No. 08-437

In the
Supreme Court of the United States

JOSEPH C. COLACICCO, INDIVIDUALLY
AND AS EXECUTOR OF THE ESTATE OF
LOIS ANN COLACICCO, DECEASED,
AND
BETH ANN MCNELLIS, ON BEHALF OF THE ESTATE OF
THEODORE DEANGELIS, DECEASED,
AND IN HER OWN RIGHT,
Petitioners,

v.

APOTEX, INC.; APOTEX CORP.,
A SUBSIDIARY OF APOTEX, INC.;
SMITHKLINE BEECHAM D/B/A GLAXOSMITHKLINE;
AND PFIZER, INC.
Respondents.

On Petition for a Writ of Certiorari
to the United States Court of Appeals
for the Third Circuit

REPLY BRIEF ON PETITION FOR A WRIT OF CERTIORARI

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The briefs in opposition provide no reason to deviate from the Court's usual practice of holding petitions for certiorari when a case pending before this Court raises identical or similar issues and therefore is likely to affect the decision in the case in which Petitioner seeks certiorari.[1] The Court heard oral argument in *Wyeth v. Levine* on November 3, 2008. That argument confirmed that the determination of the issues before the Court in *Levine* will certainly affect, and might well determine, the outcome of this case.

I. THE COURT SHOULD HOLD THIS PETITION PENDING ITS DECISION IN *WYETH V. LEVINE.*

Petitioners in this case assert the same basic claim made by Diana Levine: that the drug manufacturer should have complied with federal regulations by proposing or adding an adequate warning to the label previously approved by FDA. *See* Tr. 12, *Wyeth v. Levine,* No. 06-1249 (Nov. 3, 2008) ("*Levine* Tr.") ("[The drug company] could have done that at any time, and it simply didn't do it.")(Question by Souter, J.).

The reality that risk information will evolve as drugs perform in the marketplace underlies federal regulation of drug labeling. Because of the limitations on FDA's post-approval authority – both statutory and practical – federal regulations place the responsibility to review and analyze this evolving safety information on drug manufacturers. *See* 21 C.F.R. § 314.80(b). The regulations mandate that a drug's label be revised to

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[1] *See* Robert L. Stern et al., *Supreme Court Practice* 255, 311 (8th ed. 2002).

include appropriate warnings "as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e)(App. 236-37).[2] Because the nature of the system envisions that prudent drug manufacturers will discover additional hazards as they discharge their post-approval duties, they have the power to add warnings *without* prior FDA approval. *See id*. § 314.70(c)(6)(iii)(A)(App. 238-41).

A. The Court's Determination of *Levine* Will Likely Affect the Analysis and Outcome of this Case. The power and duty expressly conferred by the federal regulations negates conflict preemption based on impossibility. *See Levine v. Wyeth*, 944 A.2d 179, 188-89 (Vt. 2006), *cert. granted*, 128 S. Ct 1118 (2008)(No. 06-1249); App. 71 (Ambro, J., dissenting). If a drug manufacturer never proposes or adds an appropriate warning, moreover, a drug manufacturer's claim that FDA would have rejected any such warning is hypothetical and cannot form the basis of conflict preemption. *See Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982).

Levine and this case present analogous facts with respect to preemption. Just as Wyeth never discharged its duty to provide a strengthened, adequate warning about Phenergan prior to Diana Levine's injury, Respondents in this case never proposed or added any warning at all of increased suicidality associated with their drugs prior to the prescriptions to Mr. DeAngelis

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[2] Confirming the importance of this regulation, counsel for Diana Levine began his argument by quoting it. *Levine* Tr. 24.

or Ms. Colacicco.[3] The claims for preemption in both cases rest on the unsubstantiated notion that, *if* they had proposed or added warnings, FDA would have rejected them.

A decision by this Court in *Levine* on the threshold issue of whether there can be conflict preemption where a drug manufacturer has neither proposed nor added a warning that would be adequate under state law will necessarily affect the analysis and outcome of this case. If the Court concludes that there is no actual conflict presented where the manufacturer never gives, or even proposes, an additional or stronger warning, the Court's holding in *Levine* will certainly mandate reversal of this case.

