NO. 09 - 1039

IN THE

Supreme Court of the United States

ACTAVIS ELIZABETH, INC.,

Petitioner,

v.

GLADYS MENSING,

Respondent.

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

RESPONDENT'S BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether state law products liability claims brought by injured patients against manufacturers of generic drugs are impliedly preempted by the Food, Drug and Cosmetic Act?

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RESPONDENT'S BRIEF IN OPPOSITION

Respondent Gladys Mensing respectfully requests that this Court deny the petition for review of the decision of the United States Court of Appeals for the Eighth Circuit, which held that Ms. Mensing's state products liability claims against the manufacturers of the generic drugs that injured her are not impliedly preempted by the Food, Drug and Cosmetic Act (FDCA), or the Hatch-Waxman Amendments thereto.

The decision below does not conflict with any decision of another federal court of appeals or of a state court of last resort, and it is consistent with relevant decisions of this Court. In fact, it is a straightforward application of the reasoning in this Court's decision last term in *Wyeth v. Levine*, --- U.S. ----, 129 S. Ct. 1187 (2009), to a state failure-to-warn suit brought against manufacturers of a generic drug. Every court to take up the question since the *Levine* decision has concluded that state failure-to-warn claims against generic drug companies are not preempted.

Petitioner seeks a special immunity from liability for generic drug companies, an immunity that is not available to name-brand drug companies or other manufacturers. Given that seventy percent of all prescriptions are now filled with generic drugs, preemption of state tort claims against such companies would leave most persons injured by inadequately labeled drugs, including Ms. Mensing, remediless. Congress's silence regarding preemption of these cases is "powerful evidence that Congress did not intend" such a draconian result. *Id.* at 1200.

COUNTERSTATEMENT OF THE CASE

Gladys Mensing developed tardive dyskinesia, a severe and irreversible neurological disorder, as a result of her long-term use of the prescription drug metoclopramide, which was prescribed to treat her diabetic gastroparesis. At the time,[1] the metoclopramide label indicated that the risk of any "extrapyramidal symptom" from metoclopramide use, including tardive dyskinesia, was "approximately 1 in 500 patients." In fact, the actual incidence of tardive dyskinesia in patients using metoclopramide long-term was many times higher, perhaps as high as 1 in 5 patients.

Despite mounting evidence that the risks of tardive dyskinesia were much greater than reflected in the product label, no manufacturer of metoclopramide ever proposed to the Food and Drug Administration (FDA) that the warnings on the metoclopramide label should be changed to reflect that greater risk. In February 2009, too late for Ms. Mensing, the FDA—acting on its own initiative pursuant to powers granted to the agency in the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (FDAAA)—ordered manufacturers of metoclopramide to add a "Boxed Warning" to their labels. That warning stated, in relevant part: "Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia."

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[1] Ms. Mensing took metoclopramide from March 2001 through March 2005.

Ms. Mensing sued the manufacturers of the generic metoclopramide she had used, including Petitioner, for failure to adequately warn her of the risks of long-term metoclopramide use.[2] The district court, ruling before *Wyeth v. Levine* was decided, granted the generic-drug-company defendants' dispositive motions on the grounds that Ms. Mensing's state failure-to-warn claims were preempted by the Hatch-Waxman Amendments to the FDCA and the federal regulatory scheme governing generic drugs. The Eighth Circuit, following *Levine,* unanimously reversed, ruling that Congress had not intended to preempt such state tort claims against generic drug companies.

Federal Regulation of Generic Drugs

As this Court recognized in *Levine,* "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate." 129 S. Ct. at 1197-98.

This principle applies with equal force to both name-brand and generic drug companies. All drug companies are under a statutory obligation to maintain adequate warnings on their labels. 21 U.S.C. § 352(f)(2) (App. 1a)("A drug . . . shall be deemed to be misbranded . . . unless its labeling bears . . . such adequate warnings against use . . . where its use may be dangerous . . . as are necessary

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[2] She also sued the manufacturers of the name-brand version of metoclopramide, Reglan, for misrepresention. The district court dismissed those claims on state law grounds and the Eighth Circuit affirmed.

for the protection of users"). Both name-brand and generic drug manufacturers have an obligation to revise their labels "to include a warning 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. § 201.57(e) (2005).[3] As the FDA has specifically instructed manufacturers of generic drugs, "[a]fter approval of an [Abbreviated New Drug Application], if an ANDA holder believes that new safety information should be added, it should provided adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised"). 57 Fed. Reg. 17,950, 17,961 cmt. 40 (Apr. 28, 1992).

