IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

DURK PEARSON, et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	**No. 00-2724 (GK)**
	)	
DONNA E. SHALALA, et al.,	)	
	)	
Defendants.	)	

PLAINTIFFS' MEMORANDUM IN REPLY TO OPPOSITION TO APPLICATION FOR PRELIMINARY INJUNCTION

Plaintiffs, by counsel and pursuant to LCvR 65.1(c); LCvR 7.1(d),(e); and Fed.R.Civ.P. 65, hereby file this memorandum in reply ("Reply") to the Defendants' opposition ("Opposition") to the Plaintiffs' application for preliminary injunction ("Application").[1]

I. DEFENDANTS APPLY THE WRONG STANDARD OF REVIEW.

The Defendants apply the wrong standard of review. They argue that Plaintiffs' First Amendment challenge must be reviewed not under First Amendment standard applied by the Court of Appeals in Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999), but under the more facile arbitrary and capricious standard of the Administrative Procedure Act (APA), 5 U.S.C. § 706(2)(A)[2] (explained principally in Chevron, U.S.A., Inc. v. Natural Resources Defense

[1] The Defendants have filed a consolidated opposition and motion to dismiss to Plaintiffs' application for preliminary injunction. By doing so, the Defendants would have this Court delay decision on the application for preliminary injunction until the conjoined motion to dismiss (and pleading cycle related to it) is completed. Because the two pleadings involve different standards of review (and because expedition is warranted in evaluation of the application for preliminary injunction), the Plaintiffs have chosen to respond to Defendants' opposition to the application in a pleading separate from Plaintiffs' opposition to defendants' motion to dismiss. That will enable the Court to keep the application for preliminary injunction on a fast track, as it appropriately deserves given the profound First Amendment and public health issues at stake.

[2] Defendants cite two cases (Cf. Kraft, Inc. v. FTC, 970 F.2d 311 (7th Cir. 1992) and FTC v. Brown & Williamson Tobacco Corp., 778 F.2d 35 (D.C. Cir. 1985)) for their misplaced assertion that the APA substantial evidence standard of review, not the First Amendment standard, applies. Both cited cases are FTC appeals that deal with marketed claims not with FDA's pre-market approval process. Plaintiffs claim, by contrast, has never entered the market. In the FTC cases, the agency presented evidence from the market to show misleadingness. In this case

Council, Inc., 467 U.S. 837, 842-843 (1984)). The Defendants are wrong.[3] The correct standard is the one applied in Pearson v. Shalala, 164 F.3d at 653. [4] Pearson is the governing law for this case on remand from the Pearson Court decision. The Pearson Court's First Amendment standard of review is the one FDA was required to follow in the remand proceeding and is the one to which FDA is answerable before this Court. The Pearson Court evaluated FDA's suppression of the specific health claim here in issue ("0.8 mg of folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form") and held the claim not "inherently misleading" but protected under the First Amendment. The review was *constitutional* first and foremost; the more deferential APA standard was not a part of the Court's evaluation of the health claim's suppression. Indeed, the Court compelled FDA to answer the Plaintiffs "most powerful constitutional claim, that the government has violated the First Amendment . . . ***because the requested remedy stands apart from appellants' request under the APA that the FDA flesh out its standards.***" 164 F.3d at 655 (emphasis added). The Pearson Court utterly rejected the view that precedent "mandates a more deferential review of government regulations on potentially misleading commercial speech," explaining that "[I]t is clear . . . that when government chooses a policy of suppression over disclosure -- at least where there is no showing that disclosure would suffice to cure misleadingness -- government disregards a 'far less restrictive' means." Pearson, 164 F.3d at 657.

FDA is assuming that the statements are misleading without a scintilla of evidence in support. Thus, the cited cases are inapposite.

[3] On page 27 of their Opposition, the Defendants state that "FDA denied plaintiffs' proposed claim because it is misleading, not because it lacked scientific agreement," thus revealing that not even they truly believe their decision below properly rests on administrative grounds (i.e., the agency's standard of health claims review).

[4] Any speech restriction by any government federal or state must be evaluated under the appropriate First Amendment standard the Supreme Court has prescribed for assessing that restriction. Indeed, the landmark holding in Pearson, against which the FDA argued and lost, recognizes that health claims restricted by the agency are

Moreover, the Application for Preliminary Injunction rests not on an Administrative Procedure Act (APA) challenge (the APA is not a part of the Application). Rather, the application rests exclusively on a First Amendment challenge (as the Defendants recognize, Opposition at 11). The Application comes in response to the FDA's denial (for a second time) of a health claim held unconstitutionally suppressed in violation of the First Amendment in Pearson v. Shalala, 164 F.3d at 661.[5] In its evaluation of FDA's speech suppression, the Court of Appeals held Plaintiffs' claim not suppressable outright (not "inherently misleading"). See Pearson, 164 F.3d at 658-59. The Court applied the three part First Amendment standard defined in Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of New York, 477 U.S. 557, 566 (1980) and its progeny, not the APA standard. See Pearson, 164 F.3d at 653. Based on its holding that FDA's suppression of the claim violated the First Amendment, the Court of Appeals ordered the agency to reconsider its action by evaluating means to cure any *provable* potential to mislead with corrective disclaimers. See Pearson, 164 F.3d at 661. On remand, FDA was to act consistent with the Court of Appeals' decision, but FDA did not. FDA's letter ruling did not evaluate the Plaintiffs' claim under the three part Central Hudson test.[6] FDA did not adduce any evidence that the claim actually misleads consumers. FDA failed to establish that *no* disclaimer could be added to the claim to cure any *proven* potential to mislead. It thereby violated the Pearson mandate.