If the Court takes a more specific approach in *Levine* and examines whether FDA would have "rejected" or "prohibited" a strengthened warning, its decision will still affect the analysis and outcome of this case. In *Levine*, Wyeth argued primarily that the existence of some warning of the risk of gangrene on the label demonstrated that FDA had considered the risk posed by IV-push administration and had determined

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[3] FDA recently amended § 314.70(c)(6)(iii)(A) to allow a drug manufacturer to add or strengthen a warning without prior FDA approval only if the added warning was based on "newly acquired information." 73 Fed. Reg. 49,603 (2008). Although § 314.70(c)(6)(iii)(A) contained no such restriction in 2003, the government has conceded that the "evolving information" that ultimately led to added warnings on antidepressants would have been "new information" within the meaning of the amended regulation. *Levine* Tr. 17. Thus, there is no question in this case that the drug manufacturers *could* have added a warning without prior FDA approval.

that no stronger warning was justified. Here, there was no warning at all on the labels of an association between the drugs and suicidality prior to 2004, but Respondents argue that FDA's refusal to require such a warning prior to 2004 constituted an authoritative federal determination prohibiting one.

B. FDA Has Never Rejected a Warning of the Association Between Antidepressants and Increased Suicidality. Neither of the briefs in opposition provides any basis for denying this petition before the Court renders its decision in *Levine*. Indeed, Respondents Apotex and GSK devote their response almost exclusively to merits issues and make no attempt to argue that the Court should deny this petition now. Respondent Pfizer, for its part, tries to distinguish this case from *Levine,* implying that the two cases are sufficiently different that this case need not be held for that one.

Pfizer argues that the Third Circuit correctly held that FDA had "rejected" a warning of the association between antidepressants and increased suicidality at the time of the prescriptions in this case (even though it is undisputed that FDA subsequently issued public health advisories of this association and requested additional warnings for all antidepressants). Pfizer's effort to differentiate this case from *Levine* is unavailing.

Significantly, Respondents do not dispute the applicability of *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), to this case. In response to Petitioners' assertion that "*Sprietsma* controls the analysis and outcome of this case," Pet. 2, 22, Apotex and

GlaxoSmithKline do not even cite it; and Pfizer acknowledges (at 35-36) its applicability, but unsuccessfully attempts to distinguish it factually. For any "rejection"of an added warning to be preemptive, therefore, the parties agree that it must rise to the level of an "authoritative federal determination" prohibiting such a warning. 537 U.S. at 67; *see also Altria Group, Inc. v. Good*, No. 07-562, slip op. 19 (Dec. 15, 2008) ("agency nonenforcement of a federal statute is not the same as a policy of approval"). There is no such evidence in this case.

FDA approved Zoloft for treatment of adult depression on December 30, 1991, Pfizer Opp. 8, and approved Paxil for treatment of adult depression in December 1992, Apotex Opp. 4-5. At the time these antidepressants were prescribed to Mr. DeAngelis and Ms. Colacicco in 2003, therefore, the drug manufacturers had twelve years of post-marketing data review and analysis. *See* 21 C.F.R. § 314.80(b). At the argument in *Levine*, the government acknowledged that there was "evolving information" with respect to the relationship between antidepressants and increased suicidality. *Levine* Tr. 17. FDA's discovery of that evolution began in 2002, with respect to pediatric patients. *See* Pet. 7-8. Significantly, when FDA's advisory committee convened to examine the reanalyzed pediatric data in February 2004, the chairman observed that "we do not believe that this data [concerning the association between antidepressants and suicidality] until now has been provided *to us* in a way that would permit us to interpret it fully."[4] FDA did not fully

[4] Fe b. 2004 PDAC, Hearing Tr. at 24 (italics added) (*see* Pet. 9 n.10).

analyze the evolving information with respect to *adult* patients until after it completed its review of the pediatric data, long after the deaths of Mr. DeAngelis and Ms. Colacicco.

The duty to review and analyze the data, to provide it to FDA in a way that would permit full analysis and to add appropriate warnings without prior FDA approval was the drug manufacturers' to discharge. But antidepressant manufacturers "simply didn't do it."[5] *Cf. Levine* Tr. 12 (Question by Souter, J.). Under these circumstances, it is clear that there had been no authoritative federal determination rejecting or prohibiting a warning of increased suicidality as of 2003.