It is not necessary for a drug company to conduct new clinical studies in order to conclude that "reasonable evidence" supports an additional warning. As this Court recognized in *Levine*, a new warning may be justified by adverse drug experience reports, 129 S. Ct. at 1197; all drug manufacturers are required to collect information on adverse drug

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[3] In 2006, the FDA issued amended labeling regulations for prescription drugs. 71 Fed. Reg. 3,922 (Jan. 24, 2006). That rulemaking, which became effective on June 30, 2006, redesignated § 201.57(e) as 21 C.F.R. § 201.80(e) and it remains the regulatory standard for drugs labeled under the old labeling rules, such as metoclopramide. 71 Fed. Reg. at 3,988, 3,996. A virtually identical requirement applies to drugs labeled under the new regulation. 21 C.F.R. § 201.57(c)(6)(i) (2010) ("In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established."). 71 Fed. Reg. at 3,990. Petitioner inadvertently included the post-2006 version of § 201.57 in the appendix to its petition, rather than the version in effect during the time at issue in this litigation. *See* App. 2a.

experiences and to report them to the FDA. 21 C.F.R. §§ 314.80 (NDA holders) & 314.98 (2010) (ANDA holders). Reports in the medical literature can also provide evidence to support a labeling change; indeed, the FDA letters ordering manufacturers of metoclopramide to add a boxed warning justified the change by referencing published studies. *See* Letter from Joyce Korvick, Center for Drug Evaluation and Research ("CDER"), to Health Care Professionals, 1 & nn.1-3 (Feb. 26, 2009), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf; Letter from Gary Buehler, CDER, to Health Care Professionals 1-2 & nn.1-3 (Feb. 26, 2009), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111378.pdf.

There are two procedures by which both brand-name and generic drug companies may change their labels: (1) a Prior Approval Supplement, required for "Major Changes," 21 C.F.R. § 314.70(b) (2005) (App. 3a), or (2) a Changes Being Effected (CBE) Supplement for "Moderate Changes," 21 C.F.R. § 314.70(c) (2005) (App. 5a), under which a manufacturer may proceed with the change upon notification to the agency, unless the FDA disapproves. Labeling changes to "add or strengthen a contra-indication, warning, precaution, or adverse reaction," may be made through the CBE process. 21 C.F.R. § 314.70(c)(6)(iii)(A) (2005). 21 C.F.R. § 314.97 (2010) (App. 7a) instructs generic drug companies to follow these procedures "regarding the submission of supplemental applications and other changes to an approved abbreviated application."

Even before a product label can be revised, drug companies may warn health care professionals by other means, such as a "Dear Doctor" letter, whenever possibly harmful adverse effects associated with use of the drug are discovered. 44 Fed. Reg. 37,434, 37,447 (June 26, 1979).

Thus, drug labels are not fixed as of the date of FDA approval. Nor should they be: name-brand drugs receive initial approval based upon very limited clinical trials and there is a substantial likelihood that new risks, complications, and contraindications will only be identified or confirmed after the drug—and its generic equivalents—have been prescribed more widely. *See* Karen E. Lesser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J.A.M.A. 2215, 2218 (May 1, 2002) ("Only half of newly discovered serious ADRs are detected and documented in the Physicians' Desk Reference within 7 years after drug approval."). For this reason, a drug company's obligation to provide physicians and patients with up-to-date warnings and precautions continues as long as the product is being marketed and prescribed to patients. 21 U.S.C. § 352(f)(2); 21 C.F.R. §§ 201.57(c)(6)(i), 201.80(e) (2010).