DOJ now has the unenviable position of having to defend the agency's decision without a First Amendment defense in the record below (there is no reasoned First Amendment analysis in

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"speech" within the meaning of the First Amendment and may not be restricted without satisfying the applicable First Amendment standard of review. See Pearson, 164 F.3d at 661.

[5] The Court's holding that the suppression of the Plaintiffs' folic acid claim violated the First Amendment was a decision on an "as applied" challenge.

the FDA's letter ruling and no record of First Amendment analysis therefore upon which to base a defense). In a transparent manner, DOJ has tried to induce this Court to use the wrong standard of review, but this Court should not be fooled. The Court should follow the law of the case, laid down by the Court of Appeals, and reject DOJ's plea for release from the constitutional requirements of the Pearson decision.

Under the First Amendment standard, the Defendants have the burden of proof. See Ibanez, 512 U.S. at 146; Edenfield, 507 U.S. at 771. They cannot shift that burden to Plaintiffs. They have not adduced the empirical evidence required to prevail; they have not analyzed the evidence they have adduced under the controlling First Amendment standard; and they have not established that disclosure with disclaimers in lieu of outright suppression would not suffice to cure any potential to mislead.[7] FDA cannot argue that it has complied with its First Amendment burden of proof when in its letter ruling it did not even conduct the First Amendment review required by the Court of Appeals.[8] Accordingly, having not satisfied its burden, its speech restriction is unconstitutional. The injunctive relief requested by Plaintiffs should issue forthwith.

In sum, then, the Defendants' reliance on the more facile APA standard of review to evaluate the First Amendment challenge here in issue is misplaced and is an error of dispositive significance. Defendants' error not only violates the Pearson mandate but also stands for the

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[6] In a part of the decision separate from its First Amendment analysis, the Court held the more facile APA standard violated by FDA due to its failure to define a standard for review of health claims in general. Pearson, 164 F.3d at 660-61.

[7] Defendants mislead this Court when they suggest that Plaintiffs were not agreeable to corrective disclaimers until after this suit was filed. Opposition at 9. To the contrary, since the start of the rulemakings seven years ago, Plaintiffs have repeatedly stated that they would accept any reasonable disclaimer. That representation was indeed made again in two of Plaintiffs' comments filed with the agency during its remand proceeding. See Application Exhibits 2 at 17, 18, & 38.

[8] That FDA has failed to engage in the required First Amendment review is doubly remarkable when one considers that her Honor ruled in the Defendants' favor on a pre-decision motion for preliminary injunction to afford FDA ample time within which to comply with the Pearson Court's mandate.

unlawful proposition that an agency of the federal government, held to have violated the First Amendment by enactment of a speech ban, may nevertheless continue to restrict that speech without satisfying its high burden under the First Amendment, so long as it satisfies a lesser burden under the APA. That is not the law. See generally Ibanez v. Florida Dept. of Business and Professional Regulation, Bd. of Accountancy, 512 U.S. 136, 143 (1994) ("The State's burden is not slight; the 'free flow of commercial information is valuable enough to justify imposing on would-be regulators the costs of distinguishing the truthful from the false, the helpful from the misleading, and the harmless from the harmful," citing Zauderer v. Office of Disciplinary Counsel of Supreme Court of Ohio, 471 U.S. 626, 646 (1985)); see also Pearson, 164 F.3d at 659, citing Ibanez, 512 U.S. at 146 ("If the protections afforded commercial speech are to retain their force, we cannot allow rote invocation of the words 'potentially misleading' to supplant the [government's] burden to demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree") and citing Edenfield, 507 U.S. at 771. [9]

In their Opposition, the Defendants, like the FDA below, present *no* argument under the First Amendment standard. They do not explain, through empirical evidence, how outright suppression in lieu of disclosure with disclaimers advances the government's interests in promoting public health and avoiding consumer fraud. They do not present (as they cannot because they have not adduced evidence of it on remand) any evidence to prove that Plaintiffs' claim will in fact harm the public and that outright suppression of the claim will advance the government's interests in promoting public health or in avoiding consumer fraud in a *direct* and

[9] Even if the arbitrary and capricious standard of review was the appropriate standard, the Defendants have clearly not even met that standard. FDA's conclusions are contrary to those of its sister agencies the United States Centers for Disease Control and Prevention (CDC); the National Center for Environmental Health (NCEH); the National Council on Folic Acid (NCFA); the Food and Nutrition Board of the Institute of Medicine (IOM) and of the American Academy of Pediatrics (AAP). Its position contradicts the best available scientific evidence and promotes the proposition that food folate is as effective as supplemental folic acid when that has not been established.

material way. Indeed, as explained below, we are now told that FDA's perceived harm is a most *indirect* one: the Plaintiffs' claim is said not to state, *but to imply*, connotations to which FDA objects. The Defendants present no foundation for their argument that Plaintiffs' claim implies facts not stated. Defendants present no evidence (despite 18 months of review time, they have adduced none) that the public understands the claim to imply what the FDA claims it implies. In short, FDA's argument concerning implications is wholly unfounded and entirely speculative.[10] The Defendants do not explain how outright suppression of Plaintiffs' claim, rather than allowance with disclaimers, can overcome the constitutional presumption in favor of disclosure nor do they explain how the draconian measure of outright suppression constitutes a reasonable fit between means and ends when the less restrictive alternative of disclaimers could have been used (and was the central matter remanded to FDA by the Court of Appeals).

