No. 12-6077

United States Court of Appeals for the Tenth Circuit

ANNABEL DOBBS, Individually and as
Personal Representative of the
Estate of Terry Dobbs, Deceased,

Plaintiff-Appellant,

v.

WYETH PHARMACEUTICALS,

Defendant-Appellee.

On Appeal from the United States District Court
for the Western District of Oklahoma,
Judge Stephen P. Friot,
District Court No. 5:04-cv-01762-F

Brief For The Product Liability Advisory Council, Inc., As *Amicus Curiae* In Support of Appellee

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RULE 26.1 CORPORATE DISCLOSURE STATEMENT

Amicus Curiae The Product Liability Advisory Council, Inc., does not have a parent corporation, nor does any publicly held corporation own 10% or more of its stock.

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INTEREST OF THE *AMICUS CURIAE*[1]

The Product Liability Advisory Council, Inc. (PLAC) is a non-profit association with 100 corporate members representing a broad cross-section of American and international product manufacturers. Its corporate members make and sell a wide array of products, including automobiles, aircraft, electronics, chemicals, pesticides, pharmaceuticals, and medical devices.[2] PLAC's primary purpose is to contribute to the improvement and reform of law in the United States and elsewhere, with an emphasis on the law governing the liability of manufacturers of products. Toward that end, since 1983 PLAC has filed over 850 *amicus* briefs in the state and federal courts, including numerous briefs in this Court. PLAC filed an *amicus* brief in an

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[1] All parties have consented to the filing of this brief under Rule 29(a) of the Federal Rules of Appellate Procedure.

[2] A list of PLAC's corporate members is attached as Appendix A. Although not a PLAC member, Defendant-Appellee Wyeth Pharmaceuticals is an unincorporated division of Wyeth, which in turn is a wholly owned subsidiary of Pfizer Inc., a corporate member of PLAC. See Wyeth Br. i. Membership in PLAC, however, is neither necessary nor sufficient to obtain PLAC's *amicus* support; PLAC selects cases on the basis of their jurisprudential importance, not whether they involve a member. Neither Pfizer nor Wyeth made a contribution to the fee paid for PLAC's brief (other than Pfizer's ordinary annual dues as paid by all corporate members of PLAC). PLAC never accepts funds earmarked for any particular *amicus* brief.

earlier appeal in this case.

This appeal raises issues of considerable importance to PLAC and its members. It presents important questions concerning the scope of implied conflict preemption, and in particular how courts should analyze the defense of "impossibility" preemption following the Supreme Court's decision in *Wyeth* v. *Levine*, 555 U.S. 555 (2009). PLAC and its members have a strong interest in ensuring that courts uphold conflict preemption where, as here, a federal regulatory agency has addressed an issue as repeatedly and thoroughly as the United States Food and Drug Administration (FDA) has done, and where clear evidence shows that the plaintiff's state-law claim conflicts with the agency's regulatory actions and scientific and public-health judgments.

STATEMENT

This case arises from the tragic suicide of Terry Dobbs, a 53-year-old man already diagnosed with severe depression, in December 2002. When he died, Mr. Dobbs was taking Effexor, a prescription antidepressant drug belonging to a class of drugs known as Selective Serotonin Reuptake Inhibitors (SSRIs). Effexor is manufactured by Defendant Wyeth Pharmaceuticals (Wyeth). After his widow (Plaintiff)

brought suit under Oklahoma law alleging that Wyeth failed to warn adequately that Effexor could cause suicide, two different district judges carefully evaluated the massive regulatory record concerning (i) the evolution of Effexor's labeling and (ii) suicide risks allegedly associated with Effexor and other SSRIs. Both judges reached the same conclusion that warning-related claims were preempted because FDA would have rejected the additional warning sought by Plaintiff as unsupported by credible scientific evidence. See Aplt. App. 1168; Aplee. Supp. App. 41.

The first ruling, by Judge DeGiusti in 2008, declined to address broader issues such as judicial deference to FDA's preemption views because, "on the particular facts of this case, . . . this case presents a narrower issue." Aplee. Supp. App. 41. The court explained:

> The record establishes that the express type of warning which Plaintiff claims Defendant should have included in its Effexor label had been considered and rejected by the FDA as not supported by credible evidence at the time Mr. Dobbs used Effexor. Where the FDA has evaluated scientific evidence regarding an alleged risk associated with a drug, has considered whether that evidence warrants a labeling warning, and has expressly rejected the need for such warning as not supported by credible evidence, a state law determination that such a warning is required creates a conflict for the manufacturer as between federal and state law . . . .

Ibid. (footnoted omitted). That conclusion was based on an extensive,

careful review of the regulatory record concerning the labeling of Effexor and other SSRIs. See *id.* at 28-33. Taken as a whole, this regulatory evidence "establishes that, at the time Mr. Dobbs took . . . Effexor, the FDA had concluded there was no credible evidence that a link existed between adult use of antidepressants and suicidality or an increased risk of suicide." *Id.* at 32. Preemption was required by a line of Supreme Court decisions establishing that "conflict preemption applies only if the need for it is *clear*." *Id.* at 23 (emphasis added) (citing *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 885 (2000)); see also *ibid.* (reiterating the need for a "clear" conflict).