REASONS FOR DENYING THE PETITION

I. There is No Conflict Among the United States Courts of Appeals and/or State Courts of Last Resort.

Review is unwarranted because there is no conflict among the lower courts with regard to whether federal law preempts failure-to-warn claims

involving generic drugs. The ruling below was the first appellate decision to apply the reasoning of *Wyeth v. Levine* to state tort claims against generic drug companies, but it is far from the only court ruling on preemption of such claims. To date, three federal courts of appeals—the Fourth, Fifth, and Eighth Circuits—have addressed the issue of generic drug companies' potential liability for failure to warn of the risks posed by their products; each has concluded, without dissent, that the federal regulatory scheme permits generic drug companies to strengthen label warnings and that such companies may be held liable under state law for inadequate warnings.[4]

Shortly after the decision below, the Fifth Circuit joined the Eighth Circuit in rejecting a generic drug company's preemption defense. In *Demahy v. Actavis, Inc.*, 593 F.3d 428 (5th Cir. 2010), the court of appeals applied the reasoning of *Levine* and concluded that the plaintiff's failure-to-warn claims were not preempted because the generic-drug-company defendant could have sought to strengthen its warnings through the CBE process or the prior approval process or by sending warnings directly to health care providers. *Id.* at 439-445. The court rejected the argument that the responsibility for

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[4] As Petitioner notes, the issue of preemption of state claims against generic drug manufacturers is pending before both the Sixth and Ninth Circuits. *Morris v. Wyeth, Inc., et al.*, No. 09-5460 (6th Cir. filed Apr. 27, 2009); *Smith v. Wyeth, Inc., et al.*, No. 09-5460 (6th Cir. filed Apr. 16, 2009); *Wilson v. Pliva, Inc., et al.*, No. 09-5466 (6th Cir. filed Apr. 20, 2009); *Gaeta v. Perrigo Pharmaceuticals Co.*, No. 09-15001 (9th Cir. filed Jan. 6, 2009). To Respondent's knowledge, no case raising the issue has reached the highest court of any state.

strengthening label warnings rested solely on the name-brand drug company:

> The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. *Who* prompts the FDA to consider necessary changes to that shared label is immaterial.

Id. at 445 (emphasis in original).

The Fifth Circuit viewed its decision as following naturally from this Court's ruling in *Wyeth v. Levine*: "While not directing our result, it shadows our conclusion that the federal regulatory regime governing generics is also without preemptive effect." *Id.* at 430.

Even before *Levine*, the U.S. Court of Appeals for the Fourth Circuit had reached a similar conclusion regarding a generic drug company's potential liability for inadequate warnings. In *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994), that court opined:

> When a generic manufacturer adopts a name brand manufacturer's warnings and representations without independent investigation, it does so at the risk that such warnings and representations may be flawed. . . . The statutory scheme governing premarketing approval for drugs simply does not evidence Congressional intent to insulate generic drug manufacturers from liability for misrepresentations

> made regarding their products, or to otherwise alter state products liability law. Manufacturers of generic drugs, like all other manufacturers, are responsible for the representations they make regarding their products.

Id. at 169-70.

Every court of appeals to address this question has reached the same conclusion. The absence of conflict in the lower courts strongly supports denial of the petition for certiorari in this case.

II. The Lower Courts Are Not Confused About the Application of *Wyeth v. Levine* to Claims Against Generic Drug Companies.

As the foregoing discussion demonstrates, the Fifth and Eighth Circuits have had no problem applying the lessons of *Levine* to preemption defenses asserted by generic drug companies: both courts recognized that that decision carried "important implications" for generic drug companies as well. Pet. App. 9a. But they are not alone in finding the application of preemption doctrine clear in this context. At least a dozen courts have taken up the issue of preemption of state tort claims against generic drug manufacturers since *Wyeth v. Levine* was decided. Every one of them has concluded, in light of *Levine,* that the plaintiffs' claims are not preempted. *See, e.g., Demahy*, 593 F.3d 428; *Mensing v. Wyeth,* Pet. App. 1a; *Dorsett v. Sandoz, Inc.*, No. CV06-7821, 2010 WL 1174204 (C.D. Cal. Mar. 26, 2010); *Swicegood v. Pliva, Inc.*, No. 1:07-cv-1671, 2010 WL 1138455 (N.D. Ga. Mar.