The government's omission of argument under the First Amendment is not only telling (you cannot argue on a record void of requisite proof), it is also of decisional significance (you cannot adopt the Defendants' arguments without rejecting the controlling standard of review).

The utter void of First Amendment argument in the Defendants' brief is a glaring one made understandable only by virtue of the fact that DOJ cannot argue anew on appeal what FDA failed to argue below in its letter ruling. It is plain then that having not even attempted to argue compliance with all three elements of the applicable First Amendment test, FDA cannot prevail on the First Amendment argument. At minimum, it must be said that under such circumstances

[10] In its letter ruling, Application Exhibit 1, FDA states in a conclusory manner that Plaintiffs' claim is "inherently misleading" but presents no proof that the claim actually misleads consumers in any way. See Peel v. Attorney Registration and Disciplinary Comm'n of Illinois, 496 U.S. 91, 110 (1990) (the "State may not . . . completely ban statements that are not actually or inherently misleading"). We are left with no argument by the FDA that would explain (and this Court cannot explain for the FDA) how a record void of empirical evidence of *real* harm to consumers (and void of explanation as to why disclaimers would not suffice) can meet the government's First Amendment burden of establishing that the harms it recites are *real* and that outright suppression in lieu of disclosure with disclaimers advances FDA's interests in a *direct* and *material* way and is the only reasonable alternative. See Pearson, 164 F.3d at 661.

Plaintiffs do have a substantial likelihood of success warranting grant of the injunctive relief they request.

The Supreme Court has held that unsupported assertions and mere speculation or conjecture about harm and direct advancement of government interests are insufficient to justify speech suppression; the government must adduce empirical evidence to *prove* misleadingness and to *prove* that its chosen means *will in fact* promote its interests in a *direct* and *material* way as a condition precedent to speech suppression. See Central Hudson, 447 U.S. at 566. On remand, FDA had that obligation but failed to meet it. FDA has adduced *no* empirical evidence that consumers will be misled, or harmed in any way, by Plaintiffs' statement. FDA's conclusion that the claim is "inherently misleading" is thus entirely unfounded.

Indeed, the substantive position FDA takes conflicts with that of the CDC; the NCEH; the NCFA; the IOM; and the AAP. The agency's position is not simply a difference in interpretation; it is contrary to the weight of the scientific evidence and to the scientific recommendations of every other federal health agency that has studied folic acid and neural tube defects. The statements those latter entities have published to the public are recited here and are quoted in Plaintiffs' memorandum in support of their application and are appended as exhibits to that memorandum. Those statements confirm that food folate is less effective than synthetic folic acid (the kind in dietary supplements and fortified foods). They are based on a wealth of scientific evidence generally accepted in the scientific community. It is thus the case that those agencies' public pronouncements, like Plaintiffs' claim here, are truthful and nonmisleading. To be sure, Plaintiffs' claim is not only demonstrably true, it is indispensable to effecting a significant reduction in the risk of NTDs. As long as FDA denies fertile women access at the point of sale to the message that folic acid in dietary supplements and fortified foods is more

effective in reducing NTDs than lower amounts in foods in common form (what it calls "conventional foods"), this government must bear responsibility for every preventable NTD that occurs (approximately 11 per day) due to public ignorance of that fact. Every day that passes without Plaintiffs' claim in the market is one in which some woman in America who could be taking an .8 mg folic acid supplement daily and could be protected from an NTD bears, unknowingly, a heightened risk of giving birth to a child afflicted with that horrible condition. Rather than pouring its labor and resources into semantic games in a desparate effort to suppress a health claim that could save women and their children from this horrible affliction, FDA should be doing everything in its power to make sure that the Plaintiffs' message reaches all women of childbearing age in this country. FDA's contrary record is an embarrassing and disgraceful chapter in the agency's history. Plaintiffs fervent hope is that this Court will see the error of FDA's ways and correct it – for the benefit of all.

II. THE SCIENTIFIC EVIDENCE CONFIRMS THAT SYNTHETIC FOLIC ACID IS MORE EFFECTIVE AND MORE BIOAVAILABLE THAN FOOD FOLATE.

The Defendants present a tortured and illogical argument. They argue against the weight of the scientific evidence that food folate is as effective as synthetic folic acid. They also argue against the weight of the scientific evidence (and simple logic) that the greater bioavailability of synthetic folic acid over food folate (i.e., the greater absorption of folic acid by intestinal cells) does not correlate with greater effectiveness in reducing NTDs. Those two positions are novel for FDA.[11]

As explained below, FDA's new position on food folate being as effective as synthetic folic acid in reducing NTDs has not been demonstrated scientifically. Entities no less expert in

the scientific evaluation of folic acid than the IOM, the CDC, the NCFA, the NCEH, the BDDD, and the AAP have all concluded, identically, that the scientific evidence does not demonstrate that food folate is as effective as synthetic folic acid in reducing NTDs.

FDA's new position that greater bioavailability does not correlate with greater effectiveness not only conflicts with basic logic but also with the scientific premise for its own authorized folic acid/NTD claims in 21 C.F.R. § 101.79 and its food fortification program as well as with the premise underlying IOM, CDC, NCEH, and BDDD's statements that synthetic folic acid (the kind found in supplements and fortified foods) is more effective than food folates in reducing NTD risk.