The Supreme Court issued its decision in *Wyeth* v. *Levine*, 555 U.S. 555 (2009), while the first summary judgment ruling was on appeal. In *Levine*, the Court stated that, to establish "impossibility" preemption in this setting, a drug manufacturer must present "clear evidence" that "FDA would not have approved" the change sought by a plaintiff in the drug's labeling. *Id.* at 571. This Court vacated and remanded to allow trial court consideration of *Levine* as well as an opportunity for the parties to "submit additional evidence" concerning the preemption defense. Aplt. App. 1149.

On remand, a new judge, Judge Friot, reached the same result, again conducting a careful and extended analysis of the regulatory record and again concluding that it contained "clear evidence that the FDA would have rejected an expanded Effexor warning for patients in Mr. Dobbs's age group prior to his 2002 suicide." Aplt. App. 1168; see also *id.* at 1156-1168 (exhaustively reviewing record evidence). The district court's "narrow basis for granting the original partial summary judgment motion," Judge Friot explained, was "not impacted by *Levine* because it is essentially the same as that expressly recognized by *Levine* as warranting conflict preemption – the FDA would not have approved the label warnings urged by the plaintiff." *Id.* at 1156. Judge Friot applied *Levine*'s "clear evidence standard," explaining that application of that standard "is necessarily fact specific" and requires an inquiry into "FDA's regulation of the warnings accompanying antidepressants, including Effexor." *Ibid.* On the basis of that fact-, agency- and risk-specific analysis, the district court again ruled that Plaintiff's failure-to-warn claim was impliedly preempted.

INTRODUCTION AND SUMMARY OF ARGUMENT

Implied conflict preemption is an important legal doctrine rooted in the Supremacy Clause, which provides: "This Constitution, and the laws of the United States . . . shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby; any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. State and local laws that conflict with federal law are preempted "by direct operation of the Supremacy Clause." *Brown* v. *Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984). The Supremacy Clause serves a vital structural role in our Nation's government by protecting federal law and programs against encroachment and interference by subordinate governments. It also helps to create unified and rational markets for nationally distributed goods and services by ensuring that uniform federal regulation – often the product of expert agency decision-making pursuant to authority delegated by Congress – is not undermined or subverted by state and local law, including state tort law as applied by lay juries.

The Supreme Court's decisions interpreting the Supremacy Clause and articulating the doctrine of implied conflict preemption stretch back to the earliest days of the Republic. See *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 516 (1992); *Gibbons* v. *Ogden*, 22 U.S. (9 Wheat.) 1 (1824). The Court's precedents have separately discussed "'conflicts' that prevent or frustrate the accomplishment of a federal objective" (so-called "obstacle" preemption) and "'conflicts' that make it 'impossible' for private parties to comply with both state and federal law" ("impossibility" preemption). See *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 873-74 (2000). But such "terminological" distinctions cannot obscure the fundamental principle that the Supremacy Clause reaches *all* cases where there is an *actual* or *direct* conflict between state and federal requirements. *Id.* at 873.

This case presents an important application of the standards articulated in *Wyeth* v. *Levine* for "impossibility" preemption arguments relating to prescription-drug labeling – a large category of cases – and may also affect "impossibility" arguments in other regulatory settings. See, *e.g.*, *PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567, 2577-82 (2011) (discussing "impossibility" preemption defense and *Levine* standard in

distinct regulatory setting of generic drugs). As we explain below, Plaintiff (and a handful of lower courts) have misconstrued *Levine* as somehow changing the Court's longstanding requirement of a "clear" basis for preemption.

In contrast, Judge Friot understood and properly implemented *Levine*'s requirements in upholding Wyeth's preemption defense based on a careful, painstaking review of a regulatory record that plainly shows that FDA would *not* have approved the additional warning sought by Plaintiff. This Court should take this opportunity to clarify the nature of the inquiry that is appropriate in cases such as this, involving implied conflict preemption defenses that are contingent upon what a federal regulatory agency empowered (as FDA is here) to take actions that conflict with state or local law would have done under specified circumstances.

Specifically, this Court should make clear that, under *Levine*, a manufacturer must provide "clear evidence" showing, by a preponderance of the evidence, that FDA would have rejected Plaintiff's advocated warning at the relevant time if the manufacturer had sought to provide it through the "Change Being Effected" (CBE) process.

Levine did not invent a novel, hybrid burden of persuasion falling somewhere between the preponderance and clear-and-convincing standards. *Levine*'s insistence upon "clear evidence" reflects and expresses well-settled precedent establishing that conflict preemption requires demonstration of an *actual*, rather than merely a hypothetical or possible, conflict between federal and state law.

This Court should also make clear that the proper counterfactual inquiry under *Levine* must focus on FDA's evaluation of the specific warning in question, at the relevant time, under the governing legal standards applicable to new warnings. The proper inquiry must also take into account FDA's scientific standards as well as the public-health concerns that animated FDA's labeling decisions. Plaintiff's arguments against preemption here reflect a misunderstanding of the proper inquiry required under *Levine*. Equally misplaced is Plaintiff's reliance on a handful of post-*Levine* decisions that have rejected the "impossibility" defense in cases involving SSRIs, including Effexor. Those cases rest on flawed understandings of *Levine*, are factually distinguishable, or both, as the district court correctly concluded. Under the proper contours of *Levine*'s mandated inquiry into what FDA

"would have" done, it is readily apparent that Wyeth has easily proven its preemption defense. The judgment should be affirmed.