22, 2010); *Weilbrenner v. Teva Pharm. USA, Inc.*, No. 7:08-CV-23, 2010 WL 924915 (M.D. Ga. Mar. 10, 2010); *Vitatoe v. Mylan Pharm., Inc.*, No. 1:08cv85, 2010 WL 1008788 (N.D. W. Va. Mar. 5, 2010); *Fulgenzi v. Wyeth, Inc.*, No. 5:09CV1767, 2010 WL 649349 (N.D. Ohio Feb. 19, 2010); *Munroe v. Barr Labs.*, 670 F. Supp. 2d 1299, 1303 (N.D. Fla. 2009); *Bartlett v. Mutual Pharm. Co.*, 659 F. Supp. 2d 279 (D.N.H. 2009); *Stacel v. Teva Pharm., USA*, 620 F. Supp. 2d 899, 907 (N.D. Ill. 2009); *Schrock v. Wyeth*, 601 F. Supp. 2d 1262, 1265 (W.D. Okla. 2009); *Couick v. Wyeth, Inc.*, No. 3:09-CV-210-RJC-DSC, 2009 WL 4644394 (W.D.N.C. Sept. 30, 2009); *Pustejovsky v. Wyeth*, No. 4:07-CV-103-Y, 2009 WL 3336032, at *1 n.4 (N.D. Tex. Sept. 4, 2009); *see also Kellogg v. Wyeth*, 612 F. Supp. 2d 437, 442 (D. Vt. 2009) (post-*Levine* decision rejecting generic drug company defendant's request to certify pre-*Levine* ruling denying preemption for interlocutory appeal).

In short, the lower courts have had no difficulty applying *Levine's* teachings. There is accordingly no need for this Court to grant a petition for certiorari to provide guidance to the lower courts.

III. Petitioner Seeks Special Protection From Tort Liability That Is Not Available to Other Manufacturers and That Finds No Support in the Hatch-Waxman Amendments.

It should not be surprising, especially in the wake of *Levine*, that the lower courts have had little difficulty rejecting preemption claims by generic drug companies. Petitioner seeks a special shield against tort liability that is not available to other manufacturers, including the manufacturers of

name-brand drugs. Seventy percent of prescriptions in this country are today filled with generics. Susan Okie, *Multinational Medicines—Ensuring Drug Quality in an Era of Global Manufacturing*, 361 New Eng. J. Med. 737, 738 (2009). A finding of preemption would leave all consumers of inadequately labeled generic drugs, including Ms. Mensing, without legal remedy. As the Fifth Circuit observed in *Demahy*, it would be a "bizarre conclusion that Congress intended to implicitly deprive a plaintiff whose doctor prescribes a generic drug of *any* remedy, while under *Levine*, that same plaintiff would have a state-law claim had she only demanded a name brand drug instead." 593 F.3d at 449. "If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005).

Despite the alarmist tone of the petition, the Eighth Circuit's decision does not threaten to drive generic drugs off the market or to endanger the viability of the generic drug industry. Suits against drug manufacturers for inadequate warnings have existed since long before there was an FDA, *see, e.g.*, *Thomas v. Winchester*, 6 N.Y. 397 (1852), and the generic drug industry has thrived despite the risk of tort liability.

As both the Fifth and Eighth Circuits have recognized, generic drug companies need not undertake expensive clinical trials in order to protect themselves from liability. All they need do is review the adverse drug experience reports they already receive, and monitor the medical literature for studies identifying new risks associated with the

products they sell. Pet. App. 19a-20a; *Demahy*, 593 F.3d at 447. If the name-brand company is properly strengthening its label warnings "as soon as there is reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.80(e), its generic competitors can simply tag along with those label changes; but where the name-brand manufacturer fails to propose necessary warnings, generic drug companies cannot just rely upon that inaction: "In these circumstances, § 201.57(e) [now 21 C.F.R. § 201.80(e)] does not permit generic manufacturers passively to accept the inadequacy of their drug's label as they market and profit from it." Pet. App. 12-13a.

There is not a hint anywhere in the Hatch-Waxman Amendments or their legislative history that Congress intended to shield generic drug companies from state tort liability. As this Court said in *Levine*:

> If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history. But despite its 1976 enactment of an express pre-emption provision for medical devices, Congress has not enacted such a provision for prescription drugs. Its silence on this issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness. As

> Justice O'Connor explained in her opinion for a unanimous Court: "The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there [is] between them."

Levine, 129 S. Ct. at 1200 (quoting *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989)) (other citations omitted).

This analysis applies with full force to Petitioner's preemption argument. As the court of appeals observed:

> The Hatch-Waxman Amendments are part of this 70 year history and they do not explicitly preempt suits against generic manufacturers. Congress could have crafted a preemption provision for generic drugs in its 1984 amendments, having done so for medical devices less than 10 years earlier. It chose not to do that.

Pet. App. 9a.

CONCLUSION

The petition for a writ of certiorari should be denied.

April 21, 2010

Respectfully submitted,

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