The Defendants' Position that Food Folate Is As Effective As Synthetic Folic Acid Conflicts with the Scientific Conclusions of IOM, CDC, NCEH, BDDD, NCFA and AAP. In its letter ruling and in its Opposition, FDA takes the scientifically unproven position that food folate is as effective as folic acid (the kind found in dietary supplements and fortified foods) in reducing NTD risks. Opposition at 9 ("[the evidence] does not support a claim that folic acid (in supplements or fortified foods) is more effective than food folate in reducing the risk of NTDs"); Application Exhibit 1: FDA's Letter Ruling at 14 (" . . . the evidence for a protective effect from folic acid also supports the same protective effect for naturally occurring folate"). FDA's position directly conflicts with IOM's position, which is: "At this time the evidence for a protective effect from folate supplements is much stronger than that for food folate. It is certainly *conceivable* that, if taken in adequate quantity, food folate will be shown to be as effective as folic acid, *but it remains to be demonstrated.*" Application Exhibit 7: IOM Report at

[11] FDA never argued them during the seven years from the time it first evaluated the Folic Acid/NTD claim until the conclusion of the Court of Appeals argument. It never argued those points to the Court of Appeals or to this Court when the matter was first before either.

259 (emphasis added). FDA's position conflicts directly with the CDC, NCEH, and BDDD's repeatedly stated position, to wit:

> There are a few studies that suggest food folate may reduce the risk for NTDs. However, this is still in question (citing IOM in a footnote).

Application Exhibit 19 at 14. And,

> **Synthetic folic acid is absorbed better than natural food folate.**

Application Exhibit 19 at 10 (emphasis in original). And,

> There are so many factors affecting the bioavailability of naturally occurring food folates that we have not quantified food folate in the food items [recommended for NTD risk reduction]. In addition, although it is conceivable, *it has not been demonstrated that food folate protects against NTDs as well as synthetic folic acid.*

Application Exhibit 19 at 18 (emphasis added).

The FDA's position also conflicts with that of the AAP:

> The average diet in the United States contains 200 ug of naturally occurring food folate, which is less bioavailable than folic acid. Additional intake of foods rich in folate could raise the average intake, but *it has not been demonstrated that increased consumption of food folate would prevent NTDs as effectively as a daily vitamin supplement containing 400 ug of folic acid*.

Application Exhibit 22 at 326 (emphasis added).

Indeed, the FDA's position conflicts with the advice it received from its own Folic Acid Subcommittee in 1993 as reported in 58 Fed. Reg. 53265: ". . . the majority of the Folic Acid Subcommittee members did not believe that the data on a specific relationship between folic acid, at levels attainable from usual diets, and NTD's was strong enough to support a claim."

If the Court is to accept the position FDA argues in its letter ruling to Plaintiffs and in its Opposition, it must necessarily reject the contrary scientific determinations of the IOM, the CDC, the NCEH, the NCFA, the BDDD, the FNB, and the AAP. To be sure, the foregoing entities have based public pronouncements on the best available science. The best available

science simply does not support FDA's conclusion that food folate is as effective as synthetic folic acid. As those other scientific bodies have concluded, FDA's proposition "has not been demonstrated."

The Defendants' Position that Greater Bioavailability Has Nothing to Do with Greater Effectiveness Conflicts with the Premise Underlying Its Authorized Folic Acid/NTD Claim; with Its Food Fortification Program; and with the Positions of the IOM, the CDC, the NCEH, and the BDDD. The Defendants' position that greater bioavailability does not equal greater effectiveness is a logical absurdity. In Defendants' Opposition at 22, they take the extraordinary position that "[t]here is simply no support in the data for a correlation between bioavailability and effectiveness." That same position is stated in FDA's letter (Application Exhibit 1 at 14). Bioavailability, as Webster's Dictionary explains, means "the extent to which a nutrient or medication can be used by the body." To suggest that a nutrient not absorbed by the cells of the body is as effective as a nutrient that is absorbed is patently ridiculous, and yet that is what the Defendants are reduced to arguing before this Court.

The Defendants' position is also grossly inconsistent with FDA's own prior pronouncements. FDA has already recognized in its decision granting a health claim for the association between folic acid and NTD risk that greater bioavailability equals greater ***"potency,"*** i.e., effectiveness***.*** Examine FDA's own words from its 1993 folic acid decision authorizing a claim: **"It is well recognized**," said FDA, **"that the bioavailability of free folic acid, the form included in fortified foods and in dietary supplements, is severalfold higher than that of naturally occurring food folates. Estimates of the increased bioavailability ('potency') of free folic acid relative to food folates range from at least twofold to fourfold or greater."** 58 Fed. Reg. 53273 (emphasis added). Note well FDA's association between

bioavailability and potency. That association is the very one the Defendants now say does not exist. They misrepresent their own position. Their view is schizophrenic -- at war with itself.

FDA finally accepts after years of denying the claim that folic acid can reduce NTDs; certainly ensuring the absorption of folic acid by the body has a definite and unmistakable role in ensuring its effectiveness. Folic acid not absorbed is useless. Only folic acid absorbed reduces neural tube defects. By the Defendants' new logic, one would expect that 400 mcg (.4 mg) of folic acid in a dietary supplement consumed on an empty stomach (absorbed at 100%) would be equal in effectiveness to any lesser amount obtained from food folate (absorbed at between 25% and 75%) because FDA is said now to view there to be *no correlation* between bioavailability and effectiveness. But in truth not even FDA accepts the position DOJ argues for it in this proceeding. Indeed, FDA's own rulemaking adopting authorized claims for folic acid/NTD risk reduction and for the fortification of certain grain products with folic acid belies its current contention.