ARGUMENT

The district court in this case reached the correct result – twice. Plaintiff's contrary arguments are largely smoke and mirrors, reinventing her failure-to-warn claim on appeal, invoking unreliable "expert" evidence that was properly excluded from the record, and torturing language in the district court's second opinion in a failed effort to attribute misunderstandings of how FDA regulates prescription-drug labeling. The Court should not be misled. See Wyeth Br. 29-33, 54-58 (addressing and refuting all of these arguments). Instead, this Court should affirm the judgment below and, in so doing, provide much-needed clarification of the nature of the inquiry required under *Levine*. See Aplt. App. 1156 (noting correctly that *Levine* "does not define 'clear evidence[]'").

I. Under *Levine*, A Pharmaceutical Manufacturer Must Present "Clear Evidence" That, By A Preponderance Of The Evidence, FDA Would Not Have Approved The Additional Warning Sought By The Plaintiff

Federal preemption is an affirmative defense. In civil actions, the ordinary or default burden of persuasion is proof by a preponderance of

the evidence. Thus, a defendant ordinarily must prove the defense of preemption by a preponderance of the evidence. Although preemption is a *legal* defense "present[ing] only a legal question for the court" (Aplt. App. 1150), often the defense can hinge on case-specific regulatory facts and circumstances. In every conflict preemption case, however, a court (1) ascertains the meaning of state law; (2) determines the meaning of federal law; and (3) makes a judgment whether the former conflicts with, or serves as an obstacle to, the latter. See *Perez* v. *Campbell*, 402 U.S. 637, 644 (1971) ("Deciding whether a state statute is in conflict with a federal statute and hence invalid under the Supremacy Clause is essentially a two-step process of first ascertaining the construction of the two statutes and then determining the constitutional question whether they are in conflict."). These fundamental background principles are not disputed in this case.

A. *Levine* Did Not Alter The Formal Burden Of Proof For The Affirmative Defense Of Preemption

In *Wyeth* v. *Levine*, the defendant advanced, and the Supreme Court, rejected two specific – and very broad – conflict-preemption arguments in the prescription drug arena. First, it rejected an "obstacle" preemption argument that it would "obstruct the purposes

and objectives of federal drug labeling regulation" to permit juries in tort actions to evaluate drug labeling that Congress has instead entrusted to an expert agency, the FDA. 555 U.S. at 563-64, 573-81. Second, and more relevant for present purposes, the Court rejected the manufacturer's "impossibility" defense. *Id.* at 563, 568-73. After reviewing FDA oversight of prescription drug labeling, and determining that the drug manufacturer could have provided the additional disputed warning through the CBE process, the Court observed that FDA nevertheless retained authority to reject such CBE changes. "But absent clear evidence that the FDA *would not have* approved a change to Phenergan's label," the Court explained, "we will not conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements." *Id.* at 571 (emphasis added).

The Court's unelaborated reference to "clear evidence" does not overturn the usual preponderance-of-the-evidence burden of proof. On the contrary, *Levine*'s reference to "clear evidence" invoked the Court's general, well-settled principle that the proponent of a conflict preemption defense must demonstrate an *actual* conflict between state and federal law – potential or hypothetical conflicts are not enough.

The preemptive conflict must be "clear." See, *e.g.*, *Geier*, 529 U.S. at 884 (conflict preemption "turns on the identification of 'actual conflict[]'"); *English* v. *General Electric Co.*, 496 U.S. 72, 90 (1990) (rejecting conflict preemption argument where conflict was "too speculative"); *Rice* v. *Norman Williams Co.*, 458 U.S. 654, 664 (1982) (Court's decisions "enjoin seeking out conflicts between state and federal regulation where none *clearly* exists") (emphasis added; quotation marks omitted) (cited with approval at Pl. Br. 47 n.26)). "Clear evidence" in this setting thus means what it always has – a persuasive demonstration of an actual, as opposed to merely a hypothetical or potential, conflict.

This reading is amply confirmed by *Geier*, which, as Wyeth correctly notes (Br. 51-52), enunciated the "clear evidence" formulation in evaluating proof of conflict preemption. Specifically, the Court in *Geier* reasoned that conflict preemption "turns on the identification of 'actual conflict[]'" and then explained that "a court should not find pre-emption too readily in the absence of *clear evidence* of a conflict." 529 U.S. at 884-85 (emphasis added).

In referring to "clear evidence," the Court in *Geier* cited a portion of its previous decision in *English*. In the relevant portion of *English*,

see 496 U.S. at 90, the Court addressed whether administrative anti-retaliation provisions for employees in the nuclear power industry, established by Section 210 of the Energy Reorganization Act of 1974, 42 U.S.C. § 5851(a), preempted emotional distress tort claims under state law. Rejecting the argument that Congress's inclusion of "expeditious time-frames" in the federal administrative remedy preempted state claims with longer deadlines, the Court expressed skepticism that "employees will forgo their § 210 options and rely solely on state remedies for retaliation." *English*, 496 U.S. at 89-90. "Such a prospect," the Court explained,

> is simply too speculative a basis on which to rest a finding of pre-emption. The Court has observed repeatedly that pre-emption is ordinarily not to be implied absent an 'actual conflict.' See, *e.g.*, *Savage* v. *Jones*, 225 U.S. 501, 533 (1912). The 'teaching of this Court's decisions . . . enjoin[s] seeking out conflicts between state and federal regulation where none *clearly* exists.' *Huron Portland Cement Co.* v. *Detroit*, 362 U.S. 440, 446 (1960).

