson Court Decision and Whether Claims of Effects on Existing Diseases May Be Made as Health Claims)
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) **Docket No. 00N-0598**
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**JOINT COMMENTS OF
PURE ENCAPSULATIONS, INC.;
JULIAN M. WHITAKER, M.D.;
AMERICAN PREVENTIVE MEDICAL ASSOCIATION;
and
DURK PEARSON and SANDY SHAW**

Pure Encapsulations, Inc.; Julian M. Whitaker, M.D.; the American Preventive Medical Association; and Durk Pearson and Sandy Shaw (collectively, "Joint Commenters"), by counsel and in response to the FDA's solicitation of comments in the Federal Register, 65 Fed. Reg. 14219 (March 16, 2000) (hereinafter "Notice"), hereby submit the following.

BACKGROUND OF THE JOINT COMMENTERS

Pure Encapsulations, Inc. Pure Encapsulations, Inc. (Pure) is a Massachusetts corporation engaged in the business of manufacturing, distributing, and selling over 250 pharmaceutical grade dietary supplements for human and companion animal consumption. Pure manufactures and produces several dietary supplements containing antioxidant vitamins, fiber, omega-3 fatty acids, and folic acid. Pure wants to place the health claims listed in *Pearson*, disclaimed as necessary to avoid misleadingness, on the

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labels and in the labeling of those supplements and, thus, seeks allowance of the health claims.

Julian M. Whitaker, M.D. Julian M. Whitaker, M.D. is a physician licensed to practice medicine in the states of California and Washington. He graduated from Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University of California Medical School. From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: ***Reversing Heart Disease*** (1985), ***Reversing Diabetes*** (1987), ***Reversing Health Risk*** (1989), ***Natural Healing*** (1994), and ***What Your Doctor Won't Tell You About Bypass*** (1995). Since August of 1991 he has been the editor of ***Health & Healing***, currently the nation's largest single editor health newsletter. In 1998, ***Health & Healing*** had over 500,000 subscribers. He receives royalties from the distribution and sale of several dietary supplements based on formulas he develops and licenses. Among the supplements which Dr. Whitaker has formulated (and from which he receives royalty payments) are several containing antioxidant vitamins, fiber, omega-3 fatty acids, and folic acid. He wants to place the health claims listed in *Pearson*, disclaimed as necessary to avoid misleadingness, on the labels and in the labeling of his supplements and, but for FDA's extant bar on labeling use of the claims, would do so. Accordingly, he seeks FDA allowance of the claims.

American Preventive Medical Association. The American Preventive Medical Association (APMA) is a non-profit organization located in Virginia. APMA was

founded in October of 1992 and is dedicated to ensuring consumer access to preventive therapies and the rights of health care providers to offer those therapies. APMA was a plaintiff in the *Pearson v. Shalala* case. Several APMA physicians sell dietary supplements that contain antioxidant vitamins, fiber, omega-3 fatty acids, and folic acid. APMA and its practitioner members, and their hundreds of thousands of patients, would benefit from approval of the health claims proposed in *Pearson* because it would enable those practitioner members to communicate, and their patients to receive, nonmisleading health information on labels and in labeling concerning the effects of antioxidant vitamins, fiber, omega-3 fatty acids, and folic acid on reducing the risk of, respectively, certain kinds of cancer, heart disease and neural tube defects.

Durk Pearson and Sandy Shaw. Pearson and Shaw are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller *Life Extension: A Practical Scientific Approach* (1982). They have also published three other health books, two of which were best sellers: *The Life Extension Companion* (1984); *The Life Extension Weight Loss Program* (1986); and *Freedom of Informed Choice—FDA Versus Nutrient Supplements* (1993). Durk Pearson and Sandy Shaw were plaintiffs in the *Pearson v. Shalala* case. Pearson and Shaw license for manufacture, sale, and distribution, several dietary supplements containing antioxidant vitamins, fiber, omega-3 fatty acids, and folic acid. Pearson and Shaw wish to communicate the health claims, disclaimed as necessary to avoid misleadingness, on the labels and in the labeling of their dietary supplements.

INTRODUCTION TO COMMENTS

The Joint Commenters address each of the specific questions raised by FDA in its Notice along with matters of safety and disclaimer effectiveness raised by panelists at the FDA's April 4 public meeting on *Pearson* implementation.¹

Based on apposite law, empirical economic data, and scientific evidence, the Joint Commenters establish: (1) that FDA *must* as a matter of constitutional law allow each of the four *Pearson* claims to be made with disclaimers; (2) that FDA has the burden of proof under the First Amendment and may not suppress any health claim unless it establishes based on empirical evidence that the claim is inherently misleading and may not be rendered nonmisleading through the addition of a disclaimer; (3) that FDA *must* as a matter of constitutional law allow every health claim to be made that can be rendered non-misleading through the addition of a corrective disclaimer; (4) that disclaimers are an effective means of communicating the qualitative level of scientific support for claims; (5) that effective disclaimers are specific, direct, concise, located in close proximity to the claim and presented in a readable type size; and (6) that the disclaimers recommended by

¹ As a preliminary matter, concerning the four health claims at issue in *Pearson*, FDA has announced that by October 10, 2000, it will determine definitively whether it will authorize the four claims under "significant scientific agreement" or allow them with disclaimers. For reasons fully articulated within the *Pearson* plaintiffs' legal memoranda in support of their Application for Preliminary Injunction and in reply to the Government's opposition thereto (*Pearson v. Shalala*, Civil Action No. 95-1865 (GK) (D.D.C. 2000)(both incorporated here by reference), FDA must *immediately* discontinue enforcement of its prohibition on use of the four claims and authorize them on an interim basis (between now and its ultimate decision date) with the disclaimers recommended by the *Pearson* Court. See *Pearson v. Shalala*, 164 F.3d 650, 658-659 (D.C. Cir. 1999). To do otherwise is to countenance continuing suppression of claims held to be protected commercial speech in the *Pearson* decision without a basis in empirical evidence to satisfy FDA's prima facie burden of proof under the First Amendment. See *Pearson*, 164 F.3d at 659 (the Government "must . . . meet its burden of justifying a restriction on speech . . ."); *Peel v. Attorney Registration and Disciplinary Comm'n of Illinois*, 496 U.S. 91, 109 (1990) (the Government carries a "heavy burden of justifying a categorical prohibition" on commercial speech); *In re R.M.J.*, 455 U.S. 191, 203 (1982). To do otherwise is to countenance continuing defiance of the Court's order which invalidated the agency's prohibitions on the claims. See *Pearson*, 164 F.3d at 661.

the *Pearson* court are fully adequate to inform consumers of the qualitative level of scientific support for the four *Pearson* claims.

COMMENTS

Compliance with *Pearson* is a matter of constitutional importance and necessity. The agency must therefore be governed by the principles of First Amendment law that guided the *Pearson* court, must construe those principles in strict accordance with the *Pearson* court's reasoning as a whole, and must apply those principles and authorize the four *Pearson* claims with corrective disclaimers. The *Pearson* plaintiffs will accept any reasonable disclaimers that aid consumers in comprehending accurate information concerning the nutrient-disease relationships presented in their health claims. Likewise, they will accept any reasonable warning statement designed to alert population subgroups of any documented adverse effects. Their aim is to convey accurate information to improve the ability of consumers to make informed choices about the dietary supplements they sell.

To aid the agency, the Joint Commenters have divided their comments into several parts. First, they explain the proper legal order: the supremacy of the First Amendment, the deference due the *Pearson* court by this agency, and the canons of statutory construction which forbid interpretation of statutory mandates in ways that conflict with the Constitution. Second, they explain through a careful analysis the meaning of the *Pearson* decision within the context of the First Amendment precedent cited in the decision and with reference to the statutory scheme Congress has given FDA for the regulation of dietary supplements. Third, they explain how *Pearson* deals with the issue of adverse effects. Fourth, they present additional evidence on the safety of the

dietary supplements here in issue. Fifth, they present evidence on the effectiveness of disclaimers and, in particular, the *Pearson* court's recommended disclaimers. Sixth, they address each of the questions posed by the agency in its Notice.

A. THE FIRST AMENDMENT STANDARD: PARAMOUNT LAW

This agency should begin its analysis with a frank recognition that it must adhere to certain basic propositions of law that govern its actions in responding to the constitutional mandate from the *Pearson* court. Those propositions are:

(1) The Constitution and laws made in pursuance of it are Supreme. U.S. Const. Art. VI, cl. 2. Laws, including rules and policies of this agency to the contrary, are invalid. In *Marbury v. Madison*, 5 U.S. 137, 177-178 (1803), Justice Marshall put it this way:

Those then who controvert the principle that the constitution is to be considered, in court, as paramount law, are reduced to the necessity of maintaining that courts must close their eyes on the constitution, and see only the law.

This doctrine would subvert the very foundation of all written constitutions. It would declare that an act, which, according to the principles and theory of our government, is entirely void; is yet, in practice, completely obligatory

That it thus reduces to nothing what we have deemed the greatest improvement on political institutions—a written constitution—would of itself be sufficient, in America, where written constitutions have been viewed with so much reverence, for rejecting the construction

(2) It is the duty and province of the federal courts, not other departments of the government, to construe the Constitution and say what the law is. *Id.* at 177.

Accordingly, due respect is owed by this agency to the *Pearson* court, particularly to its construction of the meaning of the Constitution. Were FDA to interpret the Constitution in a manner inconsistent with the interpretation given it by the *Pearson* court, it would be acting unlawfully. Were FDA to disobey the *Pearson* court's order to refrain from taking

an unconstitutional act, it would be acting unlawfully and contumaciously. Rather, FDA is duty bound to adhere faithfully and fully to the constitutional interpretation given it by the *Pearson* court.

(3) Wherever possible, in construing statutory law, this agency (like the federal courts) must avoid a construction that would violate the Constitution. *De Bartolo Corp. v. Florida Guild Coast Building & Construction Trades Council*, 485 U.S. 568, 573 (1988); see also *Syracuse Peace Council*, 2 FCC Rcd. 5043 (1987) (refusing to enforce FCC “Fairness Doctrine” rules in recognition of their First Amendment invalidity).

B. THE MEANING OF THE PEARSON DECISION

As an initial matter, 21 U.S.C. § 343(r)(5)(D) delegates to FDA the authority to construe its standard for review of health claims in a way that will not violate the First Amendment. As the Court explained in *Pearson* that section “delegated to the FDA the task of establishing a ‘procedure and standard respecting the validity of [the health] claim.’” *Pearson*, 164 F.3d at 653. Inherent in the power to define a standard is the power to define a standard in a *constitutional* way. Thus, it is immediately clear that FDA has the statutory discretion to avoid a First Amendment violation and, thus, the statute need not be stricken. *Pearson*, 164 F.3d at 655 (“... the general regulation does not in haec verba preclude authorization of qualified claims”). Indeed, under the canons of statutory construction articulated above, FDA must avoid any interpretation of its health claims review standard that would be contrary to the Supreme law of the First Amendment. Thus, while FDA *may authorize* claims under a defined standard that requires *more* evidence than the First Amendment standard articulated in *Pearson*, it cannot stop there but *must also allow* all claims containing *less* evidence if they are non-

misleading (by the plain English meaning of their wording) or if they can be rendered non-misleading through the addition of a mandated disclaimer (albeit FDA may require such unauthorized claims to bear the disclaimer, “The FDA does not approve this claim,” 164 F.3d at 659).² That statement is the gist of the *Pearson* decision. Below, we offer a careful review of the decision and its meaning within the broader context of the First Amendment cases cited by the *Pearson* Court.

What did the *Pearson* Court decide?

(1) The Court accepted, and the parties did not dispute, that health claims are commercial speech that must be evaluated under the commercial speech doctrine. 164 F.3d at 655 (“It is undisputed that FDA’s restrictions on appellants’ health claims are evaluated under the commercial speech doctrine”).

(2) The Court recognized that the Government, not the health claim petitioner, carries the burden of proof to justify speech restriction. *Pearson*, 164 F.3d at 659 (the Government “must . . . meet its burden of justifying a restriction on speech . . .”); *Peel v. Attorney Registration and Disciplinary Comm’n of Illinois*, 496 U.S. 91, 109 (1990) (the Government carries a “heavy burden of justifying a categorical prohibition” on commercial speech); *In re R.M.J.*, 455 U.S. 191, 203 (1982).

In *Ibanez v. Florida Dep’t of Business and Prof’l Reg*, 512 U.S. 136 (1994), the Supreme Court put it this way:

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

²FDA may not define a health claims review standard that requires proof of validity of the nutrient-disease relationship to a degree greater than that intended by Congress (note well below Congress expressly rejects the drug standard of near conclusive proof which FDA has in fact adopted in its Guidance), but it may not use any validation test of the relationship to prohibit an otherwise truthful and nonmisleading nutrient-disease association claim or a potentially misleading nutrient-disease association claim that can be rendered non-misleading through the addition of a disclaimer.

harmless from the harmful.” [citation omitted]. “[M]ere speculation or conjecture” will not suffice; rather the State “must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.” [citations omitted].

(3) The Court rejected unequivocally the Government’s argument that the Plaintiffs’ health claims are inherently misleading. The Court held the claims, at worst, only potentially misleading, noting that the problem with the claims “was not a dearth of supporting evidence” but that FDA had concluded that the claims were “inconclusive for one reason or another and thus failed to give rise to ‘significant scientific agreement.’” *Pearson*, 164 F.3d at 653; see also *id* at 657 (“The government does not assert here that appellants’ health claims convey no factual information, only that the factual information conveyed is misleading”). Concerning the Government’s argument that health claims lacking “significant scientific agreement” are by that fact “inherently misleading,” the Court deemed the position “almost frivolous” and “reject[ed] it.” *Id.* at 655. That finding is particularly revealing within the context of the decision as a whole. Note well that the Court held that FDA had not defined “significant scientific agreement” (*Id.* at 653: “But the FDA never explained just how it measured ‘significant’ or otherwise defined the phrase”), never gave “some definitional content to the phrase ‘significant scientific agreement.’” *Id.* at 660 (in two places).³ Thus, the Court recognized that *regardless* of how FDA defined its *validation* standard, it still had to satisfy the First Amendment by avoiding suppression of truthful and nonmisleading speech, or of potentially misleading

³ Indeed, as the Joint Commenters have explained in comments filed in response to FDA’s Guidance on “significant scientific agreement,” the Government has still not explained how it measures “significant” or given meaningful definitional content to the phrase. But for establishing that it accepts near conclusive proof of a nutrient-disease association and certain causality, equivalent to the “substantial evidence” drug pre-approval standard, FDA has utterly failed to define the phrase and certainly has failed to do so in a way consistent with the intent of Congress. We incorporate here the Joint Commenters’ comments in response to the Guidance and reattach them as Exhibit 1. FDA should not make the mistake of following the

speech that could be rendered non-misleading through the addition of a disclaimer. This explains the Court's reasoning:

Normally we would discuss the non-constitutional argument first, particularly because we believe it has merit. We invert the normal order here to discuss first appellants' most powerful constitutional claim, that the government has violated the First Amendment by declining to employ a less draconian method—the use of disclaimers—to serve the government's interests, because the requested remedy stands apart from appellants' request under the APA that the FDA flesh out its standards. *That is to say, even if “significant scientific agreement” were given a more concrete meaning, appellants might be entitled to make health claims that do not meet that standard—with proper disclaimers.*

Id. at 654. CFSAN Director Levitt appears to comprehend this meaning. On two occasions (in letters dated October 5, 1999 and February 17, 2000 (attached as Exhibits 2 and 3)) he has assured counsel for the *Pearson* Plaintiffs that, to quote the October 5 letter:

[W]e agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim.

