No. 09- 09-993

In The
Supreme Court of the United States

PLIVA, INC.; TEVA PHARMACEUTICALS USA, INC.; UDL LABORATORIES, INC.,

Petitioners,

v.

GLADYS MENSING,

Respondent.

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

PETITION FOR WRIT OF CERTIORARI

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QUESTION PRESENTED

The Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Amendments"), which amended the federal Food, Drug, and Cosmetic Act ("FDCA") allow for the approval of low-cost generic versions of previously approved drug products through an abbreviated application process.

The question presented is:

Whether the Eighth Circuit abrogated the Hatch-Waxman Amendments by allowing state tort liability for failure to warn in direct contravention of the Act's requirement that a generic drug's labeling be the same as the FDA-approved labeling for the listed (or branded) drug.

LIST OF PARTIES

Pursuant to Rule 14.1(b), the following list identifies all the parties to the appellate proceeding in the Eighth Circuit Court of Appeals, whose judgment is sought to be reviewed:

A. Defendants-Appellees

PLIVA, Inc.
Teva Pharmaceuticals USA, Inc.
UDL Laboratories, Inc.
Actavis Elizabeth, LLC
Wyeth, LLC

B. Plaintiff-Appellant

Gladys Mensing

CORPORATE DISCLOSURE STATEMENTS

As required by the Court's Rule 29.6:

Petitioner Pliva, Inc., hereby discloses that (1) its parent companies are: Property Asset Management USA, Incorporated, Barr Laboratories, Inc., Barr Pharmaceuticals, LLC, Teva Pharmaceuticals USA, Inc., Orvet UK, Teva Pharmaceutical Holdings Cooperatieve U.A., Teva Pharmaceuticals Europe B.V., and Teva Pharmaceutical Industries Ltd.; and (2) Teva Pharmaceutical Industries Ltd., an Israeli corporation, is the only publicly-traded company that owns – through the aforementioned chain – 10% or more of Pliva, Inc.

Petitioner Teva Pharmaceuticals USA, Inc. hereby discloses that (1) its parent companies are: Orvet UK, Teva Pharmaceutical Holdings Cooperatieve U.A., Teva Pharmaceuticals Europe B.V., and Teva Pharmaceutical Industries Ltd.; and (2) Teva Pharmaceutical Industries Ltd., an Israeli corporation, is the only publicly-traded company that owns – through the aforementioned chain – 10% or more of Teva Pharmaceuticals USA, Inc.

Petitioner UDL Laboratories, Inc. hereby discloses that it is a wholly owned subsidiary of Mylan Inc., which is a publicly-traded company. Mylan Inc. is the only publicly-traded company that owns 10% or more of UDL Laboratories, Inc.

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The decision of the Eighth Circuit Court of Appeals is reported at 588 F.3d 603 (8th Cir. 2009) and reprinted in the Appendix ("App.") at 1a-23a. The district court's decisions finding that the claims against the generic drug manufacturers were preempted are reprinted at App. 24a-48a and 49a-63a.

JURISDICTION

The Eighth Circuit Court of Appeals rendered its decision on November 27, 2009, App. 1a-23a. This Court has jurisdiction under 28 U.S.C. §1254.

STATUTORY PROVISIONS INVOLVED

The pertinent constitutional, statutory, and regulatory provisions are set forth in the Appendix, App. 64a-113a.

INTRODUCTION

In 1984, as the cost of prescription drugs was spiraling out of control and many individuals were faced with choosing between their medications and the basic necessities of life, Congress enacted the Hatch-Waxman Amendments to allow the federal Food and Drug Administration ("FDA") to approve generic versions of approved drugs under an abbreviated application process. Before Congress passed the Hatch-Waxman Amendments, the approval and post-marketing requirements of the FDCA and FDA's implementing regulations

applied equally to all drugs – branded and generic. The Hatch-Waxman Amendments, however, exempt generic drug manufacturers from the requirement of conducting the clinical trials previously necessary for approval of their drug products. Instead, FDA is permitted to approve an abbreviated new drug application ("ANDA") showing that the generic product is bioequivalent to a previously approved branded drug (the "listed drug"). *See* 21 U.S.C. §355(j), App. 65a. Before FDA may approve an ANDA, a generic drug manufacturer also must demonstrate that the labeling proposed for the generic drug is the same as the labeling approved for the listed drug. *See* 21 U.S.C. §355(j)(2)(A)(v), App. 67a.