Id. at 90 (emphasis added). The references to "clear evidence" in *Geier* and "clear" conflicts in *English* are thus nothing more than a restatement of the "actual conflict" principle.

If the Court in *Levine* had meant more than the "clear" evidence required in *Geier* and *English* – if it had meant to reject the ordinary

civil burden of proof – it plainly would have said so. The Court, like Congress, "does not . . . hide elephants in mouseholes." *Whitman* v. *American Trucking Assns., Inc.*, 531 U.S. 457, 468 (2001).

Indeed, in *Geier* the Court expressly *rejected* an argument that a defendant must shoulder a "special burden" of proof in certain subcategories of implied preemption cases. 529 U.S. at 870-74. Such a "special burden," the Court explained, "find[s]" no "basis . . . in this Court's precedents" and would "promise practical difficulty by further complicating well-established pre-emption principles that already are difficult to apply." *Id.* at 872-73. In light of that unambiguous holding, *Geier*'s reference to "clear evidence" obviously did not alter the formal burden of proof. Nor is it plausible to conclude that the Court in *Levine* intended to adopt the very kind of "special burden" of proof rejected in *Geier* (without even mentioning, much less expressly overruling, this aspect of *Geier*).

This reading is further confirmed by *PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567 (2011), which *upheld* an "impossibility" defense against failure-to-warn claims challenging *generic* drug labeling. Under FDA regulations, generic drug labeling must be "the same" as corresponding

brand-name drug labeling, and thus generic drug manufacturers have no CBE process allowing them unilaterally to alter their labeling. In *PLIVA*, the Court rejected the plaintiffs' contention that compliance with state law was not impossible because generic manufacturers could have asked FDA to change both their own and brand-name labels, and such a request might have resulted in FDA permission to change the generic-drug labeling. *Id.* at 2578-79. Because the manufacturers did not even *try* to persuade FDA to do so, plaintiffs contented, the manufacturers could not prove impossibility. The Court rejected that argument, explaining that "[i]f these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes," then conflict preemption would be rendered "largely meaningless." *Ibid.* Thus, the Court held, once again, that impossibility preemption does not turn on mere "possibility." *Id.* at 2581 n.8. Once clear evidence establishes preemption, it takes clear evidence to defeat it.

For all of these reasons, this Court should clearly reject any suggestion that *Levine* altered the formal burden of proof by adopting a novel standard of proof falling somewhere between preponderance and proof by clear and convincing evidence. In addition to being foreclosed

by *Geier*, such a rule would add still more complexity and uncertainty to the law of federal preemption. This Court should clarify that under *Levine* a defendant in this setting need only make a persuasive ("clear") showing that an actual conflict exists because it is more likely than not that the proposed warning would have been rejected by FDA. See Aplt. App. 1156 (noting that other post-*Levine* cases "do not contain precise definitions of clear evidence"). That burden was overwhelming satisfied in this case.

B. The Proper Counterfactual Inquiry Under *Levine* Focuses On FDA's Likely Action On The Warning In Question, At The Relevant Time, Under The Governing Legal Standards, The Scientific Standards Employed By The Agency, And The Public-Health Concerns Animating The Agency's Labeling Decisions

Under *Levine*, a successful "impossibility" defense in the prescription-drug setting requires "clear evidence" that "FDA *would not have* approved" the change sought by a plaintiff in the drug's labeling. 555 U.S. at 571 (emphasis added). The Court specified "would not" – not "did not." In cases where a manufacturer *actually proposed* to add the warning in question but that proposal *was rejected* by FDA, the preemptive conflict is not just "clear," but indisputable. See *Robinson* v. *McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010) (*Levine*

standard satisfied where, after plaintiff was injured, FDA refused to approve warning advocated by plaintiff); compare Pl. Br. 20 (inexplicably suggesting that "rejected attempts" to add the warning in question "cannot" provide "clear evidence" under *Levine*). In the cases *Levine* contemplated, however, the relevant inquiry is *counterfactual* in nature: it relies on a judicial determination of whether FDA likely *would have* rejected the additional warning in question *if* the warning had been proposed. See *PLIVA*, 131 S. Ct. at 2580 (plurality) (noting that inquiry focuses on "the counterfactual conduct of the FDA").

Impossibility preemption is not impossible. Rather, counterfactual inquiries are commonplace in the law. See generally Robert Strassfeld, *If . . . : Counterfactuals in the Law*, 60 GEO. WASH. L. REV. 339, 345-48 (1992). In tort law, for example, they arise with respect to issues of causation (but for the defendant's conduct, would the injury have occurred?) and remedies (absent tortious conduct, what damages would the plaintiff have avoided?). In failure-to-warn cases involving avoidable risks, the question whether a plaintiff would have heeded a warning not provided requires counterfactual inquiry. As made clear by *Levine*, *PLIVA*, and *Buckman Co.* v. *Plaintiffs' Legal*

Committee, 531 U.S. 341, 354 (2001), counterfactual issues arise with regularity even in the quite limited setting of implied preemption arguments involving regulatory decisions by FDA and other federal agencies.