See Exhibit 2.

We note that FDA's recent promulgation of its Guidance on Significant Scientific Agreement violates the Administrative Procedure Act and the *Pearson* Court decision. Under the APA, FDA may not interpret “significant scientific agreement” in a manner contrary to the way in which Congress intended the agency interpret 21 U.S.C. § 343(r)(5)(D) but must do so in conformity with congressional intent. See 5 U.S.C. § 706(2)(c). However, as set forth in Exhibit 1 hereto, FDA has failed to explain what level of proof --short of that which it would deem conclusive to a near certain degree

approach specified in the Guidance in re-evaluating the *Pearson* claims for the reasons articulated in the attached comments.

(large, lengthy, very expensive double-blind placebo-controlled intervention studies and proof of direct causation, the so-called “drug certainty” standard)--it would deem adequate to authorize a claim under “significant scientific agreement.” Congress, by contrast, fully expected the agency to approve health claims that were based on proof that was not “complete” and that would not satisfy the “drug certainty” standard. Congress expected FDA to approve health claims that were backed by “a significant segment of scientists having relevant expertise” who believe that “consumers are reasonably likely to obtain the claimed health benefit” and were based on “evidence from a broad range of reliable scientific sources,” not limited to intervention studies. In Committee, Congress explained in detail:

The Committee notes that the significant scientific agreement standard is, by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires a demonstration of safety and effectiveness based on “adequate and well-controlled clinical investigations.” While the intake of a nutrient on which a health claim is based must be safe, there is no requirement that health claims be derived from clinical trials, and, by its terms, the standard recognizes that scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support.

In emphasizing the significant scientific agreement standard, FDA will be expected to take full advantage of the flexibility of the standard to maximize the availability on food and dietary supplement labels and labeling of disease-related information consumers can prudently use to affect their risk of disease.

This includes recognizing that there will nearly always be some remaining scientific uncertainty about the validity of any diet-related health claim; that some individuals consuming or avoiding a nutrient in response to a health claim may benefit, while others may not; and that the benefits for any individual may consist not of absolutely avoiding a disease, but rather of reducing her or his risk of a disease.

The end point for evaluation of the adequacy of support for a claim should not be definitive proof that the nutrient has the stated effect for all populations, but that the nutrient will produce the stated effect in the majority of a target population the

majority of the time. In addition, the scientific evidence supporting a claim should not be held to the same standard used in evaluating new drug applications.

Under the significant scientific agreement standard, the FDA should authorize claims when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit. This is consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved.

Senate Report 103-410, at 24.

(4) The Court stated that FDA may not ban health claims it deems not *validated* or *scientifically proven* and may not ban health claims it deems *incomplete* but must *allow* them so long as corrective disclaimers can cure a perceived misleading connotation. The focus of the First Amendment standard, unlike the agency's health claims review, is upon the veracity of the claim: i.e., "Is the claim accurately stated or, if not, can it be rendered so through a corrective disclaimer?", not "Is the association *scientifically proven or scientifically validated?*" Under the First Amendment, the standard is literal truthfulness (i.e., veracity), not scientific conclusiveness (i.e., definitive proof of the nutrient-disease association), as the *Pearson* decision makes clear. In that regard, the argument that information is "incomplete" may not be used as a justification for barring information that is otherwise "correct." The *Pearson* Court quoted at length from *Bates v. State Bar of Arizona*, 433 U.S. 350 (1977), to establish this point:

In *Bates v. State Bar of Arizona* . . . the Supreme Court addressed an argument similar to the one the government advances. The State Bar had disciplined several attorneys who advertised their fees for certain legal services in violation of the Bar's rule, and sought to justify the rule on the ground that such advertising is inherently misleading "because advertising by attorneys will highlight irrelevant factors and fail to show the relevant factor of skill." *Id.* at 372. The Court observed that the Bar's concern was "not without merit," but refused to credit the notion that "the public is not sophisticated enough to realize the limitations of

advertising, and that the public is better kept in ignorance than trusted with correct but incomplete information.” *Id.* at 374-75. Accordingly, the Court held that the “incomplete” attorney advertising was not inherently misleading and that “the preferred remedy is more disclosure, rather than less.” *Id.* at 376. In more recent cases, the Court has reaffirmed this principle, repeatedly pointing to disclaimers as constitutionally preferable to outright suppression. *See Peel*, 496 U.S. at 110; *R.M.J.*, 455 U.S. at 206 n.20; *Shapero*, 486 U.S. 466 at 478, 100 L.Ed.2d 475, 108 S.Ct. 1916.

164 F.3d at 657.

The following example will help demonstrate protected commercial speech in the form of health claims that are *accurate* but are not *scientifically proven or scientifically validated*. Assume that there exists only preliminary scientific evidence suggesting a possible association between consumption of Nutrient X and a reduction in the risk of Condition Y. Assume that the claim submitted to FDA reads: “Preliminary scientific evidence suggests that Nutrient X may reduce the risk of Condition Y.” That statement is quite literally true but the association between Nutrient X and Condition Y is not scientifically proven to a *conclusive* degree or scientifically validated to a *conclusive* degree. The statement must be allowed by FDA. The First Amendment compels the agency to favor disclosure of the statement over its suppression and to avoid suppression in every other instance where a disclaimer can render the claim non-misleading.

The following example will help demonstrate protected commercial speech in the form of health claims that are *accurate* but *incomplete*. Assume that there exists scientific evidence supporting an association between consumption of Nutrient X and a reduction in the risk of Condition Y. Assume further that empirical evidence indicates that Nutrient X may increase the risk of Condition Y in people who consume a high fat diet. Assume that the claim submitted to FDA reads: “Nutrient X may reduce the risk of Condition Y.” The statement must be allowed by FDA but FDA may require a

disclaimer to render it complete (perhaps: “Warning: Consumption of Nutrient X by those who consume a high fat diet may increase the risk of Condition Y”). Although not *complete*, the submitted claim is literally accurate and, thus, protected from suppression under the First Amendment commercial speech standard. The First Amendment compels the agency to favor disclosure of the statement over its suppression. As the *Pearson* Court reasoned:

[T]he government’s interest in preventing the use of labels that are true but do not mention adverse effects would seem to be satisfied—at least ordinarily—by inclusion of a prominent disclaimer setting forth those adverse effects.

164 F.3d at 659.

FDA must avoid suppression in every other instance where a disclaimer can render the claim complete.

(5) The Court stated that FDA must favor disclosure over suppression and may not outright suppress health claims when a less restrictive and more precise means exists as an alternative to suppression. The *Pearson* Court rejected “the government’s position that there is no general First Amendment preference for disclosure over suppression” (holding the contrary proposition to be the law: i.e., that there is a general First Amendment preference for disclosure over suppression) and also cited favorably to that part of *SUNY v. Fox*, wherein the Supreme Court emphasized that when Government suppresses speech at times when disclaimers could suffice to cure misleadingness, its actions are “substantially excessive, disregarding far less restrictive and more precise means” which it may not do under the third prong of the *Central Hudson* standard. *Pearson*, 164 F.3d at 658 (citing *Fox*, 492 U.S. at 479); *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm’n of New York*, 447 U.S. 557, 566 (1980). *Pearson*

encapsulated these principles in the following statement; “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.” 164 F.3d at 658.

(6) The Court stated that FDA may not presume disclaimers insufficient to cure misleadingness but could only rule them out in an individual case based on empirical evidence of their actual ineffectiveness. The Court drafted specific disclaimers which it suggested for use with each of the *Pearson* health claims and expressed skepticism, but did not rule out, the possibility that FDA would find its disclaimers incapable of correcting for deceptiveness and might elect other disclaimers to cure perceived misleading connotations. 164 F.3d at 659-660 (“[W]hile we are skeptical that the government could demonstrate with empirical evidence that disclaimers similar to the ones we suggested above would bewilder consumers and fail to correct for deceptiveness, we do not rule out that possibility”).

(7) The Court stated that when evidence in support of a claim is outweighed by evidence against the claim or where evidence in support of a claim is qualitatively weaker than evidence against the claim, the FDA may deem it incurable by a disclaimer (if FDA can *prove* that such is the case) and ban it outright. In its reasoning, the Court offered the following example of a claim that would not be curable with a disclaimer:

For example, if the weight of the evidence were against the hypothetical claim that ‘Consumption of Vitamin E reduces the risk of Alzheimer’s disease,’” the agency might reasonably determine that adding a disclaimer such as “the FDA has determined that no evidence supports this claim” would not suffice to mitigate the claim’s misleadingness.

164 F.3d at 659.

Note well that under the First Amendment assessment, as under the Court’s analysis here, the focus is upon the *precise language* of the claim presented, not on the nutrient-disease association *per se*. Thus, the question--as explained above--is upon the *veracity* of the *actual* claim, not the *validation* of the perceived association. Therefore when the actual claim presented is one for which disclaimers cannot cure misleadingness, it may be prohibited outright. In the example given, the Court hypothesizes that the “weight of the evidence” contradicts (is “against”) the precise claim and that “no evidence supports this claim.” *Id.* at 659. That situation differs from the one the Court found with respect to each of the *Pearson* claims; there the Court recognized that there “was not a dearth of supporting evidence” but, rather, that FDA had concluded the evidence was “inconclusive for one reason or another and thus failed to give rise to ‘significant scientific agreement.’” *Id.* at 653. The Court plainly contemplates that *inconclusive* claims will be allowed if properly disclaimed. *Id.* Thus, the Court does not consider “inconclusiveness” to be a bar to claim allowance. Rather, it conceives of circumstances where claims would be disallowed as those (1) where *no supporting evidence* exists or (2) where the supporting evidence is *outweighed* by opposing evidence and where disclaimers could not inform the public of the weakness of the evidence and cure misleadingness. Viewed within the context of the decision as a whole, and the applicable First Amendment precedent, the determining factor is not scientific *validation* but *accuracy*. Thus, in instances where the information can be presented in a non-misleading way through the addition of a disclaimer, it must be; but in those instances where the claim cannot be presented in a non-misleading way through the addition of a

disclaimer, it need not be. *Id.* at 656. Proof of misleadingness requisite to suppression must be empirically based and may not be speculative. *Id.* at 659.

The all-important focus for the agency is the *actual language* of the claim, its plain English meaning. Under the First Amendment standard the Court requires this agency to allow an accurate claim, even when based on preliminary or inconclusive evidence. Thus, if there is only preliminary evidence for a claim, and the claim reads, “Nutrient X *may* reduce the risk of Disease Y,” FDA would violate the First Amendment by prohibiting the claim on the basis that the evidence was inconclusive unless empirical evidence proved no disclaimer capable of eliminating misleadingness. FDA might reasonably conclude based on empirical evidence that a disclaimer should accompany the claim to clarify that the evidence was inconclusive or had not reached a point at which there was general scientific agreement to support it.

If, however, the weight of the evidence confirmed that Nutrient X *does not*, as opposed to *may not*, reduce the risk of Disease Y (i.e., if there is conclusive scientific evidence that Nutrient X *does not* reduce the risk of Disease Y), FDA may suppress the claim that “Nutrient X *may* reduce the risk of Disease Y” but, of course, it could not suppress the claim “Nutrient X *does not* reduce the risk of Disease Y” or “Nutrient X *may not* reduce the risk of Disease Y,” the latter constituting a claim which FDA may rightly conclude based on empirical evidence must be accompanied by a disclaimer reciting that the evidence appears conclusive that it does not). In short, every health claim is *sui generis* but the First Amendment principles are unchangeable and focus on ensuring that consumers are provided *accurate* information (as accurate as is reasonably possible in an imperfect world). The basic rule is that accuracy and truth, not scientific validation, must

be the FDA's guide under the First Amendment evaluation and that disclosure, not suppression, is the general rule.

C. PEARSON PLAINLY CONTEMPLATES THAT ADVERSE EFFECTS CAN BE DISCLAIMED

In the case of dietary supplements, the Food Drug and Cosmetic Act imposes on FDA a burden of proof to show that they are injurious to health as a condition precedent to restricting their availability. See 21 U.S.C. § 342(f)(1). The *Pearson* decision complements the statutory scheme by identifying disclaimers as a reasonable solution to the problem of "adverse effects" which do not rise to the level of causing the agency to satisfy its burden of proof under Section 342(f)(1) for removal of the product from the market. Thus, the *Pearson* Court advises this agency that "the government's interest in preventing the use of labels that are true but do not mention adverse effects would seem to be satisfied—at least ordinarily—by inclusion of a prominent disclaimer setting forth those adverse effects." 164 F.3d at 659.

D. THE SUPPLEMENTS AT ISSUE IN PEARSON ARE SAFE

The substances at issue in *Pearson* are found in or extracted from foods in common form and have a long history of safe use in the United States. Antioxidant vitamins are commonly found in fruits, vegetables, and grains. Omega-3 fatty acids are commonly found in fish. Dietary fiber is commonly found in grains. Folic acid may be found in fruits and green leafy vegetables. In addition, the record before the agency is replete with substantial scientific evidence documenting the safety of these elements.⁴ Moreover, FDA has promulgated health claims for foods in common form analogous to

⁴ The Joint Commenters hereby incorporate by reference the comments and scientific evidence they filed in dockets numbered 91N-0101; 91N-0103; 91N-0098; and 91N-100H.

those the *Pearson* plaintiffs seek for their dietary supplements, based in part on recognition of the safety of these substances. See *Pearson*, 164 U.S. at F.3d at 656.

Antioxidant Vitamins. The safety of long term use of therapeutic doses of Vitamins A, C and E has been demonstrated in multiple cohort population based studies and case controlled and other clinical trials. Patterson et al. (1997)⁵ present a table summarizing 16 studies of vitamin supplements and cancer risk that are based on 8 cohort studies. Almost all of the studies involve vitamin A, E, C, multivitamins, selenium, or combinations of these antioxidants. The article discusses the results of the studies and presents a tabular summary of those cohort studies. All of the studies report either protection or no effect, but none report harm. This extraordinary body of research clearly shows that antioxidant vitamins “may protect against cancer.” The data show no evidence of a downside risk at levels commonly sold in the marketplace and sold by the Plaintiffs.