As a result, virtually all data regarding the safety and efficacy of drug products, including pre-approval study data and post-approval adverse event data, lies in the hands of the listed drug manufacturer and FDA. At the time of approval, generic drug manufacturers possess only the data from the bioequivalence studies they must conduct to obtain approval for their products. Generic drug manufacturers do not have the clinical safety and efficacy data upon which FDA relies in approving the generic drug or the detailed post-marketing adverse event data received by the listed drug manufacturer and FDA before the drug's eligibility for generic versions.

While recognizing that generic drug manufacturers are not required to undertake expensive, time-consuming clinical studies to obtain approval to market their drugs, the Eighth Circuit's decision requires them to obtain the data,

post-approval, necessary to provide the scientific substantiation to support changes in the risk-benefit analysis reflected in a drug's labeling. That decision, if allowed to stand, strips the Hatch-Waxman Amendments of their salutary purpose of providing American consumers and state and federal governments with low-cost generic drugs, for it essentially requires generic drug manufacturers to generate the scientific data necessary to craft their own labeling. It also subjects generic drug manufacturers with products already on the market to absolute liability under state law for complying with the federal law that governs them.

The Eighth Circuit's solution to the dilemma faced by generic drug manufacturers – to simply stop selling the products – highlights the conflict between state-law tort duties and federal-law requirements governing generic drug manufacturers. If the impact of imposing liability under state law is the withdrawal of generic drugs from the market, Congress's principal goal in enacting Hatch-Waxman will be thwarted.

The Court of Appeals' heavy reliance on this Court's decision in *Wyeth v. Levine*, 555 U.S. ---, 129 S. Ct. 1187 (2009), was misplaced. That decision, holding that the FDCA does not preempt state law failure-to-warn claims against brand manufacturers, did not address the Hatch-Waxman Amendments or the critical legal and factual differences between generic drug manufacturers and manufacturers of listed drugs.

In partially abrogating provisions of the Hatch-Waxman Amendments and FDA regulations, the Eighth Circuit Court of Appeals has created a question of first impression for this Court. The Court should grant review here to remove the obstacle created by the decision below to the accomplishment of Congress's objective of making low-cost generic drugs available to the consuming public and to clarify the scope of its decision in *Wyeth v. Levine*.[1]

STATEMENT OF THE CASE

A. REGULATORY BACKGROUND

1. The Hatch-Waxman Amendments

In 1984, Congress enacted the Hatch-Waxman Amendments to the FDCA to address the ever-increasing need of the American people and

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[1] The Fifth Circuit Court of Appeals also has held that claims against generic drug manufacturers are not preempted. *See Demahy v. Actavis, Inc.*, --- F.3d ---, 2010 U.S. Dist. LEXIS 430 (5th Cir. 2010). In addition, three cases raising the issue are pending in the Sixth Circuit Court of Appeals, *Morris v. Wyeth, Inc., et al.*, 6th Cir. Case No. 09-5509; *Smith v. Wyeth, Inc., et al.*, 6th Cir. Case No. 09-5460; and *Wilson v. Pliva, Inc., et al.*, 6th Cir. Case No. 09-5466; another is pending in the Fifth Circuit, *Pustejovsky v. Pliva, Inc.*, 5th Cir. Case No. 09-10983, and yet another is pending in the Ninth Circuit, *Gaeta v. Perrigo Pharmaceuticals Company*, 9th Cir. Case No. 09-15001. To Petitioners' knowledge no case has reached the highest court of any state.

state and federal governments for low-cost drugs.[2] The Amendments codified the procedures FDA used to approve duplicate versions of pre-1962 drugs, for application to duplicate (generic) versions of post-1962 drugs.