The scope of the counterfactual inquiry in this case was necessarily fact- and case-specific and limited by virtue of its regulatory context. *First*, because the manufacturer must present "clear evidence" that "FDA would not have approved" the change sought by a plaintiff in the drug's labeling (*Levine*, 555 U.S. at 571), the inquiry obviously focuses on the precise warning that the plaintiff alleges was missing: here, a warning concerning Effexor's supposed risks of suicidal behaviors and thoughts in adult patients. *Second*, the inquiry is necessarily limited *temporally* – it focuses on the likelihood of FDA action on or immediately before December 2002, when Mr. Dobbs took his own life.

Third, the counterfactual inquiry necessarily focuses on a particular decisionmaker – FDA. *Fourth* and relatedly, it focuses on the applicable regulatory standard for addition of new warnings in prescription-drug labeling – namely, whether there was "reasonable evidence of an association" between adult suicidality and Effexor. Wyeth Br. 5-6

(quoting and citing 44 Fed. Reg. 37,434, 37,463 (June 26, 1979), and 21 C.F.R. § 201.57(e) (2002)). That legal standard, of course, necessarily informs FDA's decisions on whether to approve prescription-drug labeling – and whether to reject warnings added through the CBE process.

Fifth, the counterfactual inquiry here necessarily takes into account the *scientific* standards that FDA would have applied in evaluating Plaintiff's desired warning. In this regard, Wyeth's regulatory evidence in the record clearly demonstrated that, in FDA's view, "the scientifically preferred way to analyze antidepressant suicide risk, including the risk or lack of risk associated with Effexor, was through pooled analysis of controlled-trial data." Wyeth Br. 40. Moreover, FDA clearly focused on the risk of suicide as it pertained to *patients in different age groups*. In addition, the regulatory evidence showed that, at least with respect to the issue of suicide, FDA treated all SSRIs as a class and took the view that "the best way to convey the information to physicians was through identical, class-wide warnings." *Ibid.*; see also *ibid.* (noting FDA's documented "concern that . . . drug-specific suicide-related warnings would cause confusion").

Sixth, the inquiry into whether FDA would have rejected Plaintiff's advocated warning must also take into account the competing *public-health concerns* that would have informed and animated the agency's judgment. Thus, it is highly significant that FDA has long been concerned about the detrimental effects of *overwarning* with regard to unsubstantiated risks of suicide associated with the use of SSRIs. See Wyeth Br. 7, 21, 24-26; Aplt. App. 106-109, 111-136, 144-146, 169. As the district court put it, "the lengthy regulatory history of SSRIs reflects the FDA's . . . reluctance to consider a warning which it believed might reduce the use of antidepressants and thereby undermine the benefits of their use in treating depression" (a serious condition that, if left untreated, can result in suicide). Aplt. App. 1167.[3] Because FDA's expressly enunciated public-health concern would have informed any FDA decision on the warning at issue in this case, it must

[3] This public-health concern is significant. Studies conducted on the effect of FDA's enhanced *pediatric* SSRI warnings (which, unlike the warnings Plaintiff advocated for in this case, *are* supported by empirical data) have reported an overall decrease in SSRI prescriptions, and an overall increase in suicides, for pediatric patients. See, *e.g.*, R.D. Gibbons *et al.*, *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 AM. J. PSYCHIATRY 1356 (2007).

be considered in conducting the counterfactual inquiry required under *Levine*.

Seventh and finally, the counterfactual inquiry is necessarily limited to the record evidence of the parties. There is no dispute that Plaintiff had ample opportunity (both before and after remand) to present evidence relevant to the counterfactual inquiry. The appellate record should not be expanded with evidence that the parties failed to present below.

The district court correctly adhered to all of the foregoing parameters of the counterfactual inquiry required under *Levine*. It focused carefully on: the warning in question (Aplt. App. 1149, 1159, 1174 & n.12); the relevant time frame (*id.* at 1161-1163, 1166, 1168, 1169 1174); the regulatory record developed by the parties (*id.* at 1158-1168); the legal standard governing FDA's decisions on new warnings (*id.* at 1155, 1157-58, 1159, 1161-1162); FDA's actual scientific approach to SSRI warnings concerning suicide, including the agency's exclusive reliance on controlled-studies data, concern for different age groups of patients, and access to SSRI-wide data beyond that possessed by Wyeth (*id.* at 1159, 1161-62, 1164-65, 1166, 1167-68, 1169-70, 1171);

and the competing public-policy concerns about overwarning actually increasing the incidence of suicide in patients suffering from depression (*id.* at 1159, 1167). The district court correctly analyzed all the right factors under *Levine* and reached the correct result.[4]

C. Plaintiff's Arguments Against Preemption Rest On A Fundamental Misunderstanding Of The Proper Inquiry Required By *Levine*

In contending that the district court erred, Plaintiff relies on several misunderstandings about how *Levine*'s counterfactual inquiry should be conducted – and what is required to present "clear evidence that the FDA would not have approved" the change sought by a plaintiff in the drug's labeling. 555 U.S. at 571.

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[4] This case is significantly different from *Levine* in several respects bearing on the preemption analysis. First, as previously noted, FDA's decisions reflect a concern that excessive or unfounded SSRA suicide warnings could bring about the very same adverse effects that Plaintiff's proposed warning was supposedly aimed at reducing – increasing the risk of suicidal thoughts and acts. In *Levine*, by contrast, the relevant risk was limited to a particular technique of drug administration, and thus was avoidable by using other methods of administration. Second, FDA's thorough investigation here ensured that no manufacturer had more information than the agency. Compare *Levine*, 555 U.S. at 569, 572-73, 578-79 (referring to manufacturers' "superior access to information about their drugs"). Because FDA treated SSRIs as a class, demanded the data of multiple SSRI manufacturers, and analyzed the combined data itself, FDA had superior knowledge concerning the risk of suicide and suicidal thought when compared to Wyeth or any individual manufacturer.