Patterson et al. (1997) also reviewed 36 case control studies and summarized those results in 5 tables, each of which deals with different organ cancers. Almost all of the studies involve the antioxidant vitamins and find either benefit or, if not, at least no evidence of harm.⁶

⁵ Full citations for scientific journal articles cited herein are included in the bibliography attached as Exhibit 16.

⁶We note that the Federal Trade Commission has observed the following with respect to the status of the scientific evidence concerning antioxidant vitamins and cancer: “[A]n extensive scientific literature had developed suggesting a positive relationship between dietary intake of certain antioxidant vitamins (principally beta carotene and vitamins C and E) and a reduction in the risk of several cancers.” FTC Health Claim Study at 42 (Exhibit 14). In a note to that statement, FTC writes: “This literature included a long record of animal tests with positive results for antioxidant vitamin supplementation, numerous epidemiologica studies showing an inverse relationship between dietary intake of carotenoids and cancer risk, and matched case studies and serum level studies supporting a protective effect of beta carotene intake for lung cancer and oral cavity cancers. Epidemiologic evidence and serum level studies also pointed to the efficacy of Vitamin C in reducing the risk of oral cancers and cancers of the esophagus and stomach. The results of studies investigating Vitamin E were less consistent. For a review of the scientific literature on

Some studies suggest that the antioxidant beta-carotene may increase the risk of lung cancer in smokers. There are several reasons to doubt the applicability of those studies to the general population (Pryor, 2000). The Physicians' Health Study (PHS), which was the longest and largest trial of beta carotene, found no benefit or harm from approximately the same level of supplementation with beta carotene as was used in the ATBC trial (Hennekens, et al., 1996). About 11% of the 22,000 physicians in the PHS study remained smokers throughout the study. Moreover, cigarette smoke contains numerous carcinogens and it is not possible to discern reliably whether any evidence of an increased risk of cancer arose from the combination of toxic elements in cigarettes and beta-carotene or arose from the toxic elements alone.⁷ If FDA were to find that scientific research documented a reasonable potential for smokers to experience an increased risk of lung cancer with beta-carotene consumption, that concern could easily be accommodated through the addition of an appropriate disclaimer, such as: "Warning: Smokers should not consume dietary supplements that contain high dose beta-carotene." The *Pearson* plaintiffs would accept such a disclaimer requirement if the evidence warranted the conclusion. Of course, mandating the use of such a warning absent sound empirical evidence would violate the First Amendment and would mislead the consuming public.

Concerning antioxidant Vitamin C, numerous studies confirm its safety. The MRC/BHF Heart Protection Study (1999) is a large randomized trial that includes a wide

antioxidant vitamins and cancer risk, see J. Dorgan and A. Schatzkin: *Antioxidant Micronutrients in Cancer Prevention*, *Hematology Clinics of N. America*: 5: Feb., 1991." Exhibit 14 at 42.

⁷ There seems to be significantly varying sensitivity among the different smoking populations in the beta-carotene intervention studies. Some showed a slightly increased incidence of cancer, while others did not. Only those who smoked twenty or more cigarettes per day showed an increased incidence of cancer. See Hathcock (1997); Pryor (2000); Exhibit 16. That heavy smoking group would be expected to have the

range of patients at high risk of vascular events. It has followed thousands of subjects taking cholesterol lowering medications, antioxidant vitamins, or placebo. The treatment regimens being studied are well-tolerated with the antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C, and 20 mg of beta-carotene daily) producing rare, if any, side effects.

Meyers, Maloley and Weeks (1996) reviewed adverse event reports for vitamins E, C and beta carotene. The data revealed that no adverse reports had been reported for beta-carotene. The data revealed reported ascorbic acid reactions extremely rare at doses less than 4 gm per day.

Johnston (1999) reviewed more than 75 peer-reviewed journal articles and official government reports concerning evidence about tolerable upper intake levels for vitamin C. Johnston analyzed current and past research that examined potential adverse effects of supplemental vitamin C. The evidence overwhelmingly demonstrates that very high intakes of vitamin C (2-4 gms per day) are well tolerated. The scientific evidence has yet to define a supportable upper limit for healthy adults. Vitamin C (ascorbic acid) (Bass, 1998) and Vitamin E (Messer et al., 1993; Bell, 1989) have been shown to be safe when used in premature infants to prevent oxidant lung injuries.⁸

Hathcock (1997) reviewed scientific literature concerning safe and adequate consumption of vitamin and mineral supplements. Hathcock concluded that supplementation with higher than RDA doses of vitamins C and E is safe and that many widely discussed putative adverse effects of vitamins C and E have “little factual basis.”

lowest serum levels of protective vitamins E and C because the destruction of those vitamins is related to the amount of cigarettes smoked (Pryor, 2000). See Exhibit 16.

⁸ The National Academy of Sciences has estimated the tolerable upper limit of vitamin C is 2,000 mg per day. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids* (2000) at 95.

Weber, Bendich and Machlin (1997) reviewed scientific literature and identified that daily consumption of vitamin E much higher than current recommendations can contribute to human health. In addition, the authors concluded that daily consumption of 200-800 IU of vitamin E is safe.

There is very substantial consensus among experts that vitamin E is safe at levels up to 800 IU/day and probably safe at levels at least twice that (Bendich 1988, 1993; Kappus and Diplock, 1992; Meydani et al., 1998). In human studies with double-blind protocols and large population studies, oral vitamin E supplementation resulted in very few side effects in dosages as high as 3200 IU/day (Kappus and Diplock, 1992; Bendich, 1988). Meydani et al. (1998) observed no side effects in older adults with long term oral supplementation with 60, 200, or 800 IU of vitamin E.⁹ In a comprehensive review of literature including basic research, animal studies, and human epidemiological and clinical studies, Pryor (2000) concluded that there is little risk in taking supplement up to 800 IU of vitamin E per day.

Khajehdehi (2000) demonstrated that daily consumption of 200 mg of vitamin C and 200 mg of vitamin E were well tolerated and did not produce adverse effects in hemodialysis patients.

Shklar and Oh (2000) reviewed clinical, animal and experimental studies concerning the chemoprotective properties of vitamin E. They concluded that the evidence supports the safety of oral consumption of vitamin E at therapeutic levels.

⁹ The National Academy of Sciences has estimated the tolerable upper limit of vitamin E is 1,000 mg per day. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000) at 186.

Vatassery, Bauer and Dyskan (1999) reviewed scientific literature concerning the use of vitamin E in patients with central nervous system disorders. That review revealed that two-year consumption of 2000 IU/day of vitamin E was safe.

Fillmore, et al. (1999) reviewed the scientific literature to determine the levels of safety and efficacy of commonly used dietary supplements. Fillmore and his colleagues concluded that vitamin E was one of the nutrients that have “essentially no toxicity.”

Sibulesky et al. (1999) assessed the long-term effect of vitamin A supplementation. In the study of 146 adult men and women (18-54 years old), three groups consumed an average of 5583 RE of vitamin A per day for 5 years. The researchers concluded that prolonged daily consumption of less than 7500 RE (25000 IU) of vitamin A can be considered safe in 18-54 year old adults.

Kappus and Diplock (1992) reviewed tolerance, toxicological considerations, and the safety of vitamin E. They conclude that there are no side effects up to 800 TE (about 1200 IU). The therapeutic range is given as 200 to 1,600 TE. Kappus and Diplock state:

Side effects are only expected to begin at doses of 1,000 to 3,000 TE/d [that is, to begin at about 1,500 IU/d], and to consist of “gastrointestinal complaints, creatinuria and impairment of blood coagulation, which are, however, generally not severe and which subside rapidly on reducing the dosage or on discontinuing the administration of vitamin E Thus, the entire range from the minimal requirement up to a dose of approximately 3,000 mg [of d-alpha-tocopherol] can be considered as a safe range. There is a risk of adverse effects above intakes of 3,000 mg vitamin E per day.

Thus, the levels of vitamin E consumed as a result of supplementation with 400 or even 800 IU/d is well within safe limits. Vitamin E does decrease platelet adhesion and may increase clotting times at high levels of supplementation (Kim, 1996). It may therefore be prudent to include a notice to those who take anticoagulants that they should not consume the product until first consulting with a physician. The *Pearson* plaintiffs intend

to include such a disclaimer on the labels of their dietary supplements and would accept a reasonable disclaimer requirement to that effect.

The recent report of the National Academy of Sciences is currently the subject of severe criticism in the scientific community. An analysis of the safety aspects of the report is attached as Exhibit 17.

Omega-3 Fatty Acids. The *Pearson* plaintiffs submitted more than 75 scientific journal articles in support of the claim that omega-3 fatty acids may reduce the risk of coronary heart disease. In addition, more than 50 additional articles were submitted to FDA in response to the agency's request for more scientific information concerning the relationship between omega-3 fatty acids and coronary heart disease. Those articles and scientific studies document not only the effectiveness of omega-3 fatty acids in reducing heart disease risk but also provide strong evidence for the safety of omega-3 fatty acid supplements.

Harris (1989, 1996, 1999) critically reviewed more than 75 studies on the impact of fish oil and omega-3 fatty acids on hypertriglyceridemia and cardiovascular health. Problems with excessive bleeding and worsening glycemic control did not materialize in the dozens of studies of thousands of subjects taking large doses of the fatty acids. Harris notes that results of the studies strongly support the safety of therapeutic doses of fish oils and omega-3 fatty acids.

Connor WE and Connor SL (1990, 1997) examined data from more than 40 studies concerning the effects of Omega-3 fatty acids. Connor and Connor concluded that 6 to 15 g/day of omega-3 fatty acids was safe and effective in healthy subjects and those at high risk for coronary heart disease.

The GISSI study (1999) of 11,325 adult survivors of heart attacks examined the effects of Omega-3 fatty acids or vitamin E on the incidence of repeat cardiac events. The five year study indicated that daily consumption of 1 gram of omega-3 fatty acids for more than three years is well tolerated and presents no safety concerns.

Von Schacky (1999) conducted a study of 223 patients with angiographically proven coronary artery disease. The patients who received 6 g/day of omega-3 fatty acids for three months followed by 3 g/day for an additional 21 months tolerated those doses and no toxic effects were observed.

Dietary Fiber. The scientific literature has consistently concluded that consumption of increased amounts of dietary fiber is safe. The FDA recognized the safety of soluble dietary fiber in dietary supplements and foods in conventional form in its 1998 Final Rule, 63 Fed. Reg. 8111-8115. FDA further determined that authorization of the health claim for foods enriched with fiber would most likely not result in potential fiber consumption exceeding safe levels. 63 Fed. Reg. 8111. The agency approved the Kellogg Company's Petition for a Health Claim for Psyllium Fiber when the psyllium fiber claim is accompanied by an appropriate notice to consumers to consumer adequate liquids when ingesting the product. *Id.* The *Pearson* plaintiffs would agree to the same or a similar disclaimer for use in conjunction with the fiber/colorectal cancer health claim.

Jansen, et al. (1999) reported on the results of sixteen cohort studies that were part of the Seven Countries Study of dietary fiber and colorectal cancer mortality. The sixteen cohort studies identified that fiber, especially from whole grains, rather than other

plant components, is the relevant nutrient for lowering colorectal cancer risk. The 25-year study of 12,763 men revealed no adverse effects from high fiber consumption.

Trock, Lanza and Greenwald (1990) performed a meta-analysis of 23 case-controlled studies, seven international correlation studies, eight single country correlation studies, and three longitudinal studies. The results of that analysis led the authors to conclude that the evidence is strong for a lower risk of colon cancer associated with fiber rich diets and that the benefits of increased fiber consumption are “undeniable” with “little likelihood of adverse consequences.”

Faivre (1999 and 1998) reviewed scientific literature concerning the effects of high fiber consumption on the reduction in colorectal cancer risk. The author concludes that if studies now in progress prove “efficient” they will confirm that increased dietary fiber consumption through supplementation is a safe and inexpensive prophylaxis for colorectal cancer.

Gordon (1990) reports on an extensive review of experimental, animal and clinical data and concludes that increased consumption of dietary fiber “should not be associated with impaired mineral absorption and long-term mineral status.” While soluble fiber delays circulatory zinc absorption, Gordon points out that that should not be interpreted as decreased utilization and the increased total dietary fiber intake “remains desirable.”

Kelsay’s (1982 and 1990) reviews of clinical and experimental data conclude that any reported decreases of vitamin bioavailability because of the presence of fiber or related components in foods have been small and “likely would not affect nutritional status when vitamin intakes are adequate.”

Folic Acid. Dietary folates and folic acid (as used in food fortification and dietary supplements) are safe in large doses. There are believed to be no concerns limiting dietary folate intake. Specific quantitative clinical laboratory assays are now used for diagnosing vitamin B12 deficiency. Moreover, the Joint Commenters' formulations containing over 200 mcgs of folic acid also contain far more than the RDI of vitamin B12.

Folic acid has no known toxicity in humans (American Academy of Pediatrics Committee on Genetics, 1999). Intakes of 1000 mcg/day for 5 years have had no adverse effects (Butterworth and Tamura, 1989), although intakes greater than 1000 mcg/day may reduce the effectiveness of some anticonvulsant medications (Czeisel, 1998; Dansky, et al., 1987). Folic acid supplements taken by women have not caused long-term developmental, behavioral, or neurologic effects in their children (Holmes-Seidle, et al, 1992). Contrary to an earlier speculation, folic acid supplementation does not decrease the incidence of fetal neural tube defects by increasing the rate of fetal death (Czeisel, 1998) or by increasing the risk for miscarriage (relative risk: 1.06; 95% confidence interval: 0.79 – 1.43) (Holmes-Seidle, et al., 1992). To the contrary, a recent review by Ray and Laskin indicates that women with low levels of folate have higher miscarriage rates (1999).