Nonetheless, Respondents identify several events prior to 2004 that they claim to be "rejections" of increased warnings. First, they claim that FDA's denials of three citizen petitions concerning Prozac constitute a "rejection" of added warnings for Paxil and Zoloft. *See* Pfizer Opp. 8-13; Apotex Opp. 7-8. But these three antidepressants are sufficiently biologically distinct that each was issued a separate patent. Refusals to require a warning with respect to *Prozac* (which is not at issue in this case) in 1991, 1992 and 1997 were no "rejection" of an added warning with

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[5] As FDA's own scientists have recognized, drug makers resist added warnings because additional warnings decrease drug sales. *See* Staff of H. Comm. on Oversight and Gov't Reform, *FDA Career Staff Objected to Agency Preemption Policies* 6 (Oct. 2008)("Companies rarely press for meaningful risk information or additional warnings. And they always oppose black box warnings."), *available at* http://oversight.house.gov/documents/20081029102934.pdf.

respect to *Zoloft* or *Paxil* (the drugs at issue here) in 2003. Furthermore, even while denying the citizen petition in 1991, FDA emphasized that "nobody in the agency dismisses the possibility that antidepressants in general or fluoxetine [Prozac] in particular may have – and I emphasize 'may' – the capacity to cause untoward injurious behaviors, acts, and/or intensify them."[6] Accordingly, denial of the citizen petitions was not an authoritative federal determination prohibiting a warning even as to Prozac, much less as to Zoloft or Paxil. *See* Pet. 23-24.

Although both Mr. DeAngelis and Ms. Colacicco were prescribed antidepressants for depression, Respondents also emphasize subsequent approvals for indications other than depression as evidence that FDA "rejected" a stronger warning. *See* Pfizer Opp. 11-12; Apotex Opp. 5. They fail to mention that these supplemental NDA's did not propose or suggest a stronger warning. FDA's approval of these antidepressants for indications from which neither Mr. DeAngelis nor Ms. Colacicco suffered (including Zoloft's approval for premenstrual dysphoric disorder "only seven months before [Mr.] DeAngelis's demise," *see* Pfizer Opp. 12, 20) – unaccompanied by any discussion of an added warning that the drug might be paradoxically associated with increased suicidality, especially early in treatment – is hardly a "rejection" of an added warning with respect to depressed patients.

Respondent Pfizer cites (at 13) the amicus brief filed by FDA in September 2002 – ironically, the month before the Paxil pediatric data first revealed to FDA an

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[6] 1991 PDAC, Hearing Tr. 126 (*see* Pet. 7 n.4).

increased risk of suicidality, *see* Pet. 7-8 – as evidence that FDA had rejected an additional warning. Because no antidepressant manufacturer had ever submitted a supplemental NDA proposing an added warning, however, FDA necessarily made its submission in that case based on the evidence that had been provided *to it* as of 2002. Curiously, its litigation position remained the same even after its regulatory position changed in 2004, when FDA issued its first public health advisory regarding antidepressants, *see* Pet. 10. Although Pfizer cites (at 16-17) FDA's 2005 amicus brief as evidence of "rejection," the divergence of FDA's regulatory and litigation positions actually underscores the lack of any persuasive power in FDA's litigation position. *See* Pet. 32.

Because of the change in FDA's regulatory position, the Court should not consider FDA's statements prior to 2004 – which Respondents cite as further evidence of "rejection," *see* Apotex Opp. 8-9; Pfizer Opp. 14 – without considering FDA's acknowledgment that it could not "interpret [the data] fully" before 2004. FDA had made no authoritative federal determination prohibiting an added warning prior to 2004 because antidepressant manufacturers had not provided the relevant data to it in an understandable form.[7]

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[7] This Court has indicated that a defendant claiming preemption cannot rely on agency inaction when it has failed to provide relevant information to that agency. *See Altria,* slip op. 19 n.14. This underscores that the Third Circuit erroneously refused to consider GSK's manipulation of the Paxil data submitted to FDA in the course of its preemption analysis. *See* Pet. 33-36. It also undercuts Respondents' arguments that Petitioners should have first pursued GSK's manipulation of the data directly with FDA,

Likewise, the class-wide portion of the labels that FDA requested in 2007 was no "rejection" of any added warning with respect to any particular antidepressant. *See* Pfizer Opp. 18-19; Apotex Opp. 11-12. Beginning in 2004, FDA began to analyze pooled data from many antidepressant manufacturers, and began to request that antidepressant labels contain a class-wide portion, uniform as to *all* antidepressants, based on the pooled data. *See* Pet. 9-11; Pfizer Opp. 18. But this did not absolve any *individual* antidepressant manufacturer from performing post-marketing analysis and issuing appropriate warnings with respect to its particular drug, and it certainly did not retroactively brand as "scientifically unsubstantiated" any prior warnings concerning individual antidepressants. FDA's reaction to the two warnings of increased suicidality actually added by antidepressant manufacturers proves that this is true.

