

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

ORIGINAL

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),

99D-5424

C2

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.

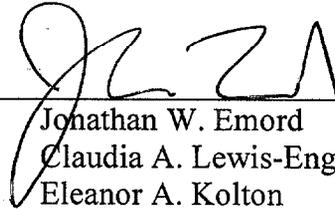
CONCLUSION

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

A handwritten signature in black ink, appearing to read 'JW Emord', is written over a horizontal line. The signature is stylized and cursive.

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.

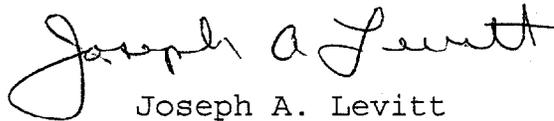
As to your second request, we agree that the court's decision requires FDA to reconsider not only whether each of the four claims meets the significant scientific agreement standard, but also, even if that standard is not met, whether the addition of a disclaimer to the claim could render it non-misleading. 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 and title.

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