Under the Amendments, a generic drug manufacturer is exempt from the requirement of conducting the onerous testing and reporting requirements imposed on branded drug manufacturers. Instead, a generic drug manufacturer may submit an ANDA, showing (with exceptions not pertinent here) that the generic drug is the same as a listed drug with respect to active ingredient(s), route of administration, dosage form, strength, and conditions of use recommended in the labeling. *See* 21 U.S.C. §355(j)(2), App. 65a-67a; 21 C.F.R. §314.92(a)(1), App. 83a. The generic drug manufacturer also must show that, with certain exceptions, the labeling of the generic drug is the same as the listed drug's label. *See* 21 U.S.C. §355(j)(2)(A)(v), App. 67a; 21 C.F.R. §314.94(a)(8), App. 86a-87a.

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[2] The overriding purpose of the Amendments was to increase the availability of low-cost generic drugs. *See* "P.L. 98-417, Drug Price Competition and Patent Term Restoration Act," H.R. Rep. No. 857(I), 98th Cong., 2d Sess. (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, App. 122a; New Drug Application: Hearings on H.R. 3605 Before the Subcomm. On Health and the Environment of the House Comm. on Energy and Commerce, 98th Cong., 1st Sess. (1983), App. 114a; Drug Price Competition and Patent Term Restoration Act of 1984, Committee Notes, 130 Cong. Rec. 24416, H.R. 3605 (Sept. 6, 1984), App. 136a; Drug Price Competition and Patent Term Restoration Act, Committee Notes, 130 Cong. Rec. 24970, S. 1538 (Sept. 12, 1984).

2. Labeling and Warnings for ANDA Drugs

Because generic drugs are approved based on the safety and efficacy data of the listed drug, the FDCA and FDA's regulations are specific as to the differences between the listed drug and the generic drug that are acceptable. *See* 21 U.S.C. §355(j), App. 65a; 21 C.F.R. §314.94, App. 84a. As part of an ANDA, a generic drug manufacturer must submit "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug ...except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers ...." 21 U.S.C. §355(j)(2)(A)(v), App. 67a. FDA's implementing regulations require the generic drug manufacturer to submit copies of the proposed label, as well as "[a] statement that the applicant's proposed labeling ...is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section." 21 C.F.R. §314.94(a)(8)(iii), App. 86a. Paragraph (a)(8)(iv) of §314.94 identifies as acceptable:

> [D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent

> or accorded exclusivity under section 505(j)(4)(D) of the act.

21 C.F.R. §314.94(a)(8)(iv), App. 86a-87a. Additional warnings are not included in that list. In fact, additional or heightened warnings are specifically excluded from the differences FDA deems acceptable. *See* Abbreviated New Drug Application Regulations – Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989).

More than one comment to FDA's proposed regulations implementing the labeling requirements of the Hatch-Waxman Amendments addressed whether an ANDA manufacturer could include warnings or precautions in addition to those on the listed drug's label. FDA rejected each suggestion. One comment, addressed specifically to the labeling requirements of 21 C.F.R. §314.94(a)(8), proposed that the labeling provisions be "revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions and other safety-related information." FDA flatly disagreed stating that the generic drug's labeling "must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval." Abbreviated New Drug Application Regulations – Final Rule ("ANDA Regs"), 57 Fed. Reg. 17950, 17961 (April 28, 1992) (codified at 21 C.F.R. Part 314), App. 108a-109a. FDA noted that "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Id.*, App. 109a.