First, as noted above, Plaintiff suggests that a manufacturer's "rejected attempts" to add the precise warning at issue would not satisfy *Levine*; only FDA's rejection of that warning *actually added through the CBE process would*. See Pl. Br. 20. In addition to requiring clairvoyance on the part of manufacturers, this argument suffers from multiple flaws. To begin with, it would encourage a manufacturer that has proposed a warning rejected by FDA to defy the agency and add it through the CBE process, to force a second rejection. Nothing in *Levine* suggests such an absurd requirement, which would both render "impossibility" preemption a dead letter and sanction disruption of the FDA scheme.

Nor is Plaintiff's position consistent with *PLIVA*, which made clear that impossibility preemption cannot be defeated by speculative arguments about what private parties or FDA might do in the future. Indeed, even the dissenting Justices in *PLIVA* (who took a less expansive view of impossibility preemption than the majority) rejected Plaintiff's position. See 131 S. Ct. at 2588 (dissent) ("If a generic-manufacturer defendant proposed a label change to the FDA but the

FDA rejected the *proposal*, it would be impossible for that defendant to comply with a state-law duty to warn.") (emphasis added).

More fundamentally, Plaintiff's argument misunderstands the counterfactual nature of the inquiry under *Levine*. The inquiry is *counterfactual* – it does not require the manufacturer to have *actually* proposed the relevant warning, much less actually added it through the CBE process. Neither does it require that FDA have *actually* rejected the warning – although the record here reflects such rejections on several occasions. On the contrary, in discussing the absence of "clear evidence" the Court in *Levine* noted various things missing from the record, including facts establishing that the manufacturer "supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." 555 U.S. at 572-73. Thus, *Levine* indicates that a manufacturer could establish impossibility in the absence of actually proposing a warning or having a warning rejected, such as by providing data demonstrating that a particular warning lacked scientific basis.

Finally, Plaintiff's cramped reading of the "clear evidence" standard flunks the common-sense test. Requiring proof that a

manufacturer actually proposed to FDA (or added through the CBE process) the precise warning sought by the plaintiff would have the perverse effect of eliminating the impossibility defense in cases involving the most scientifically unfounded risks. If a warning has no *scientific basis whatsoever* (or, indeed, is demonstrably false under the data), no rational manufacturer would even think to propose it. Such wild claims should be preempted. It should be enough for a manufacturer to show through "evaluation or analysis," 555 U.S. at 572-73, that the warning was scientifically unfounded and would have been rejected by FDA.

Second, Plaintiff attempts to significantly narrow *Levine*'s "clear evidence" standard by relying on the *dissent*'s version of the regulatory facts in that case. Pl. Br. 45-47 & n.25. For the reasons identified by Wyeth (Br. 28, 48-51), that argument is unavailing. Equally mistaken is Plaintiff's suggestion (Br. 46 n.25) that the *Levine* majority did not rest its decision on certain factual determinations made by "both the trial court and the Vermont Supreme Court," including the state courts' findings that (i) FDA had *not* intended to prohibit the manufacturer from strengthening the warnings, and (ii) neither FDA nor the

manufacturer "gave more than passing attention to the issue of IV-push versus IV-drip administration." 555 U.S. at 572. Those facts, and not the dissent's version, inform this Court's analysis of *Levine*'s holding that the manufacturer in that case did not satisfy the "clear evidence" standard.[5]

D. The Handful Of Post-*Levine* SSRI Cases Rejecting Preemption Arguments On Which Plaintiff Relies Failed To Apply The Proper Counterfactual Inquiry Under *Levine*, Or Were Based On Distinguishable Facts Or Materially Different Records

As explained above (and as recognized by the district court), the proper counterfactual inquiry under *Levine* is, by its very nature, highly case-specific and record-dependent. Aplt. App. 1156 ("application of the clear evidence standard is necessarily fact specific"), 1169 (taking note of the "fact-specific nature of the evidentiary standard"). For that reason, cases involving drugs other than SSRIs are (as the district court correctly noted) "unpersuasive" (*ibid.*), and even other SSRI cases may

[5] Plaintiff is also wrong to suggest that denial of citizen petitions in 1991, 1992, and 1997 was completely irrelevant to the counterfactual inquiry under *Levine*. See Pl. Br. 40-41. Although the probative value of those regulatory actions is less because of their timing, Plaintiff's suggestion that they are *irrelevant* again ignores the class-wide approach taken by FDA to SSRIs with respect to the precise risk at issue in this case.

be readily distinguishable if they involve patients of different ages, different warnings, different relevant time periods, or different regulatory evidence presented by the parties. Nevertheless, Plaintiff points to a handful of post-*Levine* SSRI cases that rejected impossibility preemption, arguing that they are persuasive because they involved "substantially the same evidence" as was presented here. Pl. Br. 1. Plaintiff's submission is incorrect.