Concern has been expressed over the theoretical possibility that substantial supplementation with folic acid could resolve the folate-sensitive anemia of vitamin B12 deficiency (by supplying methyl groups for DNA replication and methylation, eliminating the need for vitamin B12-dependent recycling of methyl group donors) while allowing the folate-insensitive demyelination neuropathy of vitamin B12 deficiency to

progress undiagnosed and unchecked. It has been speculated that by removing easily recognized pernicious anemia from the diagnostician's repertoire, widespread folic acid supplementation or food fortification with folic acid at biologically optimal levels might trigger an epidemic of undiagnosed and irreversible neuropathy. Despite the frequency and sometimes ardor with which this objection to maximization of the benefits of folic acid supplementation has been voiced, it has never been demonstrated that the diagnosis of vitamin B12 deficiency is in fact made more promptly in cases presenting with anemia; it also has yet to be demonstrated that folic acid hastens the progression of the neuropathy of vitamin B12 deficiency (Locksmith and Duff, 1998; 91:1027-1034). Furthermore, physicians can reliably and quickly assess potential vitamin B12 deficiency among at risk patients and those taking folate supplements. Physicians can rule out vitamin B12 deficiency through measurement of serum or urinary methylmalonic acid (Norman and Morrison, 1993; Anand, 1995; Stabler, 1995). Many experts believe that the FDA's approval of the folic acid/NTD claim was unjustifiably delayed and that "it is a tragedy that for over a decade, scores of thousands of infants every year were born with neural tube defects that could have been prevented if the international public health authorities had acted instead of advocating delay" (Schulman, 2000). In light of the recognized superior effectiveness of folic acid supplements in delivering a reliable dose of folate at optimal risk reduction levels, this agency continues to keep women in the dark about the best sources of folic acid for preventing neural tube defect births by mistakenly prohibiting the *Pearson* plaintiffs' comparative folate claim. FDA allows food with only 40 to 76 mcgs of folate (only 10-19% of the RDI) to be labeled as a "good source of folate" thereby misleading many women into believing their folate deficient diets

adequate to prevent neural tube defects. A curative disclaimer is sorely needed to correct the misleading connotation conveyed by FDA's authorized claim on folate deficient foods.

E. THE EFFECTIVENESS OF DISCLAIMERS AND, IN PARTICULAR, OF THE PEARSON COURT'S RECOMMENDED DISCLAIMERS

The economic literature confirms that the exercise of informed consumer choice hinges on the availability of accurate information at the point of sale in the consumer marketplace. See generally John E. Calfee & Janis K. Pappalardo, *How Should Health Claims for Foods Be Regulated?* 26-27 (Bureau of Economics, Federal Trade Commission 1989) *cited in Pearson*, 164 F.3d at 658 n.7 (explaining that channels other than the label and labeling impose higher search costs on consumers and reach them less effectively than claims directly on the label); see also The Hartman Group, "Organic Products—How do consumers choose?" *Natural Sensibility* 1999, 2:1-2; "Branding in the V[itamin]M[ineral and]H[erbal]S[upplement] marketplace," *Natural Sensibility*, 1998, 1:1-2 (presenting data from a survey of 4,000 households revealing that consumers most depend upon the information contained on labels of food and food products for nutrition information) (Exhibit 4 hereto).

Mathios (1998) demonstrated that suppression of health claims and health benefit information "stifles the flow of useful information to consumers especially less-educated consumers" and results in consumers changing their purchasing habits to make less healthy food purchases. See also Cox, et al. (1990).

The FTC recently confirmed the high level of consumer skepticism against the reliability of health claims on food product labels and the effectiveness of clear and concise disclaimers. The FTC Generic Copy Test of Food Health Claims in Advertising

(1998) (FTC Health Claim Study) (attached hereto as Exhibit 14) surveyed the results of a large scale advertising copy test project that was conducted jointly by the Division of Advertising Practices and the Bureau of Economics of the Federal Trade Commission. The report of that research presents three classes of health claims in either an unqualified or qualified manner. The purpose of the consumer research was to determine which of the various types of disclosures and warnings that appeared in the qualified ads would communicate most effectively information concerning the nutrient profile and health attributes of the advertised products.

The FTC research examined the effectiveness of the ads and disclaimers on a group of more than 1,700 consumers in 12 geographically dispersed cities across the United States. To provide a benchmark for gauging the effect of the qualifying disclosures, one group of consumers was shown an ad that claimed the health benefits of the margarine or vitamin supplement were a proven scientific fact. Of that group, only 27 percent of respondents stated that they were “very sure” of the certainty of the claim. Additional groups of consumers saw ads that contained a series of increasingly qualified disclosures concerning the level of scientific support for the alleged health benefits. Only 12% of the groups who saw the claims with mild disclaimers stated that they were sure of the certainty of the claim and stronger disclaimers reduced those ratings even further.

The results from the strength of science research revealed that the strong disclaimers included in the second level of qualification (such as explicit references to inconsistent study results or ongoing scientific debate) can have a significant impact on consumer perceptions of the level of proof underlying a health claim. The research results also revealed that even the respondents in the two “proof” cells were reluctant to

assign very high levels of certainty to the science supporting the nutrient/disease relationships.

The FTC studied consumer responses to unqualified and qualified health claims concerning the specific relationship between antioxidant vitamins and cancer risk reduction. FTC selected the antioxidant vitamin health claim as a test claim because the Commission found *“the level of scientific support in the two areas has advanced” and the “relationships were supported by a level of scientific evidence that could not be characterized as purely speculative or even preliminary.”* Exhibit 14 at 49. The FTC Health Claim Study evaluated consumer responses to the following health claim and disclaimers:

HEALTH CLAIM: “Scientists have known for some time about the special health benefits of fruits and vegetables that are rich in antioxidants like vitamins A, C, and E. Eating plenty of these foods can reduce the risk of certain kinds of cancer. Some medical studies are now suggesting that supplements containing these same antioxidant vitamins may also reduce the risk of cancer.”

DISCLAIMERS: (For “Qualified Claim”): “It is too early to tell for sure. Some recent studies have failed to show that these vitamins protect against cancer. Longer term research is needed. In the meantime, always eat a balanced diet with 5 to 9 servings of fruits and vegetables a day. And to make sure you get the antioxidant vitamins you want, try new ACE Antioxidant Supplement.”

(For “Highly Qualified Claim”): “It is too early to tell for sure. Some recent studies have failed to show that these vitamins protect against cancer. And in one study, high doses of certain antioxidants may actually have increased the risk of cancer for

smokers. Longer term research is needed. In the meantime, always eat a balanced diet with 5 to 9 servings of fruits and vegetables a day. And to make sure you get the antioxidant vitamins you want, try new ACE Antioxidant Supplement.”

The results of the FTC Health Claim Study show that a vast majority of consumers (73%) did not accept the unqualified health claim as certain. In addition, most of the respondents stated that their skepticism was enhanced by the lack of evidence presented in the health claim. 88% of surveyed consumers found the qualified health claim to indicate clearly the strength of science supporting the claim was in debate. The highly qualified health claim produced even greater doubt in consumers’ perception of scientists’ certainty concerning the ability of antioxidant vitamins to reduce the risk of cancer. The highly qualified claim caused consumers to rate scientists’ level of certainty as between “neither sure nor unsure” and “somewhat unsure.” Consistent with Dr. John E. Calfee’s conclusions (Exhibit 5 at 5), the FTC Health Claim Study showed that qualified claims do aid consumers in comprehending the relative level of scientific support for a claim, thus enabling informed consumer choice.

Mazis and Raymond (1997) examined consumer perception of the credibility of health claims on food labels. In that study consumers who were given more nutrition information with a health claim on a food label changed their belief about the creditability of the claim when the nutrition information conflicted with the claim. The authors conclude that the study supports the view that increased nutrition information can reduce consumer misperceptions. The results demonstrated that consumers’ belief about health claims are influenced by the health claim and nutrition information contained on food package labels.

While in a perfect world, complete or perfect information would be available, few, if any, markets for consumer goods (be they pharmaceutical products heavily regulated by FDA or foods in common form not as heavily regulated by FDA) provide complete or perfect information to consumers. Ekelund & Saurman, Advertising in the Market Place 73-74 (1988). That is because, *inter alia*, (1) science is evolutionary; new information arises almost daily that may concern the product but cannot be economically communicated in real time at the point of sale; (2) labeling space is limited; there is a reasonable limit to the quantity of information that may be communicated on the label and in labeling; (3) time, interest, and attention is frequently limited (e.g., economic studies suggest that consumers do not read the voluminous inserts required for drug products); and (4) external variables affect discernment (such as external opinions, preconceived notions, culture, and education) affect comprehension of labels and labeling.

Recognizing that imperfect information is unavoidable, the agency's goal must be to adopt disclaimers that are designed to maximize the potential that consumers will receive truthful and nonmisleading information. Because the FDA bears the First Amendment burden of proof, it may not deem disclaimers infeasible because it *lacks* conclusive evidence of their perfect utility or that not every consumer comprehends the plain meaning of the language contained in the disclaimer. No, FDA may only rule out disclaimers, based on empirical evidence that they cannot cure misleadingness, i.e., that the claim is such that no disclaimer can eliminate its misleading connotation.

As the attached report and articles (Exhibits 5 and 6 to 14) establish, economic literature confirms that consumers generally do understand health claim information and

incorporate that information into their decision making on what products to purchase. Calfee and Pappalardo (1991). The literature further confirms that consumers are far more apt to choose healthful options when they receive even incomplete health information, accurately stated, than when they are deprived of health information at the point of sale. Russo (1986); Salmon (1989).

A core assumption that has dominated FDA decision making appears contradicted by the empirical data. FDA has previously speculated without a shred of evidence that health claims, including the plaintiffs' "may" claims, although accurately stated, would nevertheless mislead consumers, inducing them to conclude (1) that conclusive proof supports the associations or (2) that they may forego medical treatment for serious disease conditions and rely on the supplements as complete substitutes¹⁰. The economic evidence reveals that the vast majority of consumers are highly skeptical of health claims on food and dietary supplement labels and do not appear to have such knee-jerk reactions. Hartman Group (1998; 2000); Moorman, 1990; FTC Health Claim Study (1998). Moreover, the evidence reveals that consumers are more skeptical of claims when they are accompanied by a disclaimer on or immediately near the claim. Moorman (1990); FTC Health Claim Study (1998). However, consumers do process and evaluate disclaimer information when it provides them specific and direct guidance. Moorman (1990); Russo (1986); Mazis (1997).

A second core assumption that has dominated FDA decision making also appears contradicted by the empirical data. FDA has often assumed that consumers are too

¹⁰ Aside from the fact that the agency has no empirical evidence to support this assumption, it is patently counterintuitive. The claims in issue indicate that the nutrients may reduce *the risk of* the diseases, not that they treat the diseases. Moreover, the concern would appear accommodated by a disclaimer reading: "If

unsophisticated to comprehend health claims and health claim disclaimers on the theory that consumers do not bring to the market sufficient knowledge to exercise discernment and may fail to recognize the intended meaning of claims and disclaimers. That assumption, never backed by a shred of evidence, appears contradicted by the empirical data. By and large consumers do seem to exercise greater discernment when given even incomplete health information and, when given that information, do tend to make choices that redound to their health benefit. Moorman (1990); Mazis (1997). Ekelund and Saurman write: “Consumers *cannot* react without information . . . Consumers are not irrational and will not consciously act in a manner that is detrimental to their own self-interest,” but they require enough information to make informed decisions. Ekelund and Saurman, *Advertising and the Market Process* 73-74, 162 (1988).

Moreover, while consumers are skeptical of advertising claims, they tend to believe government mandated information (Opinion Research Corporation (1990) and Calfee and Ringold (1988)). More than half of consumers surveyed reported that they were “not at all confident” that they could “depend on getting the truth in most advertising” (Roper Organization as cited by Calfee and Ringold, 1988). That skepticism may account for the relative lack of influence affirmative health claims have on consumer preferences (Russo, et al, 1986). Russo’s research revealed, however, that “negative” information or disclosures cause consumers to change behavior. Russo’s data also demonstrate that additional explanatory nutrition information at the point of sale increases consumer nutrition knowledge and improves consumer attitudes toward nutrition. Disclaimers that contain “arousing” or consequential information motivate

you suspect that you have [Disease], consult with a physician immediately.” A disclaimer such as this would be acceptable to the *Pearson* plaintiffs.

consumers to process information and make better decisions (Moorman, 1990).

Moorman's research demonstrated that disclaimers are effective in improving information processing and increasing decision quality. That improvement is not dependent upon the consumer's previous familiarity with the nutrition information. Mazis (1997) and Moorman (1990). Moorman also notes that disclaimers without "arousing" consequences do not improve information acquisition and decision quality to the same degree as disclaimers containing those elements. The unattractive alternatives to disclaimers to alter consumer behavior, Moorman explains, include restrictions that stifle information in toto. Based on empirical research, Moorman's conclusions may be restated as follows:

- Nutrition disclosures containing arousing negative consequences and specific guidance on ways to minimize these consequences result in higher motivation to process, higher information acquisition, higher information elaboration, and higher decision quality than do disclosures that are less arousing and specific in guidance.
- Nutrition disclosures containing reference information and consequence information evoke higher ability to process, higher information comprehension, and higher decision quality than do disclosures not containing both types of information.
- Across a diversity of consumer characteristics, nutrition disclosures containing consequence information evoke higher motivation to process, higher information acquisition, higher information elaboration, and higher decision quality than do disclosures not containing consequence information.
- Across a diversity of consumer characteristics, nutrition disclosures containing consequence and reference information evoke higher ability to process, higher information comprehension, and higher decision quality than do disclosures not containing consequence and reference information.

In Dr. John E. Calfee's report (Exhibit 5), he confirms that the economic literature supports the conclusion that consumers are more apt to make informed choices and to pursue their own self-interest if supplied with health information than if deprived of it.

Moreover, he confirms that the health information here in issue (the specific four *Pearson* claims are of a kind that consumers are most apt to understand, given the empirical data on consumer perception to date). Finally, he finds the Court's recommended disclaimers fully suitable in that they convey in a direct manner the negative message of inconclusiveness that is the core point, to wit: that the science does not conclusively associate each nutrient with each disease state.

In sum, health claims are indispensable to informed consumer choice in the dietary supplement marketplace. Informed consumer choice is indispensable to the pursuit of health and self-interest by consumers. Disclaimers for health claims are effective in aiding consumer comprehension and avoiding misleading connotations when they give specific and direct guidance. Consumer welfare is maximized by conveying accurate information, relying on specific and direct disclaimers as necessary to achieve accuracy.

F. RESPONSES TO FDA NOTICE INQUIRIES

Q. What is the best regulatory approach for protecting and promoting public health? Specifically, what approach to regulating health claims will: (a) Protect consumers from fraudulent and misleading claims; and (b) provide reliable, understandable information that will allow consumers to evaluate claims intelligently and identify products that will in fact reduce the incidence of diseases? By what criteria should implementation options be judged?

(a) The best regulatory approach for protecting and promoting public health is one where the FDA transforms itself from an agency that hinders the dissemination of nonmisleading health information concerning the nutrient-disease relationship into one that fosters the dissemination of all truthful information. The best regulatory approach is one in which FDA fulfills its constitutional and statutory duties as the Courts and the Congress intend by upholding rather than transgressing the speech rights of the American

people. The best regulatory approach assiduously avoids suppression at the point of sale of truthful and nonmisleading health information concerning the nutrient-disease relationship and allows consumers full access to that information, recognizing their constitutional rights to exercise freedom of informed choice and trusting them to pursue their own self-interest based on truthful information.