In adopting its Folic Acid/NTD claim rule in 21 C.F.R. § 101.79(c)(3)(iv) and its fortification policy in 21 C.F.R. § 104.20, the FDA accepted 400 mcg (.4 mg) as a "target *intake* goal" based in large part on the PHS recommendation that this amount was effective in reducing the risk of having an NTD-affected pregnancy. 58 Fed. Reg. 53256. PHS estimated a 50% risk reduction from 400 mcg (.4 mg) daily, which FDA deemed "reasonable." 21 C.F.R. § 101.79(b)(3) ("a reasonable estimate of the expected reduction [of NTDs] in the United States is 50 percent"). See also 58 Fed. Reg. 53256. Indeed, the RDA for folic acid was set at that same target intake goal amount. 21 C.F.R. § 101.9(c).[12] In FDA's evaluation of what levels to use in fortifying the food supply, it necessarily evaluated the extent to which foods in common form

[12] As explained in the memorandum in support of Plaintiffs' Application, FDA came to recognize the effectiveness of .4 mg (400 mcg) reluctantly.

(what it terms conventional foods) supplied folic acid useable by the body and what additional folic acid supplementation to the food supply might be necessary to reach FDA's "target" 400 mcg (.4 mg). The agency wrote: "FDA has tentatively concluded that implementation of a fortification plan for addition of folic acid to the food supply can effectively increase the folate intakes of women of childbearing age to assist them in reducing their risk of having an NTD-affected pregnancy." FDA confessed that its decision to recognize a 1 mg folic acid/day safe upper limit (a figure now rejected in light of evidence of safety with daily ingestion up to 5 mg folic acid/day) was based on the uncertainties present in food folate and the need to correct for bioavailability: "The agency's tentative conclusion to use 1 mg/day as the safe upper limit is based on: . . . .(4) the uncertainties in food intake estimates and the difficulty in correcting for bioavailability, . . ." 58 Fed. Reg. 53272.

In sum, then, FDA's present tortured argument that bioavailability does not correlate with effectiveness is a disingenuous one, contrary to its own words and actions. Moreover, it offends simple logic. It must be rejected.

III. PLAINTIFFS CLAIM DOES NOT STATE THAT .8 mg OF FOLIC ACID IS MORE EFFECTIVE THAN .4 mg OF FOLIC ACID EITHER EXPRESSLY OR IMPLIEDLY

The Defendants argue that the claim "0.8 mg of folic acid in a dietary supplement is more effective in reducing NTD risk than a lower amount in foods in common form" implies that .8 mg of folic acid is more effective than .4 mg of folic acid. That implication is ruled out by the claim itself. The claim does not compare folic acid in a dietary supplement or a fortified food with a lesser amount in a dietary supplement or a fortified food. Instead, the claim compares folic acid in a dietary supplement with a lower amount in foods in common form. Thus, it

compares folic acid with smaller, naturally occurring amounts of food folate.[13] Without question, relying on the IOM's food folate bioequivalence[14], it takes about twice as much food folate to equal the potency of a given amount of synthetic folic acid (the kind found in dietary supplements and fortified foods). Application Exhibit 17 at 16. Thus, it is established that .8 mg of folic acid in a dietary supplement is more effective than a lower amount in foods in common form. Moreover, it is accepted – and the Defendants have not challenged – that usual daily intake of food folate is about .18 mg and that a 3.7 fold increase in consumption (e.g., requiring a person to eat 15 servings of broccoli or brussel sprouts per day) would be required to yield about .66 mg of food folate. See Application Exhibit 18 at 7-8. Even then, the amount of folate absorbed would be equal to only .33 mg of folic acid, an amount below the .4 mcg "target" FDA accepts as providing a reasonable estimate of 50% NTD reduction. Thus, on every level of analysis the scientific evidence confirms the veracity of Plaintiffs' statement.[15]

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[13] Without any basis in fact, the Defendants argue that "foods in common form" include "fortified foods," despite the fact that a food is uncommon when it is supplemented with synthetic folic acid. Semantics aside, FDA could certainly correct any misleading connotation it perceives by simply accepting a reasonable qualification on the language, e.g., the one the Plaintiffs plan to use with the claim: "Foods fortified with similar amounts of folic acid may be as effective as dietary supplements in reducing the risk of neural tube defects." The Defendants mislead when they say that Plaintiffs never proposed any disclaimers to FDA in the proceeding below. As stated in their two separate comments filed with FDA, the Plaintiffs expressed a willingness to accept any reasonable disclaimer the FDA wished to add to the claim. See Application Exhibit 2 at 17, 18, & 38.

[14] Under IOM's formula, one DFE = 1 mcg food folate = 0.6 mcg of folic acid from fortified food or a supplement taken with a meal, or One DFE = 0.5 mcg of folic acid in a dietary supplement taken on an empty stomach**.** See Application Exhibit 7 at 210.

[15] In its Opposition at 20, footnote 10, the Defendants cite Combs at 379 for the proposition that "some foods, such as beef and chicken liver" yield in one serving "more folate than one 800 mcg supplement." To be sure, according to Combs, a quarter pound of ***raw*** beef liver or ***raw*** chicken liver consumed daily may yield (and we emphasize the word ***may***) between 140 to 1,070 mcg of folate (equal to 70 mcg to 535 mcg of folic acid equivalent) for beef liver and about 1,810 mcg of folate (equal to 905 mcg of folic acid equivalent) for chicken liver. Plaintiffs' claim, however, is that .8mg of folic acid in a dietary supplement is more effective than a <u>lower</u> amount in foods in common form, not than a higher amount in foods in common form. Thus, the Defendants' point is irrelevant to the claim. But, as a practical matter, who in America consumes a quarter pound of raw chicken liver or raw beef liver every day of the week? And, of the few who do, is their health enhanced by all that saturated fat and cholesterol? Finally, Combs himself recognizes that any single naturally occurring food will contain a variable amount of folic acid due to the very factors Plaintiffs have pled. Indeed, Combs stands as a good cite for Plaintiffs, not for Defendants, because he recognizes how storage and processing deplete folate stores in foods. See J.R. Exh. 18 at 380 ("Most folates in foods . . . are unstable to oxidation under aerobic conditions of storage and processing. Under such conditions (especially in the added presence of heat, light, and/or metal ions) [losses in folate occur] . . . . Substantial losses in the folate contents of food can occur as the result of leaching in cooking water when boiling