Here, the district court carefully examined each of the five decisions cited by Plaintiff (see Aplt. App. 1168-1174) and correctly concluded that they were either based on a flawed analysis, or involved readily distinguishable facts, or both. Indeed, all five of the decisions departed from the proper counterfactual inquiry under *Levine* as described in Section I.B above. As the lower court recognized, in at least three of the decisions – *Mason* v. *Smithkline Beecham Corp.*, 596 F.3d 387 (7th Cir. 2010), *Forst* v. *SmithKline Beecham Corp.*, 639 F. Supp. 2d 948 (E.D. Cal. 2009), and *Aaron* v. *Wyeth*, 2010 WL 653984 (W.D. Pa. Feb. 19, 2010) – courts failed to understand, credit or adequately factor into the analysis FDA's longstanding practice of treating all SSRI labeling with respect to suicide risks the same. See,

e.g., *Mason*, 596 F.3d at 395 ("[E]ven though Prozac and Paxil are both SSRIs, they are different drugs made by different manufacturers. Therefore, we give little weight to the administrative history of Prozac when we are concerned with whether there is clear evidence that the FDA would have rejected a labeling change in Paxil.").[6] Moreover, three of the decisions (*Mason*, *Aaron*, and *Baumgardner* v. *Wyeth*, 2010 WL 3431671 (E.D. Pa. Aug. 31, 2010)) reflect no awareness of FDA's longstanding public-health concern about the detrimental, and now scientifically established, effects of *overwarning* with regard to unsubstantiated suicide risks associated with SSRIs – a consideration clearly germane to the counterfactual analysis. See also *Dorsett* v. *Sandoz, Inc.*, 699 F. Supp. 2d 1142, 1150 (C.D. Cal. 2010) (citing earlier judicial decision rejecting as unfounded the risk of overwarning in this setting). Because these courts neglect the scientific standards and

[6] See also Aplt. App. 1169-70 (discussing *Mason*); *id.* at 1171 ("It is not clear whether the court in *Forst* was presented with the evidence, submitted in this case, that the FDA has consistently required uniform label warnings for all SSRIs."); *id.* at 1172 (noting that *Aaron* "did not discuss" FDA's "regulatory history regarding SSRI suicidality warnings").

public-health concerns that actually motivated FDA, their conclusions about what FDA would have done are necessarily suspect.

Nor are these the only departures from the proper counterfactual inquiry under *Levine*. The district court in *Aaron*, for example, concluded that preemption was defeated because even "[t]hough the FDA disagreed with certain changes to the Effexor labeling proposed by Wyeth, Wyeth *did not press its position*, it instead acquiesced to the requests made by the FDA." 2010 WL 653984, at *6 (emphasis added). As Judge Friot correctly recognized, however, *Levine* does not "impos[e] upon the drug manufacturer" any "duty to continually 'press' an enhanced warning which has been rejected by the FDA." Aplt. App. 1173. Manufacturer "acquiescence," not sabotage, is essential if FDA, with its "limited resources," *Levine*, 555 U.S. at 578, is to administer the statute effectively. As the Court made clear in *PLIVA, Inc.* v. *Mensing*, 131 S. Ct. 2567 (2011), impossibility preemption cannot be defeated merely by establishing a "possibility" that a conflict between federal and state law might be avoided by the action of a regulator or third parties. *Id.* at 2581 n.8. There is no requirement to "press" a warning FDA has rejected.

In addition to their flawed legal analysis, the cases invoked by Plaintiff are readily distinguishable. None reflects the full range of regulatory evidence that was considered by the district court in this case. *Mason*, for example, relies primarily on FDA's denial of the three citizen petitions and on the regulatory record pertaining only to Paxil. Similarly, *Baumgardner*'s minimal discussion of the regulatory record focuses on the three citizen petitions, statements made by the Psychopharmacologic Drugs Advisory Committee (PDAC), and FDA's rejection of a proposed change to Effexor's labeling. See 2010 WL 3431671, at *1. And neither *Mason* nor *Baumgardner* takes into account, for example, the factual statements made in a series of FDA *amicus* briefs concerning the agency's contemporaneous scientific judgments about the relevant risks. See Wyeth Br. 20-22; see also Aplt. App. 1171-72 (distinguishing *Dorsett* on additional grounds). Finally, *Mason*, in particular, is plainly inapposite because it involved a far younger patient in an age group that FDA concluded was *actually subject* to an enhanced risk of suicide requiring a new warning.[7] For all

[7] See Aplt. App. 1170 ("[A]s the Seventh Circuit [in *Mason*] noted, the FDA's analysis of clinical studies during the time period near [plaintiff's] suicide ultimately led to an enhanced warning for that age

of these reasons, the district court was correct to conclude that these five post-*Levine* decisions were "distinguishable or unpersuasive (or both)." *Id*. at 1174.

II. Wyeth Has Clearly Satisfied Its Burden Under *Levine*

Based on its careful review of the parties' evidence concerning FDA's oversight and regulation of the warnings concerning suicide in the labeling of Effexor and other SSRIs, the district court ruled that "there is clear evidence that the FDA would have rejected an expanded Effexor warning for patients in Mr. Dobbs's age group prior to his 2002 suicide." Aplt. App. 1168. "In fact," the court added, "the record reflects [FDA's] *repeated* conclusions, during the time period preceding and following Mr. Dobbs's 2002 suicide, that there was *no scientific evidence* to support a causal connection between SSRI's and suicidality in adult patients." *Ibid*. (emphasis added). Wyeth thus plainly satisfied its burden under *Levine* by presenting "clear evidence that the FDA would

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group [24 and under]. In contrast, none of its studies or analyses prior to, or after, Mr. Dobbs's suicide supported an enhanced suicidality warning for 53-year-old patients; in fact, FDA expressly requires SSRI manufacturers to state in their product labels that studies reflect no evidence of a causal connection between antidepressants and suicidality in that age group."); see also *id.* at 1170, 1173 (noting that the ages of the patients involved was not disclosed in either *Forst* or *Baumgardner*).

not have approved" the change sought by Plaintiff in the drug's labeling. 555 U.S. at 571.