Consumers are less apt to be misled in the market if well-enough informed. By accepting and implementing the constitutional principle of disclosure over suppression, FDA can ensure the greatest opportunity for consumers to be well-enough informed. Fraud in the dietary supplement marketplace preys upon consumers deprived of accurate health information. The current ban on health claims promotes fraud by depriving the supplement marketplace of non-misleading information on the nutrient-disease relationship. In that environment created by the claim ban fraud now flourishes, or so the agency tells us. The provision of accurate health information puts into the market good counsel that combats the bad: Out of the dross arises truth. Barriers to accurate health information leaves the market bare of good counsel to combat the bad. As the above cited and attached economic data confirm, consumers deprived of health claim information suffer debilitating constraints on their exercise of informed choice in the marketplace. With less information to guide them they are more apt to make mistakes, less able to pursue self-interest, more susceptible to fraud and more likely to be misled. The poor and less educated inevitably suffer most in an information restricted market.

(b) The approach to regulating health claims that will provide reliable, understandable information to guide consumers is the approach that naturally follows from full implementation of the *Pearson* decision. To recapitulate, FDA should define a

standard for the *authorization* of health claims that comports with the intent of Congress, as explained above. At the time FDA issues its determination on whether to *authorize* a claim under its health claims review standard (by which FDA places its imprimatur of approval upon it), the agency should also issue its decision on whether it will *allow* the claim *unauthorized* as a matter of First Amendment right. In making that latter assessment, FDA must first determine whether the claim is *inherently misleading*. An inherently misleading claim conveys *no* scientific information and may be prohibited outright. If the claim is not *inherently misleading*, it will either be truthful and non-misleading or it will be *potentially misleading*. As explained above, a health claim can be truthful but not scientifically proven. Such claims must be allowed without disclaimers if they are not *potentially misleading*. A *potentially misleading* claim is one that can be rendered non-misleading through the addition of a disclaimer. Such claims must also be allowed accompanied by mandated disclaimer language that the agency reasonably believes will eliminate the misleading connotation. In every instance of speech restriction, FDA carries the First Amendment burden of proof and must marshal empirical evidence to support the restriction. Moreover, the restriction must be no more extensive than necessary to achieve the goal of eliminating the misleading connotation.

(c) The criteria by which implementation options shall be judged is the *Pearson* decision. That decision affords FDA no option to act except in a way that comports with its holding and the First Amendment to the United States Constitution. It must be FDA's navigator; departure from its holding and reasoning is fraught with certain constitutional disaster and loss of public trust and confidence in the FDA. Public confidence in this

agency depends on its adherence to the rule of law and respect for the Constitution and the interpretation of the Constitution by the *Pearson* Court.

Q. Can qualifying language (including disclaimers) be effective in preventing consumers from being misled by health claims based on preliminary or conflicting evidence? If so, what are the characteristics of effective qualifying language? How should the agency determine what constitutes an appropriately qualified claim? If the available information is not sufficient to answer these questions, what research needs to be done, and who should be responsible for doing it?

As the economic report of Dr. John E. Calfee and the referenced studies above confirm, disclaimers have repeatedly been shown to be effective in edifying consumers about the qualitative level of support for a claim. They are thus far less likely to be misled. Effective qualifying language must be unambiguous, concise, direct, and specific. It should be placed within visual proximity of the claim it concerns and it should be cross-referenced to the claim and appear in a readable type.

To determine if a claim is appropriately qualified requires that FDA (1) identify based on the evidence an actual potential for misleadingness and (2) then, if misleadingness is demonstrated, tailor a disclaimer in plain English language designed to eliminate that misleadingness in an unambiguous, concise, direct, and specific manner.

As explained above, ample research—spanning several decades—corroborates the effectiveness of disclaimers in eliminating misleadingness. In addition, the Federal Trade Commission has observed and studied disclaimers for several decades and finds them capable of qualifying claims that are not supported by conclusive scientific proof. Finally, FTC’s recent study on qualitative disclaimers confirms that they do influence consumer behavior by educating consumers about the level of science supporting a claim.

The less certain the claim, as indicated by the disclaimer, the less likely consumers were to believe the claim established to a certainty.

Q. Is there a way to preserve the existing regulatory framework for health claims consistent with the First Amendment?

As explained above, FDA's current *interpretation* of its statutory health claims standard cannot be maintained consistent with the First Amendment. There is, however, no necessary conflict between 21 U.S.C. § 343(r)(5)(D) and the First Amendment. FDA currently prohibits all health claims that it deems not backed by "significant scientific agreement." As explained above, FDA has still not defined a standard for health claims review that comports with the intent of Congress; it is thus still in violation of the *Pearson* mandate that it explain what "significant scientific agreement" means. Congress has delegated to the agency the authority to define a standard for health claims review. FDA may not define such a standard in a way that causes potentially misleading health claims to be prohibited. It must allow all non-misleading claims (regardless of the review standard it chooses), and it must allow all potentially misleading claims (regardless of the review standard it chooses), so long as the latter can be rendered non-misleading through the addition of a disclaimer.

The best means to satisfy both the First Amendment and the intent of Congress is to adopt a two-track, simultaneously operative, review. In such a circumstance, FDA will respond to health claims petitions by determining whether it shall place its official imprimatur behind them by *authorizing* them. Authorization depends upon satisfaction of a defined health claims review standard. If FDA determines that such a standard is not met, it must then determine immediately whether the claims it reviewed are *inherently misleading* (i.e., it must determine if they convey no scientific information) or are

accurate based on a review of the views of the scientific community as expressed in the scientific literature. If it is inaccurate, the FDA must determine if it conveys scientific information. If it does, then FDA must determine if a disclaimer is needed to prevent misleadingness. If the disclaimer is needed, then the claim must be allowed with the disclaimer.

As the report of Dr. John E. Calfee (Exhibit 5) confirms, the word “may” is meaningful to consumers and does convey its plain English meaning. Consumers understand that may is a term of equivocation, as opposed to will, and that may suggests the existence of inconclusiveness. The agency’s question of whether the term “may” accurately communicates the strength of evidence supporting claims that meet the significant scientific agreement standard is a non-sequitur because the standard has not been adequately defined. To the extent that a definition is discernible, it is that claims whose evidence establishes the nutrient-disease association to a near conclusive degree and establishes direct causation for the relationship pass muster. Such claims would appear to warrant use of a “will” claim or a “likely will” claim (for those deemed established to a slightly less than near conclusive degree). Of course, as explained above, Congress anticipated that far more claims would be authorized under “significant scientific agreement” than the agency has seen fit to allow. Consequently, it is conceivable that when rightly construed and defined, the standard would warrant use of a “may” claim for those claims that are backed by science that is, in effect, proof of a relationship that is more probable than not.

- Q. If health claims are permitted based on a less rigorous standard, what actions can be taken to provide incentives to manufacturers to conduct further research on emerging substance-disease relationships?**

This question appears to start from the presumption that allowance of health claims as required by the First Amendment will reduce incentives to manufacturers to conduct research on emerging substance-disease relationships. To the contrary, as Dr. Calfee explains in his report, the opposite effect is likely to occur. Currently, the agency prohibits all nutrient-disease relationship claims but those established to a near conclusive degree. That standard dissuades companies from investing money in research on claims because they recognize that unless they expend very large sums of money and prove the claim to the agency's satisfaction, they will not be able to communicate any information on the nutrient-disease relationship. This greatly discourages research and greatly encourages the development of an underground or black market in claims.

Allowance of health claims as required by the First Amendment will broaden the quantity and kind of information that may reach the public in the dietary supplement marketplace to include not only that proven to a near conclusive degree but also that which accurately reflects lesser evidence. Broadening the quantity and kind of health information that can reach the public in the dietary supplement marketplace will encourage far more investment in corporate research and development, far more filings of health claim petitions, and far more public cognizance and interest in the evolution of science concerning the nutrient-disease relationship.

In short, FDA has severely limited the commercial market for health claim information by effectively banning all health claims except those proven to a near conclusive degree. By opening the commercial market for health claim information to include all of those required to be allowed by the First Amendment, FDA will induce far more people to believe there is a tangible economic benefit that may be derived from

filing health claim petitions and communicating health claim information. It will therefore induce parties to invest in research and development and file health claim petitions rather than exist at legal risk in a health claims black market, which the agency has repeatedly told Congress it believes exists and flourishes.

Q. The *Pearson* opinion mentions circumstances in which FDA might be justified in banning certain health claims outright (e.g., where the evidence in support of the claim is outweighed by the evidence against the claim, or where the evidence supporting it is qualitatively weaker than the evidence against it) (*Pearson*, 164 F.3d at 659 and n.10). (a) How should FDA determine when evidence supporting a health claim is outweighed by evidence against the claim? (b) How should FDA determine when evidence supporting a health claim is qualitatively weaker than the evidence against the claim? (c) Are there other circumstances in which health claims are inevitably misleading and cannot be made nondeceptive by qualifying language?

The question posed by the agency misrepresents the Court's reasoning, which may only rightly be understood within the context of the case as a whole. The Joint Commenters explain in detail above the meaning of this portion of the *Pearson* decision. FDA must focus on the *precise language* of the claim and must determine whether a disclaimer can relieve the claim, as worded, of potentially misleading connotations. Whether evidence against the claim outweighs evidence for it is heavily based on the actual wording of the claim. A claim which states a conclusive association between Nutrient X and Disease Y contradicted by scientific evidence confirming only a possible association would likely be incurable by a disclaimer. By contrast, a claim which states a possible association between Nutrient X and Disease Y for which there is scientific evidence not contradicted by conclusive proof to the contrary would likely be curable by a disclaimer. As with every balancing test, sound judgment must be exercised recognizing that the general First Amendment principle and rebuttable presumption is in

favor of disclosure. Thus, FDA bears the burden of proof to demonstrate with empirical evidence that a claim will in fact mislead and cannot in fact be rendered nonmisleading through the addition of a disclaimer as a condition precedent to outright suppression.

There are circumstances in which health claims are inevitably misleading and cannot be made nondeceptive by qualifying language. Such claims are said to be *inherently misleading* in the First Amendment case precedent. See *Pearson*, 164 F.3d at 655. Those claims convey *no* scientific information and cannot be rendered non-misleading through the addition of a disclaimer.

Q. What safety information is necessary to prevent a health claim from being misleading? For example, such information might include side effects, drug and food interactions, and segments of the population who should not use the product or should consult a physician before doing so. When a product may have adverse effects unrelated to the subject of a scientifically valid health claim, is the claim misleading? Under what circumstances, if any, should the product be allowed to bear the claim?

The *Pearson* Court answered this question concerning side effects by explaining that “the government’s interest in preventing the use of labels that are true but do not mention adverse effects would seem to be satisfied—at least ordinarily—by inclusion of a prominent disclaimer setting forth those adverse effects.” 164 F.3d at 659. If scientific evidence reveals that a dietary supplement may induce an adverse reaction in a segment of the population, the FDA can best square its First Amendment duty to favor disclosure over suppression with its public health duty by mandating the use of a warning statement in conjunction with the claim. This it has already done in the case of certain approved health claims.¹¹ See 21 C.F.R. §§ 101.74(d)(7); 101.75(d)(7); 101.77(d)(6); 101.81(d)(6); 101.82(d)(5) (requiring that, when a claim defines high or normal blood pressure (or

LDL-cholesterol levels), the labeling must warn that individuals with high levels should consult their physicians for medical advice and treatment); 21 C.F.R. §§ 101.79©(2)(iii) (prohibiting the claim on foods containing certain levels of other vitamins) and ©(3)(iii) (requiring that, when a claim discusses prior neural tube defect pregnancy, the labeling must warn that all women should consult a health care provider when planning a pregnancy). A health claim is not *per se* misleading because it omits a warning statement. That is because the health claim may be entirely accurate yet still be incomplete. Indeed, our First Amendment precedent expressly recognizes this category of speech, as explained above, and describes the “preferred remedy” to be “more disclosure” rather than less. The *Pearson* Court quoted at length from *Bates v. State Bar of Arizona*, 433 U.S. 350 (1977), to establish this point:

In *Bates v. State Bar of Arizona* . . . the Supreme Court addressed an argument similar to the one the government advances. The State Bar had disciplined several attorneys who advertised their fees for certain legal services in violation of the Bar’s rule, and sought to justify the rule on the ground that such advertising is inherently misleading “because advertising by attorneys will highlight irrelevant factors and fail to show the relevant factor of skill.” *Id.* at 372. The Court observed that the Bar’s concern was “not without merit,” but refused to credit the notion that “the public is not sophisticated enough to realize the limitations of advertising, and that the public is better kept in ignorance than trusted with correct but incomplete information.” *Id.* at 374-75. Accordingly, the Court held that the “incomplete” attorney advertising was not inherently misleading and that “the preferred remedy is more disclosure, rather than less.” *Id.* at 376. In more recent cases, the Court has reaffirmed this principle, repeatedly pointing to disclaimers as constitutionally preferable to outright suppression. *See Peel*, 496 U.S. at 110; *R.M.J.*, 455 U.S. at 206 n.20; *Shapero*, 486 U.S. 466 at 478, 100 L.Ed.2d 475, 108 S.Ct. 1916.

164 F.3d at 657.

Thus, so long as the product itself has not been held adulterated, i.e., has not been determined to be injurious to health, the proper remedy for the agency consistent with the

¹¹ Many responsible companies in the dietary supplement industry already employ disclaimers of this kind

First Amendment is to mandate use of a disclaimer to warn the public of adverse effects. FDA may not base a decision to suppress health claims on a view that the consumer is too unsophisticated to comprehend the science. Rather, if Government's concern is public ignorance, the Supreme Court has plainly stated that its solution is more speech, not less, writing in *Bates*:

Moreover, the argument assumes that the public is not sophisticated enough to realize the limitations of advertising, and that the public is better kept in ignorance than trusted with correct but incomplete information. We suspect the argument rests on an underestimation of the public. In any event, we view as dubious any justification that is based on the benefits of public ignorance. [citation omitted]. Although, of course, the bar retains the power to correct omissions that have the effect of presenting an inaccurate picture, the preferred remedy is more disclosure, rather than less. If the naivete of the public will cause advertising . . . to be misleading, then it is the [Government's] role to assure that the populace is sufficiently informed as to enable it to place advertising in its proper perspective.

433 U.S. at 374-375.

Q. What actions should the agency take to ensure that consumers receive all relevant information about the safety of products that bear health claims and about research on product safety?

FDA should rely on the use of mandated warnings, when the evidence corroborates the existence of adverse reactions. In appropriate circumstances where the evidence of adverse reaction is strong and the need for public awareness is great, it should require not only use of a warning statement but also reference to its website for further detailed information on such reactions, and it may require use of an 800-number and the provision of detailed information to that effect. Such a response is a reasonable accommodation of the First Amendment principle favoring disclosure over suppression and the agency's mission to protect public health.