In the Opposition, Defendants compare "apples and oranges" when they argue to this Court that clinical trials involving women with prior NTDs have produced results that call into question the results achieved in the Czeizel double-blind, placebo controlled clinical intervention study (Application Exhibit 18) wherein .8 mg of folic acid taken by over 2,000 women who had not had a prior NTD and yielded a 100% reduction in NTD risk. So profound were the results that the authors halted the study believing it unethical to deny women in the control group the NTD risk reduction benefits from .8 mg folic acid supplements (see Application Exhibit 18). It is well accepted that, to quote CDC, a previous NTD-affected pregnancy "increases a woman's chance of having another NTD-affected pregnancy by approximately 20 times," Application Exhibit 19 at 8. Consequently, CDC recommends that women with a prior NTD consume 4,000 mcg (4 mg) of folic acid daily to reduce their risk of a recurrence. Appliction Exhibit 19 at 11. The Defendants err when they assume, unscientifically, that the effects on women who are folic acid resistant (i.e., women with prior NTDs) are comparable to those on women who are normally folic acid responsive (i.e., women without prior NTDs). They also err when they assume, unscientifically, that results from the resistant women are appropriately applicable to all women of childbearing age (i.e, to the general population).[16] To be sure, individual results will vary from the "reasonable" 50% risk reduction estimate predicted by CDC for .4 mg (400 mcg) of folic acid to the 100% risk reduction achieved from .8 mg (800 mcg) of folic acid in the Czeizel study. The critical point is, however, that .8 mg (whether yielding a low of 50%

(losses of total folates of 22% for asparagus and 84% for cauliflower have been observed), as well as oxidation, as described above"). Thus, it is not possible to reduce effectively, substantially, and reliably one's NTD risk in reliance solely upon food folate. Only synthetic folic acid in a dietary supplement consumed on an empty stomach has been shown to provide 100% bioavailability. There is not one clinical trial documenting that NTDs can be reduced substantially and reliably (50% NTD risk reduction or more) from food folate sources alone. As explained above, CDC, IOM, NCEH, NCFA, and AAP all conclude that it has not been demonstrated that food folate protects against NTDs as well as synthetic folic acid.

[16] Resistance to the NTD preventive effects of folic acid is commonly due to specific genetic defects in the mother's DNA coding for an enzyme essential for folic acid utilization.

reduction in risk or a high of 100% reduction in risk) is a demonstrated reduction at a substantial level, whereas there simply is no (not one) clinical trial that demonstrates any reliable and significant risk reduction from food folate. The best that can be said for food folate is that one study, Bower and Stanley (1993), involving only 308 people and not meeting the "gold standard" criteria (not a randomized placebo controlled clinical trial) revealed "some" risk reduction with increased dietary folate intake. Even if we credit that study as a good one, which CDC, NCEH, NCFA, IOM, and AAP have not[17], the results are indeterminate and still far less significant than the "gold standard" results from the Czeizel study. Thus, CDC, NCEH, NCFA, IOM, and APP conclude that NTD risk reduction from food folate has not been demonstrated.

In sum, then, the best available scientific evidence confirms that .8 mg of folic acid in a dietary supplement is a very effective dose level that can substantially reduce the incidence of NTD-affected births in the general population. As the scientist on the Panel on Folate and Other B Vitamins of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board of the Institute of Medicine concluded: "The rigorous evidence obtainable (that from a "gold-standard" randomized double-blind placebo-controlled prospective trial) concerning the relationship [between folic acid and NTD risk] . . . consistently indicate that protection is not maximized by daily periconceptional folic acid intakes of less than 650 mcg/day; 800 mcg/day may be optimal." Exhibit 17 at 6.

IV. PLAINTIFFS CLAIM DOES NOT STATE THAT FOLIC ACID IN A DIETARY SUPPLEMENT IS MORE EFFECTIVE THAN FOLIC ACID IN A FORTIFIED FOOD EITHER EXPRESSLY OR IMPLIEDLY

The Plaintiffs' claim does not state that folic acid in a dietary supplement is more

[17] Indeed, below not even FDA thinks the study a good one. See Application Exhibit 1 at 10 (wherein FDA criticizes the study as "not useful for evaluating a dose/response" relationship.

effective than folic acid in a fortified food; despite that fact the Defendants argue (without any proof) that consumers will understand it to make that comparison (the Defendants say its "implied"). In the seven years that Plaintiffs' claim has been the subject of FDA rulemaking and litigation, never once until now have the Defendants argued that they understood "foods in common form" to impliedly embrace "fortified foods." That was not Plaintiffs understanding (or the understanding revealed in the Court of Appeals' decision) and the Defendants never argued to either the Court of Appeals or this court a contrary understanding, before the present. Moreover, FDA has adduced no empirical evidence to prove that consumers understand fortified foods to be a "food in common form" and, thus, their supposition rests on nothing more than sheer speculation.