C. Apotex and GSK Have Misrepresented FDA's Response to the Two Warnings Actually Added by Antidepressant Manufacturers Without Prior FDA Approval. Petitioners previously discussed (at 11-13) these added warnings. Respondents do not dispute that the warning added by Wyeth in August 2003 stood unchallenged for seven months; that the warning added by GSK in May 2006 stood unchallenged for a full year; that the warnings were added without prior FDA approval; or that FDA did not claim that the added warnings had misbranded the drugs.

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before using evidence of this manipulation to defeat preemption in the courts below. *See* Apotex Opp. 22; Pfizer Opp. 24-29.

Nonetheless, Apotex and GSK claim (at 12-13) that the "administrative history" shows that FDA "expressly rejected" the added warnings. A top FDA official has flatly contradicted this claim, however. In his September 2004 congressional testimony, FDA's Director of the Office of Drug Evaluation testified:

> Ms. DeGETTE: Well, let me ask you this. In the spring or summer of 2003, Wyeth came to the FDA, and they wanted on their own – we heard this in the last hearing – to strengthen warnings on Efexir [sic], and the FDA asked them not to do that. Is that right?
>
> Dr. TEMPLE: Not quite. They were allowed to do that, and they did it until we created a new stronger warning or – you can call it strong or not – a different warning in the warning section. It prominently said you really need to watch patients, and we thought that was a more trenchant warning. That was in response to the Advisory Committee.[8]

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[8] Sept. 23, 2004 Cong. Hearing Tr. 85 (*see* Pet. 8 n.7).

As for the warning to adult patients that GSK added in May 2006, FDA specifically acknowledged in its Third Circuit amicus brief that it "did not reject the proposed labeling change." U.S. 3d Cir. *Amicus* Brief 14.[9] Apotex's and GSK's claims that FDA rejected these added warnings are simply wrong.

II. THIS CASE PRESENTS AN IDEAL VEHICLE IN WHICH TO ADDRESS ISSUES NOT PRESENTED IN *LEVINE*.

Congress has declared that a drug is "misbranded" if its label does not bear "such adequate warnings against use in those pathological conditions . . . where its use may be dangerous to health . . . in such manner and form, as are necessary for the protection of users." 21 U.S.C. § 352(f). When GSK finally added its warning to adult patients in May 2006, confirming a more than six-fold increase in the risk of suicidality to adult patients, it admitted that Paxil had been misbranded in 2003. Mr. Colacicco's claims thus parallel federal claims for misbranding by omission. Federal law does not preempt state actions that parallel federal law. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1011 (2008).

GSK does not dispute that its added warning was based on data that predated Ms. Colacicco's death, that it concerned the same drug prescribed to her and the same side effect she suffered, or that she was in the

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[9] Contrast this statement with the government's repetition at the argument in *Levine* of the factually-unsupported (and mistaken) claim that FDA had "rejected" a warning of increased suicidality. *Levine* Tr. 17.

patient group the warning addressed. *See* Pet. 12-13, 29. It offers no explanation of why it did not give the added warning years earlier. Its own action negates the claim that federal law would have prohibited adding an appropriate warning sooner.

FDA's reaction to the warnings added by Wyeth and GSK confirms that, while it chose to request a uniform, class-wide portion of antidepressant labeling for all manufacturers to use, this in no way absolved individual drug manufacturers from issuing appropriate warnings concerning their particular drugs. Wyeth did so, and FDA commended its action. *See* Pet. 11-12. GSK did so, and FDA predictably "did not reject the proposed labeling change." U.S. 3d Cir. *Amicus* Brief 14. Unfortunately, GSK added its warning two and a half years too late to save Lois Colacicco's life.

This case involves issues that are not involved in *Levine*: a warning of the same side effect that affected the plaintiff, added by the drug manufacturer – without prior FDA approval – years after her death; subsequent modifications to the label that demonstrate that the drug was misbranded by omission at the time it was prescribed to the plaintiffs; and manipulation of the data submitted to FDA by the drug manufacturer claiming preemption, *see* Pet. 34-36. Accordingly, this case merits independent consideration by the Court.

CONCLUSION

For the reasons stated herein and in the petition for a writ of certiorari, the petition should be held pending the decision in *Wyeth v. Levine*, and then vacated or granted.

Respectfully submitted,

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