Q. Does the language and structure of the act restrict the permissible types of substance-disease relationships that can be described in a

without a regulatory requirement.

health claim? How should FDA interpret the health claim and drug provisions of the act and the medical food provision of the Orphan Drug Amendments in relationship to each other?

In 21 U.S.C. § 343(r)(1)(B), the act treats as a health claim any claim made in the label or labeling of a food or dietary supplement that “characterizes the relationship of any nutrient . . . to a disease or a health-related condition.” By its plain meaning, that language is extraordinarily broad. It embraces every relationship between a nutrient and a disease without restriction. It thus includes claims of treatment, cure, mitigation, and prevention without limitation. The *Pearson* Court understood the plain meaning of the statute and the legislative history underlying it to carve out an exception (a “safe harbor”) from the drug definition for nutrient-disease relationship claims. The Court wrote:

Although there is apparently some definitional overlap between drugs and dietary supplements under the statute, it creates a safe harbor from designation as a “drug” for certain dietary supplements whose labels or labeling advertise a beneficial relationship to a disease or health-related condition: If the FDA authorizes a label claim under 21 U.S.C.A. § 343(r), the product is not considered a drug under 21 U.S.C.A. § 343(g)(1).

* * * *

The safe harbor from “drug” status for dietary supplements bearing FDA-approved health claims did not always exist. Prior to 1984, the FDA took the position that a statement that consumption of a food could prevent a particular disease was “tantamount to a claim that the food was a drug . . . and therefore that its sale was prohibited until a new drug application had been approved.” H.R. REP. NO. 538, 101st Cong., 2d Sess. 9 (1990), reprinted in 1990 U.S. CODE CONG. & ADMIN. NEWS 3336, 3338. But during the mid-1980s, companies began making health claims on foods without seeking new drug approval, a practice that the FDA supported in regulations proposed in 1987. *Id.* at 3338-39. Congress became concerned that health claims were increasingly common in the marketplace, and that the FDA had not issued clear, enforceable rules to regulate such claims. *Id.*

Against this background, and in light of the further concern that the FDA might lack statutory authority to permit health claims on foods without also require that the claim meet the premarket approval requirements applicable to drugs, see *id.*, Congress enacted the Nutrition Labeling and Education Act of 1990 (NLEA)

[citation omitted]. The NLEA addressed foods and dietary supplements separately. Health claims on foods may be made without FDA approval as a new drug, or the risk of sanctions for issuing a “misbranded” product, if it has been certified by the FDA as supported by “significant scientific agreement.” Id. § 343(r)(3)(B)(i). Congress created a similar safe harbor for health claims on dietary supplements, but delegated to the FDA the task of establishing a “procedure and standard respecting the validity of [the health] claim.” Id. § 343(r)(5)(D).

164 F.3d at 652; 653.

There is not a shred of evidence in the legislative history to suggest that Congress intended the scope of dietary supplement health claims to embrace anything less than the full array of conceivable relationships between nutrients and diseases. The argument has been well-made in a motion for summary judgment filed against the government in *Whitaker v. Shalala*, No. 1:99CV03247 (GK) (D.D.C. filed Feb. 11, 2000). That motion is attached hereto as Exhibit 15 (minus attachments) and incorporated herein as further argument.

The FDA’s question presumes that there is a necessary conflict in the statutory scheme if health claims are given the broad meaning Congress intended. That is simply not the case. Only foods and dietary supplements may bear health claims. A substance must satisfy the statutory definition for those substances to qualify for a health claim. Consequently, if the substance does not fall within the statutory definition of those terms it may only be authorized pursuant to the statutory provisions for drug approval. A food or dietary supplement that is injurious to health when consumed in its recommended dose amounts, as instructed, is adulterated and may be removed from the market. By contrast, a drug may be injurious to health (and frequently is) when consumed in its recommended dose amounts, as instructed, but is available only by prescription and, presumably, is

capable of being monitored by a physician for adverse reactions beyond those acceptable as a part of the treatment.

Q. If FDA were to permit at least some claims about effects on existing disease as health claims, what criteria should be used to determine when a claim is a permissible health claim and when it is a drug claim under section 201(g)(1)(B) of the act?

The “health claim” versus “drug claim” construct posits a distinction not recognized in the statute. Therefore the question is flawed. As the *Pearson* Court explained in the passage quoted in response to the question immediately above, health claims are claims that were previously deemed drug claims by the agency. The NLEA created a safe harbor from the drug definition for health claims. To reinterpret the act to cause some health claims to fall back within the drug definition defeats the essential purpose of the NLEA and is an arbitrary and capricious act, contrary to the law.

Q. If FDA were to permit at least some disease treatment or mitigation claims as health claims, what about claims that are covered by an existing over-the-counter (OTC) drug monograph? For example, if there is an existing drug monograph on the use of a dietary ingredient in an OTC drug product to treat or mitigate disease, and the monograph concludes that the substance is not safe and effective for the intended use, should FDA still consider authorizing a health claim for the substance-disease relationship?

The FDA *must* follow the statutory process for evaluating health claims for dietary supplements and *must* allow unauthorized health claims as constitutionally required under the First Amendment. If a nutrient appears in an OTC drug monograph but still meets the definition of a dietary supplement, FDA may not prohibit it from carrying a health claim based on the argument that it has allowed it for a drug that also includes the ingredient. See *Pharmanex, Inc. v. Shalala*, 35 F.Supp.2d 1341 (D. Utah

1999). If FDA has concluded that a nutrient has been deemed unsafe for use in the treatment of a disease in an OTC monograph, those findings should be taken into account when considering authorization of a health claim for treatment of the disease. However, FDA must evaluate the safety issue anew under the adulteration provisions applicable to dietary supplements. Under those provisions, FDA has the burden of proof. See 21 U.S.C. § 342(f)(1). Were it to satisfy that burden, it could prohibit the sale of the nutrient.

CONCLUSION

As a matter of constitutional law, the FDA must allow health claims that do not satisfy its standard for health claims review if those claims are either truthful and non-misleading or can be rendered non-misleading through the addition of a disclaimer. The FDA must favor disclosure over suppression and may only suppress a claim based on empirical evidence that the claim in fact is misleading and that no disclaimer can cure the misleading connotation conveyed by the claim. The empirical economic data confirms that disclaimers are effective in educating the public on the qualitative level of support for health claims and that consumer welfare is maximized when they receive health claim information at the point of sale. FDA must accept the *Pearson* court's constitutional mandate and reform itself to implement that mandate fully and faithfully. In addition, FDA has no statutory authority to redefine the statutory health claim definition to embrace fewer claims than the plain language and intended meaning of that provision allow. Congress intended the health claim provision to be an exception from, a safe

harbor from, drug status for dietary supplements bearing nutrient-disease relationship claims. FDA has no authority to do an end-run around the plain language of the Act and Congress's intended meaning in a transparent attempt to remove the safe harbor from drug status that Congress codified for dietary supplements bearing health claims. FDA's long-standing bias against dietary supplements and in favor of drugs (well-documented by Congress in S. Rep. No. 103-410, at 14-31 (1994)) cannot trump either the plain meaning of the Act, the intent of Congress, or the First Amendment.

Respectfully submitted,

PURE ENCAPSULATIONS, INC.;
JULIAN M. WHITAKER, M.D.;
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DURK PEARSON and SANDY SHAW,

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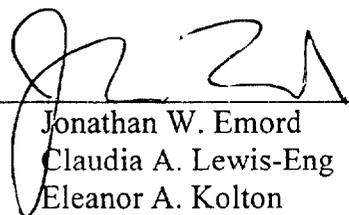
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EXHIBIT 1

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

0368 00 FEB 22 P2:58

In re: Guidance for Industry:)
Significant Scientific Agreement)
In the Review of Health Claims) Docket No. 99D-5424
For Conventional Foods and)
Dietary Supplements; Availability)

**COMMENTS OF
JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
XCEL MEDICAL PHARMACY, LTD.;
MYCOLOGY RESEARCH LABORATORIES, LTD.;
DURK PEARSON and SANDY SHAW; and
AMERICAN PREVENTIVE MEDICAL ASSOCIATION**

Julian M. Whitaker, M.D.; Pure Encapsulations, Inc.; XCEL Medical Pharmacy, Ltd.; Mycology Research Laboratories, Ltd.; Durk Pearson and Sandy Shaw; and the American Preventive Medical Association (collectively, "Joint Commenters"), hereby submit their comments in response to the agency's solicitation for comments in the above-referenced docket. See 64 Fed. Reg. 71794 (1999).

BACKGROUND OF JOINT COMMENTERS

Julian M. Whitaker, M.D. Julian M. Whitaker, M.D. ("Dr. Whitaker") is a physician licensed to practice medicine in the states of California and Washington. He graduated from Dartmouth College in 1966 with a B.S. degree and from Emory University in 1970 with an M.D. degree. He received additional training in surgery as a resident at the University of California Medical School. From 1975 to 1976 he worked as a physician at the Pritikin Institute in California. Since that time he has been the clinical director of the Whitaker Wellness Institute in Newport Beach, California. He is the author of five books: *Reversing Heart Disease* (1985), *Reversing Diabetes* (1987),

Reversing Health Risk (1989), *Natural Healing* (1994), and *What Your Doctor Won't Tell You About Bypass* (1995). Since August of 1991 he has been the editor of *Health & Healing*, currently the nation's largest single editor health newsletter. In 1996, *Health & Healing* had over 500,000 subscribers. He receives royalties from the distribution and sale of several dietary supplements. Dr. Whitaker has filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. He therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

Durk Pearson and Sandy Shaw. Durk Pearson and Sandy Shaw ("Pearson and Shaw") are scientists residing in Nevada. They design dietary supplement formulations and license them to manufacturing and retailing companies. They are authors of four books on aging and age-related diseases, including the #1, million plus copy best seller *Life Extension: A Practical Scientific Approach* (1982). They have also published three other health books, two of which were best sellers: *The Life Extension Companion* (1984); *The Life Extension Weight Loss Program* (1986); and *Freedom of Informed Choice—FDA Versus Nutrient Supplements* (1993). Durk Pearson and Sandy Shaw were plaintiffs in the *Pearson v. Shalala* case that is the subject of these comments. Pearson and Shaw license dietary supplements. They have filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. They therefore have a keen interest in how FDA interprets its health claim standard and are adversely affected by FDA's insistence on a standard more rigorous than that intended by Congress.

American Preventive Medical Association. The American Preventive Medical Association (“APMA”) is a non-profit organization in Virginia. APMA was founded in October of 1992 and is dedicated to ensuring consumer access to preventive therapies and the rights of health care providers to offer those therapies. APMA was a plaintiff in the *Pearson v. Shalala* case that sought FDA approval of four health claims. Several APMA practitioner members sell dietary supplements and would like to use the health claims on the labels and in the labeling of those supplements. APMA practitioner members are desirous of filing additional health claim petitions with FDA. In addition, APMA and its practitioner members and their hundreds of thousands of patients would benefit from an effective and meaningful health claim approval process as described herein because it would enable them to communicate and receive nonmisleading health information on labels and in labeling of dietary supplements. APMA and its members therefore have a keen interest in how FDA interprets its health claim standard and are adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

Mycology Research Labs Ltd. Mycology Research Labs Ltd. (“Mycology”) is a corporation organized in Great Britain and engaged in the business of manufacturing, distributing, and selling multiple pharmaceutical grade dietary supplements for human consumption around the world, including in the United States. Mycology is desirous of filing with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements that it manufactures, distributes, and sells in the United States. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

Pure Encapsulations, Inc. Pure Encapsulations, Inc. (“Pure”) is a Massachusetts corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human and companion animal consumption. Pure has filed with FDA several health claim petitions and would like to use the health claims on the labels and in the labeling of dietary supplements. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care. XCEL Medical Pharmacy, LTD d/b/a XCEL Health Care (“XCEL”) is a California corporation engaged in the business of manufacturing, distributing, and selling pharmaceutical grade dietary supplements for human consumption. XCEL is desirous of filing with FDA health claim petitions and would like to use health claims on the labels and in the labeling of dietary supplements that it manufactures, distributes, and sells. It therefore has a keen interest in how FDA interprets its health claim standard and is adversely affected by FDA’s insistence on a standard more rigorous than that intended by Congress.

BACKGROUND OF AGENCY NOTICE

In 21 U.S.C. § 343(r)(5(D), Congress assigned the Food and Drug Administration the task of establishing a “procedure and standard respecting the validity of [the health] claim.” The FDA, however, did not provide regulatees with a defined standard for review of health claims. On January 15, 1999, the United States District Court for the District of Columbia held the FDA’s failure to define a standard for dietary supplement health claims a violation of the Administrative Procedure Act (APA). *Pearson v.*

Shalala, 164 F.3d 650, 659-661 (D.C. Cir.1999), *reh'g denied en banc*, 172 F.3d 72 (D.C. Cir. 1999).

In particular, the Court held FDA's failure to give definitional content to the phrase "significant scientific agreement" (its lode stone in reviewing dietary supplement health claims) a violation of the APA's prohibition on arbitrary and capricious agency action. *Pearson*, 164 F.3d at 660-661. The Court reasoned that "[i]t simply will not do for a government agency to declare—without explanation—that a proposed course of private action is not approved." It further reasoned that "[t]o refuse to define the criteria [the agency] is applying is equivalent to simply saying no without explanation." *Id.*

The Court held that FDA was required either case by case or sub-regulation by sub-regulation to define the standard, to "explain what [FDA] means by significant scientific agreement or, at minimum, what it does not mean." *Pearson*, 164 F.3d at 661. The Court required FDA to define the standard in a manner that would make it "possible for the regulated class to perceive the principles which are guiding agency action." *Id.*

The Court explained that it could be possible for FDA to define a standard with sufficient particularity that would satisfy the Administrative Procedure Act but yet not define it with that degree of particularity required to satisfy the First or Fifth Amendments to the United States Constitution. *Pearson*, 164 F.3d at 660 n.12.

On December 22, 1999, the FDA responded to the APA holding in the *Pearson* Court's remand not by promulgating a new rule but by issuing a notice of a guidance. 64 Fed. Reg. 71794 (Dec. 22, 1999). In its Guidance, FDA explains that it reviews "all relevant studies" concerning the nutrient/disease relationship and does so under a hierarchy that deems interventional studies involving randomized, controlled clinical

trials as the “gold standard.” Guidance at 4-5. Next down from the randomized, controlled clinical trials are observational studies, with greater preference accorded prospective than retrospective studies. Observational studies are, themselves, given a hierarchy: (1) cohort (longitudinal) studies; (2) case-control studies; (3) cross-sectional studies; (4) uncontrolled case series or cohort studies; (5) time-series studies; (6) ecological or cross-population studies; (7) descriptive epidemiology; and (8) case reports. Below observational studies are the following in their order of relative weight and significance: (1) research synthesis studies and (2) animal and in vitro studies. Guidance at 5.