Nevertheless, even were one to accept the Defendants' argument, they are far from establishing satisfaction of their First Amendment burden of proof. FDA has not below, and neither has DOJ before this Court, explained why a disclaimer, such as Plaintiffs own ("Foods fortified with similar amounts of folic acid may be as effective as dietary supplements in reducing the risk of neural tube defects") would not suffice to apprise consumers that fortified foods could be as effective as dietary supplements. Fortified foods are, after all, foods into which a dietary supplement has been added.[18]

The Defendants argue that Plaintiffs' affidavits make a "new argument" that Plaintiffs have always understood their claim not to include "fortified foods." Opposition at 20. That is not true. Plaintiffs' affidavits by their own terms merely "confirm" that Plaintiffs understood "foods in common form" not to embrace "fortified foods." The Defendants also argue that they were never presented below with the disclaimer Plaintiffs have voluntarily agreed to use ("Foods

fortified with similar amounts of folic acid may be as effective as dietary supplements in reducing the risk of neural tube defects") and, so, could not evaluate it would suffice to cure misleadingness in the proceedings below. Opposition at 9. The Defendants misapprehend their constitutional obligation under the Pearson mandate (the Court gave FDA the "task" of "draft[ing] precise disclaimers for each of appellants . . . claims," Pearson, 164 F.3d at 659) and mislead this Court by not informing it that Plaintiffs have agreed repeatedly to accept *any* reasonable disclaimer. See Application Exhibit 2 (where Plaintiffs told FDA in the proceeding below: "If FDA finds the proposed claim not to satisfy a defined "significant scientific agreement" standard, the agency should, consistent with Pearson, authorize the claim with such disclaimer or disclaimers as may be reasonably necessary to avoid a potentially misleading connotation.") and Application Exhibit 2 (where Plaintiffs told FDA in the proceeding below: "In addition, and consistent with Pearson and the First Amendment, if the agency finds the proposed claim not to satisfy its future defined "significant scientific agreement" standard, the claim must nevertheless be authorized with such disclaimer or disclaimers as the agency reasonably deems necessary to avoid a potentially misleading connotation"). Under the First Amendment standard articulated in Pearson, FDA cannot suppress a claim unless ***it*** first ***proves*** the claim inherently misleading. If the claim is only potentially misleading, FDA cannot suppress it unless ***it proves*** that there is ***no*** disclaimer that can cure the potentially misleading connotation present. FDA's argument that Plaintiffs had to craft a disclaimer for their own claim before the agency reached its decision as to what aspects of the claim it believes to be misleading is, thus, ridiculous due to its illogic but also impermissible because it shifts the First Amendment burden from FDA to Plaintiffs.

[18] As explained in Plaintiffs' Application, the IOM has concluded that nothing, not even a fortified food, is as bioavailable as folic acid in a dietary supplement consumed on an empty stomach. That is because folic acid taken

V. THE CLAIMS FDA WILL ALLOW ARE MISLEADING

The Defendants argue that their existing and authorized claims should suffice as a substitute for Plaintiffs' claim. FDA's existing authorized and allowed claims are wholly unacceptable because they are misleading. In 21 C.F.R. § 101.79(d)(1-3), FDA presents the following authorized claims:

> (1) "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord defect" or "Adequate folate in healthful diets may reduce a woman's risk of having a child with a brain or spinal cord defect."

Those claims are misleading (a) because under FDA's rules they can appear on foods containing as little as 40 mcg of food folate (20 mcg of folic acid equivalent) per serving, a dose level not demonstrated to have any effect on reducing NTDs; (b) because, as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; and (c) because they omit the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been demonstrated more effective in reducing the risk of NTDs than lower amounts in foods in common form.

> (2) "Women who consume healthful diets with adequate folate throughout their childbearing years may reduce their risk of having a child with a birth defect of the brain or spinal cord. Sources of folate include fruits, vegetables, whole grain products, fortified cereals, and dietary supplements."

That claim is misleading (a) because under FDA rules it can appear on foods containing as little as 40 mcg of food folate (20 mcg of folic acid equivalent) per serving, a dose level not demonstrated to have any effect on reducing NTDs; (b) because, as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; (c) because it conveys the misleading impression that food folate is equally bioavailable and

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with food has been proven less bioavailable than folic acid on an empty stomach. Exhibit 7 at 208.

effective as folic acid in a dietary supplement or a fortified food when, in fact, the synthetic folic acid in supplements and fortified foods has been demonstrated more effective in reducing NTDs; and (d) because it omits the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been demonstrated more effective in reducing the risk of NTDs than lower amounts in foods in common form.

(3) "Women who consume healthful diets with adequate folate may reduce their risk of having a child with birth defects of the brain or spinal cord. Folate intake should not exceed 250% of the DV (1,000 mcg)."

That claim is misleading because (a) as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; (b) because it conveys the misleading impression that food folate is equally bioavailable and effective as folic acid in a dietary supplement or a fortified food when, in fact, synthetic folic acid in supplements and fortified foods has been demonstrated more effective in reducing NTDs; and (c) because it omits the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been demonstrated more effective in reducing the risk of NTDs than lower amounts in foods in common form.

In its letter ruling, FDA presents the following four claims:

(1) "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect. The Institute of Medicine of the National Academy of Sciences recommends that women capable of becoming pregnant consume 400 mcg folate daily from supplements, fortified foods, or both, in addition to consuming food folate from a varied diet."