Indeed, it is striking just how extensive and persuasive Wyeth's showing was in this case. Thus, Wyeth pointed to FDA's decisions and statements regarding the warnings concerning suicidality in the labeling of Effexor and other SSRIs in all of the following settings: (1) FDA's approval of New Drug Applications (NDAs) and Supplemental New Drug Applications (SNDAs) for Effexor in 1993, 1997, 1999, 2001, and February 2003 (Aplt. App. 1160-1161; Wyeth Br. 9-11); (2) FDA's approval of "more than a dozen NDAs and SNDAs for other SSRI" prescription drugs in the 1993-2002 time frame (Aplt. App. 1161; Wyeth Br. 9-12); (3) FDA's rejection, in 1991, 1992, and 1997, of citizen petitions seeking to add suicidality warnings (Aplt. App. 1162-63; Wyeth Br. 13-14); (4) the proceedings of FDA's PDAC conducted in 1991 and 2004 (Aplt. App. 1162; Wyeth Br. 12, 14-16, 17, 25); (5) FDA's reports, studies, analysis of data, and Congressional testimony in the time period 2002-2006 (Aplt. App. 1163-1164; Wyeth Br. 12, 16-19, 25); (6) FDA's *rejection* of Wyeth's proposals and efforts (including in the CBE process) to expand the pediatric suicidality warnings during 2002-

2004 (Aplt. App. 1166-1167; Wyeth Br. 22-24); and (7) multiple FDA *amicus* briefs in which the agency made factual statements about the absence of scientific evidence that would support warnings like those sought by Plaintiff (Wyeth Br. 20-22). Each of these FDA decisions or statements reflected the agency's unwavering conclusion – which remains in place today – that there is "*no scientific evidence* to support a causal connection between SSRI's and suicidality in adult patients." Aplt. App. 1168 (emphasis added). If this tsunami of evidence does not constitute "clear evidence" under *Levine*, it is difficult to imagine what would.

CONCLUSION

For the foregoing reasons, as well as those set forth in Wyeth's brief, the judgment should be affirmed.

Respectfully submitted.

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Dated: September 12, 2012

APPENDIX A:
CORPORATE MEMBERS OF THE
PRODUCT LIABILITY ADVISORY COUNCIL

as of 7/3/2012

3M
Altec Industries
Altria Client Services Inc.
Astec Industries
Bayer Corporation
BIC Corporation
Biro Manufacturing Company, Inc.
BMW of North America, LLC
Boehringer Ingelheim Corporation
The Boeing Company
Bombardier Recreational Products, Inc.
BP America Inc.
Bridgestone Americas, Inc.
Brown-Forman Corporation
Caterpillar Inc.
CC Industries, Inc.
Chrysler Group LLC
Cirrus Design Corporation
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E.I. DuPont De Nemours and Company
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The Goodyear Tire & Rubber Company
Great Dane Limited Partnership
Harley-Davidson Motor Company
Honda North America, Inc.
Hyundai Motor America
Illinois Tool Works Inc.
Isuzu North America Corporation
Jarden Corporation
Jaguar Land Rover North America, LLC
Jarden Corporation
Johnson & Johnson
Johnson Controls, Inc.
Joy Global Inc., Joy Mining Machinery
Kawasaki Motors Corp., U.S.A.
Kia Motors America, Inc. Kolcraft Enterprises, Inc.

Lincoln Electric Company
Lorillard Tobacco Co.
Magna International Inc.
Marucci Sports, L.L.C.
Mazak Corporation
Mazda Motor of America, Inc.
Medtronic, Inc.
Merck & Co., Inc.
Meritor WABCO
Michelin North America, Inc.
Microsoft Corporation
Mine Safety Appliances Company
Mitsubishi Motors North America, Inc.
Mueller Water Products
Mutual Pharmaceutical Company, Inc.
Navistar, Inc.
Niro Inc.
Nissan North America, Inc.
Novartis Pharmaceuticals Corporation PACCAR Inc.
Panasonic Corporation of North America
Pella Corporation
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Remington Arms Company, Inc.
RJ Reynolds Tobacco Company
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Shell Oil Company
The Sherwin-Williams Company
Smith & Nephew, Inc.
St. Jude Medical, Inc.
Stanley Black & Decker Inc.
Subaru of America, Inc.
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Pursuant to Fed. R. App. P. 32(a) the undersigned counsel for the *amicus curiae* hereby certifies as follows:

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CERTIFICATE OF DIGITAL SUBMISSION

The undersigned certifies that: (1) all required privacy redactions have been made; (2) the native PDF format version of this brief that was filed using the ECF filing system is an exact copy of the hard copies of this brief that are being submitted to the Clerk; and (3) the native PDF format version of this brief that was filed using the ECF filing system was scanned for viruses with the most recent version of VIPRE Antivirus (version 5.0.4464, virus definitions last updated on September 12, 2012), and, according to that program, is free of viruses.

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I hereby certify that on September 12, 2012, I:

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