The agency next discusses its method for ascertaining whether the studies include reliable measures of the substance and the disease or health-related condition. Guidance at 7. FDA states that it must identify “biomarkers (immediate or surrogate endpoint markers) for the presence or risk of disease.” Guidance at 7. FDA states that it must be able to identify and measure the substance in a food and determine the impact of that measured substance on the disease or health-related condition exclusive of other dietary components or the food itself. Guidance at 8-9.

In evaluating scientific studies, FDA will assess the susceptibility of the study to bias and confounders; quality assessment criteria (including adequacy and clarity of design; population studied; analytical methodology and quality control procedures); and the statistical methods used. Guidance at 10-13.

In evaluating the totality of the scientific evidence, FDA requires proof that “a change in the dietary intake of the substance *will* result in a change in a disease endpoint.” Guidance at 13 (emphasis added). Moreover, it requires proof of causation,

demanding strong evidence of a causal relationship. Guidance at 14-15. The agency depends primarily on use of interventional studies (randomized, controlled clinical trials) as a condition precedent to proof of causation, writing:

Causality can be best established by interventional data, particularly from randomized, controlled clinical trials, that show that altering the intake of an appropriately identified and measured substance results in a change in a valid measure of a disease or health-related condition. In the absence of such data, a causal relationship may be inferred based on observational and mechanistic data through strength of association, consistency of association, independence of association, dose-response relationship, temporal relationship, effect of dechallenge, specificity, and explanation of a pathogenic mechanism or a protective effect against such a mechanism (biological plausibility). Although these features strengthen the claim that a substance contributes to a certain health outcome, they do not prove that eating more or less of the substance will produce a clinically meaningful outcome. In many cases (for example, if the intake of the substance has not been or cannot be assessed adequately in available observational studies because it has not been commonly consumed or its intake cannot be assessed independently of other substances), controlled clinical trials are necessary to establish the validity of a substance/disease relationship.

Guidance at 15.

In determining the weight of the scientific evidence, FDA requires that two questions be answered in the affirmative: (1) whether the evidence in support of the substance/disease relationship outweighs that against it and (2) whether the evidence corroborates “that a change in the dietary intake of the substance *will* result in a change in the disease endpoint.” Guidance at 16 (emphasis added).

In the all-important matter of defining “significant scientific agreement,” FDA states that “[i]n the process of scientific discovery, significant scientific agreement occurs well after the state of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid.” Guidance at 16. The agency states that “significant scientific agreement is not consensus in the sense of unanimity, it represents considerably more

than an initial body of emerging evidence.” Guidance at 16-17. In assessing whether significant scientific agreement exists, FDA states that it will “take[] into account the viewpoints of qualified experts outside the agency. . .” Guidance at 18. It states that it will “take into account:

- *review publications that critically summarize data and information in the secondary scientific literature;*
- *documentation of the opinion of an “expert panel” that is specifically convened for this purpose by a credible, independent body;*
- *the opinion or recommendation of a federal government scientific body such as the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC); or the National Academy of Sciences (NAS); or an independent, expert body such as the Committee on Nutrition of the American Academy of Pediatrics (AAP), the American Heart Association (AHA), American Cancer Society (ACS), or task forces or other groups assembled by the National Institutes of Health (NIH).*

Guidance at 18.

SUMMARY

The United States Court of Appeals’ mandate to FDA is to “explain what [FDA] means by significant scientific agreement or, at minimum, what [FDA] does not mean.” *Pearson*, 164 F.3d at 661. The Guidance fails to comply with the mandate. While in the Guidance FDA has listed the rank it accords to varying types of scientific evidence (without specifying the comparative or cumulative weight of the different kinds of evidence) and has indicated that it expects near conclusive proof of causality as a condition precedent to claim approval, it has avoided explaining what it means by significant scientific agreement; it has also avoided explaining what it does not mean.

The Court’s mandate asks FDA to provide the regulated class sufficient information “to perceive the principles which are guiding agency action.” The Guidance does not provide information necessary for regulatees to perceive FDA’s guiding

principles. It does not explain the meaning of significant scientific agreement. While, from the Guidance, the regulated class can understand that FDA views interventional studies involving well designed randomized, controlled clinical trials as its “gold standard,” it is entirely impossible from the Guidance to perceive whether FDA will ever accept studies other than interventional or other than those involving randomized, controlled clinical trials as sufficient for claim authorization. It appears unlikely that FDA ever will because it requires proof of direct causality. Given FDA’s insistence on proof of direct causality (that a substance *will* result in a change in a disease endpoint) as a condition precedent to claim approval, it appears that only claims backed by well designed randomized, controlled clinical trials coupled with proof of direct causality will cause FDA to permit claim authorization. A large body of evidence strongly supporting, but not conclusively proving, a substance-disease relationship appears unlikely to satisfy the FDA.

Thus, the only principle that regulatees can perceive with clarity from FDA’s Guidance is that FDA will accept the same kind of near conclusive proof expected as a condition precedent for drug approval as a condition precedent for dietary supplement claim approval. That principle violates Congressional intent, however. Congress plainly expects this agency to authorize health claims for dietary supplements without requiring that those claims be backed by the same kind of near conclusive proof required for the grant of applications for new drugs. Accordingly, to the extent that FDA’s Guidance reveals a principle to the regulated class, that principle is one calling for a level of evidence that Congress has unequivocally rejected in the context of health claims for dietary supplements.

In addition, FDA's Guidance includes an unscientific bias and favoritism for certain non-governmental organizations, namely the Committee on Nutrition of the American Academy of Pediatrics, the American Heart Association, and the American Cancer Society. The agency places special emphasis upon the opinions and recommendations of these private organizations equating the value of those with the opinions and recommendations of federal government scientific bodies. It omits from specific reference the opinions and recommendations of other private bodies, such as universities, professional and scientific associations, and other scientific authorities. The action reveals an unscientific bias in favor of the private organizations listed and an arbitrary and capricious grant of privilege to the named private organizations to the exclusion of all others.

Finally, FDA's Guidance omits reference to the constitutional mandate in *Pearson*. The Guidance misleads the public and the regulated class to the extent that it suggests that a dietary supplement health claim not approved by FDA under its "significant scientific agreement" standard is prohibited on labels and in labeling. Under *Pearson's* constitutional mandate, even if claims fail the "significant scientific agreement" test, FDA must nevertheless authorize all that are, at worst, potentially misleading with corrective disclaimers. *Pearson*, 164 F.3d at 659-660. Because the constitutional mandate interprets the First Amendment to the United States Constitution and the First Amendment is the higher law against which contrary law cannot stand, FDA must make clear to the regulated class within the Guidance that a claim it deems not backed by "significant scientific agreement" will nevertheless be authorized when a disclaimer can render it nonmisleading.

For these reasons, explained in detail below, FDA should promptly revise its Guidance. It should comply with the mandate of the United States Court of Appeals for the D.C. Circuit by explaining what it means by significant scientific agreement or, at minimum, what it does not mean. In that regard, FDA cannot rest upon the highly inexact and largely vacuous and variable statement that significant scientific agreement occurs after emerging science but before unanimous agreement. The universe described is immense, so immense as to exceed any reasonable definitional boundary. Indeed, nearly all scientific evidence falls between the polar extremes of emerging science and consensus. Accordingly, FDA should define with as much specificity as possible where on the continuum of scientific evidence between emerging science and consensus “significant scientific agreement” lies. Does it occur when a significant minority or segment of scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? Does it occur when at least half of the scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? Does it occur when at least three quarters of the scientists who study the relationship agree that the claimed relationship is supported by the scientific evidence? When may it be said on the continuum of scientific evidence that significant scientific agreement has been reached? In that regard, consistent with the dictates of Congress, FDA should hold that significant scientific agreement exists when

a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are *reasonably likely* to obtain the claimed health benefit.

Senate Report 103-410, at 24.

Congress determined that the above-quoted definition it supplied in committee is “consistent with the NLEA’s goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved.” *Id.* FDA’s insistence on a higher standard, the equivalent of the drug certainty standard used as a condition precedent to grant of applications for new drugs, conflicts with Congress’s intentions and cannot stand.

ARGUMENT

A. FDA’S GUIDANCE VIOLATES *PEARSON*’S APA MANDATE BY FAILING TO DEFINE “SIGNIFICANT SCIENTIFIC AGREEMENT”

The *Pearson* Court ordered FDA to “explain what it means by significant scientific agreement or, at minimum, what it does not mean.” *Pearson*, 164 F.3d at 661. FDA’s Guidance fails to comply. Nowhere in the entire Guidance does FDA provide any reasonable explanation of what it means by significant scientific agreement (or what it does not mean). The only “definition” for the term that the agency offers in the Guidance is one so broad, so vacuous, and so inexact as to be entirely unusable by the regulated class. Indeed, the extraordinary breadth of the definition suggests that any meaning FDA imparts to the term on a case by case basis may be the product of political discretion (or anti-dietary supplement bias) as much, if not more, than rational scientific judgment. In the Guidance, the agency states that, “[i]n the process of scientific discovery, significant scientific agreement occurs well after the state of emerging science, where data and information permit an inference, but before the point of unanimous agreement within the relevant scientific community that the inference is valid.” Guidance at 16. That language embraces nearly the entire body of scientific evidence and does not afford the regulated

class sufficient information to discern where along the continuum of science between emerging data and consensus the point of significant scientific agreement exists. With the agency's definition, the regulated class certainly cannot discern the principles which guide FDA action (except that satisfaction of the drug certainty standard will probably suffice). Accordingly, the definition violates *Pearson's* APA mandate to the agency. To comply with the mandate, FDA must revise its Guidance promptly as explained below.

B. FDA'S GUIDANCE VIOLATES PEARSON'S APA MANDATE BY NOT REVEALING THE PRINCIPLES WHICH GUIDE AGENCY ACTION ON CLAIMS SUPPORTED BY EVIDENCE OTHER THAN INTERVENTIONAL STUDIES BEARING PROOF OF DIRECT CAUSALITY

From the Guidance, one may discern that FDA has adopted a hierarchy to evaluate scientific evidence, placing at its top well designed interventional studies (and at the top of such studies randomized, controlled clinical trials). Although FDA's preference for well designed interventional studies is reiterated throughout the document, the FDA does not explain whether studies other than the very lengthy and expensive randomized, controlled interventional ones will suffice and, if other studies would, what comparative and cumulative weight FDA affords evidence other than randomized, controlled interventional studies. For example, from the Guidance it is impossible to determine whether FDA would ever accept as a substitute for randomized, controlled interventional studies, a combination of observational and mechanistic studies, or—if so—what kind of such studies would suffice to substitute for randomized, controlled interventional studies.

From the Guidance, one may discern that FDA demands that the regulated class supply it with proof that “a change in the dietary intake of the substance *will* result in a

change in a disease endpoint.” FDA thus calls for conclusive proof of causality. FDA expects conclusive proof of causality regardless of the nature of the claim. Thus, a claim that a nutrient “may” reduce the risk of a disease or “may” reduce the symptoms of a disease is treated in the same manner as one that states a direct causal relationship (e.g., nutrient X will reduce the risk of disease Y, or nutrient X will reduce the symptoms of disease Y). Direct proof of causality is equal to that degree of proof required by this agency, pursuant to the “substantial evidence” standard, as a condition precedent to the grant of applications for new drugs. 21 U.S.C. § 355(e) (see generally *Weinberger v. Hynson Westcott & Dunning, Inc.*, 412 U.S. 609 (1973) and *E.R. Squibb & Sons, Inc. v. Bowen*, 870 F.2d 678, 679 (D.C. Cir. 1989).

FDA states that in evaluating the scientific evidence, it will require an affirmative answer to the following two questions: (1) whether the evidence in support of the substance/disease relationship outweighs that against it and (2) whether the evidence corroborates “that a change in the dietary intake of the substance *will* result in a change in the disease endpoint.” Thus, in light of FDA’s clear preference for randomized, controlled clinical trials and its insistence on direct evidence of causality, to the extent that a principle can be discerned from the Guidance, it is that FDA will authorize claims upon receipt of proof that they are corroborated by randomized, controlled clinical trials and upon receipt of proof of direct causality. That kind of near conclusive proof is the same as that required by FDA for approval of new drug applications. Accordingly, to the extent that FDA’s Guidance reveals a principle to the regulated class it is one calling for a level of evidence Congress has unequivocally rejected in the context of health claims for dietary supplements. FDA must revise its Guidance. It must replace it with one that

complies with *Pearson's* APA order and the dictates of Congress on interpreting "significant scientific agreement." The current Guidance fails on both accounts.

C. FDA'S GUIDANCE HARBORS AN UNSCIENTIFIC BIAS AND FAVORITISM FOR CERTAIN PRIVATE ORGANIZATIONS

In addition to its failure to explain what significant scientific agreement means (or, conversely, what it does not mean) in a manner that can enable the regulated class to discern the principles which guide agency action, the Guidance includes specific reference to a select group of private organizations. The reference gives equal weight to the opinions and recommendations of those organizations and the opinions and recommendations of federal government scientific bodies. Moreover, it fails to give equivalent weight to the opinions and recommendations of any other scientific body, e.g., any or all universities, other private scientific associations, and recognized authorities in the field of science. The agency offers no explanation for why the named private organizations (Committee on Nutrition of the American Academy of Pediatrics; the American Heart Association; and the American Cancer Society) should be given preferential treatment and status in the evaluation of health claims. For example, it does not explain (nor could it reasonably) why these private associations in particular are possessed of scientific insights, knowledge, and evidence superior to all others or why these private associations in particular should be viewed as equivalent to federal government scientific bodies. It is not at all unworthy of note that the American Heart Association and the American Cancer Society were *amicus curiae* in favor of the unsuccessful position articulated by the FDA in the *Pearson* case. Through that relationship, let alone all others between the FDA and those groups, FDA has engaged in legal and political battle against authorization of dietary supplement health claims. Thus,

far from serving as an unbiased source for opinion and recommendation, FDA has chosen precisely those entities that have a track record of partisan support for FDA's positions. For these many reasons, FDA's select listing of preferred private organizations in the Guidance constitutes arbitrary and capricious agency action and should be reversed in print as well as deed. The Joint Commenters do not object to agency acceptance of the opinion and recommendations of private scientific associations as sources of reputable information relevant to the evaluation of supplement-disease relationships, but the Joint Commenters strongly object to the arbitrary and capricious limited selection of three named associations made in the Guidance by FDA.