That claim is misleading (a) because as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; (b) because it conveys the misleading impression that food folate is equally bioavailable and effective as folic

acid in a dietary supplement or a fortified food when, in fact, the synthetic folic acid in supplements and fortified foods has been demonstrated more effective in reducing NTDs; and (c) because it omits the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been proven more effective in reducing the risk of NTDs than lower amounts in foods in common form.

> (2) "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect. The scientific evidence that 400 mcg folic acid daily reduces the risk of such defects is stronger than the evidence for the effectiveness of lower amounts. This is because most such tests have not looked at amounts less than 400 mcg folic acid daily."

That claim is misleading (a) because as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; (b) because it conveys the misleading impression that food folate is equally bioavailable and effective as folic acid in a dietary supplement or a fortified food when, in fact, the synthetic folic acid in supplements and fortified foods has been demonstrated more effective in reducing NTDs; (c) because it omits the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been proven more effective in reducing the risk of NTDs than lower amounts in foods in common form; and (d) because the last sentence of the claim implies that amounts lower than 400 mcg per day may be as effective as 400 mcg when the evidence does not support that conclusion.

> (3) "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect. Women capable of becoming pregnant should take 400 mcg folate/day from fortified foods and/or a supplement, in addition to food folate from a varied diet. It is not known whether the same level of protection can be achieved by using only food that is naturally rich in folate. Neither is it known whether lower intakes would be protective or whether there is a threshold below which no protection occurs."

That claim is misleading (a) because as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; (b) because it conveys the misleading impression that it is possible that food folate alone provides a protective effect when that has not been demonstrated; (c) because it omits the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been proven more effective in reducing the risk of NTDs than lower amounts in foods in common form; and (d) because the last sentence of the claim implies that amounts lower than 400 mcg per day may be as effective as 400 mcg when the evidence does not support that claim.

(4) "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect. Women capable of becoming pregnant should take 400 mcg of folate per day from a supplement or fortified foods and consume food folate from a varied diet. It is not known whether the same level of protection can be achieved by using lower amounts."

That claim is misleading (a) because as CDC, NCEH, BDDD, IOM and the AAP have concluded, food folate has not been demonstrated effective in reducing NTDs; (b) because it conveys the misleading impression that it is possible that food folate alone provides a protective effect when that has not been demonstrated; (c) because it omits the fact that synthetic folic acid (the kind found in dietary supplements and fortified foods) in amounts equal to or greater than .4 mg and below 1 mg have been proven more effective in reducing the risk of NTDs than lower amounts in foods in common form; and (d) because the last sentence of the claim implies that amounts lower than 400 mcg per day may be as effective as 400 mcg when the evidence does not support that conclusion.

VII. THE PRELIMINARY INJUNCTION STANDARD HAS BEEN MET AND AN INJUNCTION SHOULD ISSUE FORTHWITH

Substantial Likelihood of Success on the Merits. As explained supra, the apposite standard in this remand proceeding is the First Amendment as prescribed in Pearson, not the APA. FDA has utterly failed to do what the Pearson Court ordered it to do. It has adduced no empirical evidence to show that Plaintiffs' claim actually misleads and it has not argued under, let alone proved satisfaction of, the three elements of the Central Hudson test that define its irreducible burden of proof. Accordingly FDA has not established a basis to justify suppression of Plaintiffs' speech and the injunction must issue.

Irreparable Injury. The Defendants argue that the Supreme Court has distinguished between forms of protected speech in determining when irreparable injury is present from Government speech suppression. The Defendants are wrong. Whenever protected speech is suppressed that action constitutes irreparable injury without proof of more. The apposite cases do not articulate any distinction between the forms of protected speech (whether political, scientific, commercial, or indecent). See Elrod v. Burns, 427 U.S. 347, 373 (1976) (plurality opinion) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury") quoted in Jackson v. City of Columbus, 194 F.3d 737, 747 (6th Cir. 1999). The Pearson Court here found the speech in question subject to the protections of the First Amendment. Thus, deprivation of that speech in violation of First Amendment standards constitutes irreparable injury. As explained in Plaintiffs' Application, plaintiffs have acted with diligence. While FDA proceeded in a dilatory fashion, over eighteen months, to evaluate the entire scientific record on remand, the Plaintiffs took less than two months to accomplish the same task. FDA has no rational ground for questioning Plaintiffs'

diligence in light of its own plodding pace. Plaintiffs have proceeded responsibly, promptly and with as much haste as is possible (despite the length and complexity of the record).

The Public Interest Favors Grant of the Injunction. The Defendants have failed entirely to show any countervailing public interest that would be served by denying fertile women the truthful and nonmisleading information at the point of sale that a .8 mg folic acid dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form. Indeed, Plaintiffs have presented substantial evidence from the CDC, the NCEH, the NCFA, the BDDD, the IOM, and the AAP that giving women Plaintiffs' message will do much to reduce NTDs that still occur due in no small part to the false and misleading information FDA propounds to the public. Indeed, without Plaintiffs' speech at the point of sale, FDA's misleading message that food folate (containing as little as 20 mcg of folic acid equivalent) is effective in reducing NTDs and that food folate, fortified foods, and folic acid supplements are fungible will continue to deceive American women, contributing to NTD risk rather than lessening it. FDA's long, harmful suppression of the truth about folic acid should come to an end. For seven years this agency has done everything in its power to deprive Plaintiffs of the right to tell women (and of women of the right to receive) Plaintiffs' simple, straightforward and truthful message—a message that has the power to save children from death

due to non-survivable NTDs and to save children from a life of physical hardship and disability due to survivable NTDs. FDA's history on the folic acid claim is a shameful one that must come to an end.

Respectfully submitted,

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