D. FDA'S GUIDANCE IS MISLEADING BECAUSE IT OMITTS REFERENCE TO *PEARSON'S* CONSTITUTIONAL STANDARD AS AN ALTERNATIVE GROUND FOR AUTHORIZATION

The Director of the Center for Food Safety and Applied Nutrition has made it clear that FDA understands *Pearson's* constitutional mandate to necessitate agency authorization of health claims even when those claims fail to satisfy its "significant scientific agreement" standard. Director Levitt wrote:

... [W]e agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim.

See Exhibit A.

Indeed, the *Pearson* decision's constitutional mandate takes primacy over contrary agency rules and interpretations. It is, after all, the First Amendment which, under the Supremacy Clause, is the supreme law of the land. U.S.CONST. Art. VI. See also *Marbury v. Madison*, 5 U.S. 137, 180 (1803). Therefore, the complete omission of

the fact that a claim not authorized under significant scientific agreement may still have to be under the First Amendment is derelict of the agency. Indeed, the omission from the Guidance of reference to the *Pearson* Court's disclaimer requirement to protect First Amendment rights is a glaring one that renders the Guidance false and misleading. Its omission is material because regulatees may perceive that FDA's failure to authorize a claim under significant scientific agreement condemns the claim to indefinite suppression when, in fact, the constitutional duty of this agency is to authorize all, at worst, potentially misleading claims with corrective disclaimers. FDA must revise the Guidance to make clear to the regulated class that a claim it deems not backed by "significant scientific agreement" will nevertheless be authorized when a disclaimer can render it nonmisleading.

E. FDA'S GUIDANCE VIOLATES THE NLEA BY FAILING TO DEFINE "SIGNIFICANT SCIENTIFIC AGREEMENT" AS CONGRESS INTENDED

Congress has been severely critical of the way in which FDA has interpreted "significant scientific agreement." See Senate Report No. 103-410. In fact, Congress has documented the existence of an unscientific agency bias against dietary supplements and dietary supplement health claims that it has found wholly inconsistent with the intended meaning of "significant scientific agreement." The following are among Congress' findings on agency bias against claim approval:

In fact, the FDA has had a long history of bias against dietary supplements. S.Rep.No. 103-410, at 14 (1994).

Mindful of the persistent evidence of FDA bias against dietary supplements. . . S.Rep.No. 103-410, at 30 (1994).

Given the FDA's historical bias against dietary supplements. . . S.Rep.No. 103-410, at 31 (1994).

Despite a voluminous scientific record indicating the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a heavy-handed enforcement agenda against dietary supplements for over 30 years. S.Rep.No. 103-410, at 14 (1994).

FDA's treatment of health claims on dietary supplements and its implementation of the health claims standard is hindering, rather than fostering, the dissemination of truthful and nonmisleading information about the nutrient/disease relationship. S.Rep.No. 103-410, at 23 (1994).

The committee has heard multiple complaints that the FDA has been overly slow and rigid in considering and approving health claims for dietary supplements. S.Rep.No. 103-410, at 30 (1994).

FDA has applied [its health claims review standard] in a way that limits consumer access to important information on diet and health. S.Rep.No. 103-410, at 23 (1994).

The FDA has acted to restrict the information that the public may receive about dietary supplements. S.Rep.No. 103-410, at 16 (1994).

Despite the fact that the scientific literature increasingly reveals the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a regulatory agenda, which discourages their use by citizens seeking to improve their health through dietary supplementation. S.Rep.No. 103-410, at 14 (1994).

In December, 1991, FDA proposed rules implementing the NLEA, but rejected all but one claim for supplements (for calcium/osteoporosis in White and Asian Women). Only one other claim has been approved since that time, the claim for folic acid and neural tube defects, and that claim was only approved after intense public pressure on the FDA. S.Rep.No. 103-410, at 15-16 (1994).

The preceding examples show how the FDA has tried to "protect" the public against "unsafe" products for which there is no evidence that the product is unsafe. The FDA has also acted to restrict the information that the public may receive about dietary supplements. Folic acid is a clear example. S.Rep.No. 103-410, at 16 (1994).

Beholden as it must be to Congress for its statutory authority, FDA has acted in a most peculiar manner. Rather than comply with the dictates of Congress, it has defied them. It

has chosen (against the express congressional command that it not do so) to articulate clearly only one sure way to achieve health claim approval (i.e., establish to FDA's satisfaction that a claim is backed by randomized, controlled clinical trials and direct proof of causation, to wit, establish satisfaction of the drug certainty standard). Congress plainly and unequivocally rejected the drug certainty standard for dietary supplement health claims. It has implored this agency to adopt a definition for significant scientific agreement far less stringent, a definition that FDA does not adopt in the Guidance. In committee Congress has made its expectations clear:

The Committee notes that the significant scientific agreement standard is, by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires a demonstration of safety and effectiveness based on “adequate and well-controlled clinical investigations.” While the intake of a nutrient on which a health claim is based must be safe, there is no requirement that health claims be derived from clinical trials, and, by its terms, the standard recognizes that scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support.

In implementing the significant scientific agreement standard, FDA will be expected to take full advantage of the flexibility of the standard to maximize the availability on food and dietary supplement labels and labeling of disease-related information consumers can prudently use to affect their risk of disease.

This includes recognizing that there will nearly always be some remaining scientific uncertainty about the validity of any diet-related health claim; that some individuals consuming or avoiding a nutrient in response to a health claim may benefit, while others may not; and that the benefits for any individual may consist not of absolutely avoiding a disease, but rather of reducing her or his risk of a disease.

The end point for evaluation of the adequacy of support for a claim should not be definitive proof that the nutrient has the stated effect for all populations, but that the nutrient will produce the stated effect in the majority of a target population the majority of the time. In addition, the scientific evidence supporting a claim should not be held to the same standard used in evaluating new drug applications.

Under the significant scientific agreement standard, the FDA should authorize claims when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit. This is consistent with the NLEA's goal of assuring that consumers have access on food and dietary supplement labels to health claims that are scientifically supported, without having to wait until the degree of scientific certainty contemplated by the drug standard has been achieved.

S.Rep.No. 103-410, at 24.

Thus, FDA's Guidance has violated the intent of Congress by not defining significant scientific agreement as Congress ordered it to in Senate Report No. 103-410. FDA may not interpret significant scientific agreement to have a meaning contrary to that intended by Congress. Indeed, FDA's Guidance is wholly inconsistent with the intent of Congress on interpreting significant scientific agreement under the NLEA. Accordingly, that interpretation is invalid under *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984) because Congress has spoken to the precise matter in issue and the agency's interpretation is unreasonable in light of congressional intent.

F. JOINT COMMENTERS' RECOMMENDATIONS FOR REVISION TO THE GUIDANCE

The FDA must revise the Guidance if it is to survive judicial review. The Guidance fails to define "significant scientific agreement" as ordered by the *Pearson* Court. The Guidance indicates that a health claim is likely to be approved only if it is backed by randomized, controlled clinical trials and direct proof of causality. That benchmark is far higher than the one intended by Congress for dietary supplement health claims. Moreover, FDA has revealed an unscientific bias in favor of three private associations' opinions and recommendations. Finally, it has omitted from the Guidance the material fact that even if FDA deems a claim not backed by "significant scientific

agreement,” it has a constitutional duty nonetheless to authorize even a potentially misleading claim with a corrective disclaimer.

To cure the many defects in the Guidance, FDA should: (1) define “Significant Scientific Agreement” as Congress intended, to wit: **“when a significant segment of scientists having relevant expertise agree, based on relevant scientific evidence, that consumers are reasonably likely to obtain the claimed health benefit;”** (2) should state where on the continuum of scientific evidence between emerging science and consensus “significant scientific agreement” exists consistent with Congressional intent; (3) should state clearly that it will not require the drug certainty standard of proof (i.e., randomized, controlled interventional studies and direct proof of causality) as a condition precedent to dietary supplement health claim approval; (4) should remove reference to the Committee on Nutrition of the American Academy of Pediatrics; the American Heart Association; and the American Cancer Society from the Guidance and make clear that it will not view those organization’s opinions or recommendations as in any way more significant than the views of any other private scientific body or private scientific authority; and (5) should include reference to *Pearson*’s constitutional mandate and make clear that if a claim fails to satisfy FDA’s “significant scientific agreement” standard it will be authorized nonetheless so long as the addition of a disclaimer can render it nonmisleading.

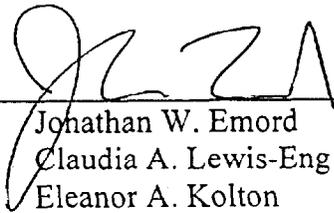
CONCLUSION

For the foregoing reasons, FDA should immediately discontinue reliance on the Guidance and revise it as recommended herein.

Respectfully submitted,

JULIAN M. WHITAKER, M.D.;
PURE ENCAPSULATIONS, INC.;
XCEL MEDICAL PHARMACY, LTD.;
MYCOLOGY RESEARCH LABORATORIES, LTD.;
DURK PEARSON and SANDY SHAW; and
AMERICAN PREVENTIVE MEDICAL ASSOCIATION,

By



Jonathan W. Emord
Claudia A. Lewis-Eng
Eleanor A. Kolton
Counsel for Joint Commenters

Dated: February 22, 2000

Exhibit A



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

OCT 5 1999

Jonathan W. Emord
1050 Seventeenth Street, NW
Suite 600
Washington, DC 20036

Dear Mr. Emord:

This is in response to your letter of September 23, 1999. Your letter made several requests relating to FDA's Federal Register notice of September 8, 1999 (64 Fed. Reg. 48841), which solicited scientific data on the four health claims remanded to the agency in Pearson v. Shalala. Specifically, you requested that FDA (1) extend the time for submitting scientific data on the four claims until 75 days after the agency publishes its guidance on the significant scientific agreement standard; (2) confirm to you in writing and publish a correction notice in the Federal Register clarifying that FDA intends to consider whether the four claims may be authorized with a disclaimer even if the agency determines that they do not meet the significant scientific agreement standard.

With respect to your first request, we agree to extend or reopen the comment period on the September 8, 1999, notice for 75 days after the significant scientific agreement guidance is published. We agree that this is an example of when taking additional time is warranted. Be assured that the agency will give careful consideration to the data that it receives during the second 75 days.

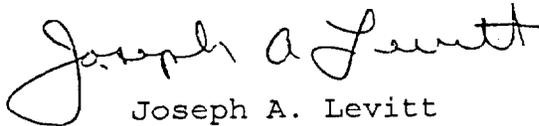
As to your second request, we agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, we will authorize the claim. We do not believe that a Federal Register correction notice is necessary, however. The September 8 Federal Register notice was only intended to solicit scientific data on the four remanded claims, not to describe the procedure and standard the agency will use to evaluate them. The notice stated that FDA was planning to reevaluate the scientific evidence for the claims "as a first step in complying with the court's decision." 64 Fed. Reg. at 48842 (emphasis added). Given the fact that the notice contained no errors and was not intended to explain the court's decision or set forth the agency's plans for implementing the decision, we see no need for a correction notice.

Page 2 - Jonathan W. Emord

Your concerns about the notice and about statements in FDA's September 17, 1999, letter seem to stem at least in part from a misunderstanding about FDA's use of the word "authorize." By saying that the four claims must be "authorized" by FDA before they may be made in labeling, we meant only that the claims cannot be used unless and until FDA issues a regulation permitting them. We did not mean to imply that we would issue such a regulation only if the claims are found to meet the significant scientific agreement standard.

We hope that the above responds to your concerns.

Sincerely,

A handwritten signature in cursive script that reads "Joseph A. Levitt". The signature is written in dark ink and is positioned above the typed name.

Joseph A. Levitt
Director
Center for Food Safety
and Applied Nutrition

EXHIBIT 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

OCT 5 1999

Jonathan W. Emord
1050 Seventeenth Street, NW
Suite 600
Washington, DC 20036

Dear Mr. Emord:

This is in response to your letter of September 23, 1999. Your letter made several requests relating to FDA's Federal Register notice of September 8, 1999 (64 Fed. Reg. 48841), which solicited scientific data on the four health claims remanded to the agency in Pearson v. Shalala. Specifically, you requested that FDA (1) extend the time for submitting scientific data on the four claims until 75 days after the agency publishes its guidance on the significant scientific agreement standard; (2) confirm to you in writing and publish a correction notice in the Federal Register clarifying that FDA intends to consider whether the four claims may be authorized with a disclaimer even if the agency determines that they do not meet the significant scientific agreement standard.

With respect to your first request, we agree to extend or reopen the comment period on the September 8, 1999, notice for 75 days after the significant scientific agreement guidance is published. We agree that this is an example of when taking additional time is warranted. Be assured that the agency will give careful consideration to the data that it receives during the second 75 days.

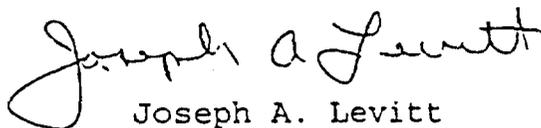
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Page 2 - Jonathan W. Emord

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We hope that the above responds to your concerns.

Sincerely,

A handwritten signature in cursive script that reads "Joseph A. Levitt". The signature is written in dark ink and is positioned to the left of the typed name.

Joseph A. Levitt
Director
Center for Food Safety
and Applied Nutrition

EXHIBIT 3



FEB 17 2000

Jonathan Emord
Emord & Associates, P.C.
1050 Seventeenth Street, N.W.
Suite 600
Washington, D.C. 20036

Dear Mr. Emord:

This is in response to your letter of January 19, in which you ask whether FDA plans to authorize the four health claims at issue in Pearson v. Shalala and, if so, by what date.

It would be premature for the agency to make a commitment to authorize the four claims or, conversely, to state an intention not to authorize them. As I said in my October 5, 1999, letter to you, the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. If the answer to either question is yes, FDA will authorize the claim. However, we cannot reach a decision on either question until interested parties have had a full and complete opportunity to submit new data on the four claims and we have had an opportunity to thoroughly review such data.

On February 11, 2000, FDA's Center for Food Safety for Food Safety and Applied Nutrition (CFSAN) issued our program priorities for the remainder of fiscal year 2000. Responding to the Pearson decision is one of the "A" List items, which receive the Center's highest priority attention. A copy of the Center's FY 2000 workplan may be accessed on our website at www.fda.gov.

As you know, the comment period for new data relating to the claims is still open. Indeed, your September 23, 1999, letter, you requested that FDA reopen the comment period for 75 days after the guidance on the significant scientific agreement standard was published so that interested parties could submit additional data after reviewing the agency's clarification of the standard. We agreed and have reopened the comment period for the requested period. The comment period will close on April 3, 2000. Once the comment period closes, the agency will thoroughly review the data received and proceed with rulemaking on each of the four claims.

Sincerely,

A handwritten signature in cursive script that reads "Joseph A. Levitt".

Joseph A. Levitt
Director
Center for Food Safety
and Applied Nutrition