Another comment recommended that "FDA accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label, provided that such information was not indicative of diminished safety or effectiveness of the generic drug product." *Id.* at 17953, App. 103a-104a. FDA again disagreed and admonished that "section 505(j)(2)(A)(v) and (j)(3)(G) of the act requires that the applicant's proposed labeling be the same as that of the reference listed drug" and that "the exceptions in section 505(j)(2)(A)(v) and (j)(3)(G) of the act are limited." *Id.*

FDA also disagreed with a suggestion that FDA accept petitions under section 355(j)(2)(C) to submit an ANDA for a product whose labeling differs from the listed drug by being "'more clear or offer better directions regarding how the drug should be taken.'" *Id.* at 17957, App. 105a-106a. FDA unequivocally advised that "[l]abeling differences [] are not proper subjects for a suitability petition" and reminded "applicants that the labeling for an ANDA product must be the same as the labeling for the listed drug product except for differences due to different manufacturers, exclusivity, etc. (*See* 21 U.S.C. 355(j)(3)(G).)" *Id.*

FDA regulations also demonstrate that generic drug manufacturers may not change labeling language pre- or post-approval where there has been no change to the labeling of the listed drug. In fact, FDA's approval of an ANDA may be withdrawn if FDA finds that the labeling for the generic drug "is no longer consistent with that for the listed drug referred to in the [ANDA]." 21

C.F.R. §314.150(b)(10), App. 92a. *See also* ANDA Regs, 57 Fed. Reg. at 17970 (agreeing with comment that provision should be added to withdraw ANDA where ANDA holder fails to modify label to match changes to listed drug's labeling), App. 110a-111a; 21 C.F.R. §314.127 (providing that ANDA will not be approved if information submitted is insufficient to show labeling proposed is same as labeling approved for listed drug), App. 91a.

In addition, an FDA rule regarding the content and format of drug labeling, published in January 2006, specifically recognized that generic drug labeling, both before and after approval, must remain the same as the labeling of the listed drug. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products – Final Rule, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006) (advising that implementation plan for revised labeling for products approved or submitted for approval under an ANDA depends on the labeling of the listed drug referenced in the ANDA). *See also id.* at 3961 ("Revised labeling for ANDA products depends on the labeling for the reference listed drug"). In responding to comments that a generic manufacturer be permitted to use the new format even though the listed drug used the old format, FDA reiterated that, under the Act and its regulations, "the labeling of a drug product submitted for approval under an ANDA must be the same as the labeling of the listed drug referenced in the ANDA." *Id.* at 3963.

A similar discussion appeared in connection with FDA's proposed rule in 2000 to revise the

content and format of prescription drug labeling. Discussing the application of the new rule to generic drugs, FDA noted that and format of drug labeling regarding the implementation of the proposed regulations to products approved under an ANDA. Specifically, FDA stated that

> the labeling of a drug product submitted for approval under an ANDA must be the same as the labeling of the listed drug referenced in the ANDA .... Thus, whether a prescription drug product that was approved under an ANDA before the effective date of the final rule, or that is submitted for approval under an ANDA after the effective date of the final rule, will be required to have labeling that complies with the final rule will depend on the status of the labeling of the listed drug referenced in the ANDA. Where a reference listed product's labeling conforms to the requirements of the final rule ...the generic product that references the listed drug in its ANDA would be required to have labeling that is the same as the listed product and would therefore be required to comply with the final rule. On the other hand, where a reference listed product's labeling does not conform to the requirements of the final rule ... a generic product that references the product in its ANDA would not be

> required to have labeling that complies with the final rule.

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels – Proposed Rule, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000).

Similarly, in its Guidance for Industry regarding Changes to an Approved NDA or ANDA, FDA expressly cautions that "[a]ll labeling changes for ANDA drug products must be consistent with section 505(j) of the Act," *i.e.*, the labeling changes must be the "same as" that of the listed drug. *See* Guidance for Industry, Changes to an Approved NDA or ANDA, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 2004 ("ANDA Guidance"), p. 24. *See also* Guidance for Industry, Revising ANDA Labeling Following Revision of the RLD Labeling, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, May 2000 (stating that generic drug products "must have the same labeling as the [listed drug]"), App. 149a.

In short, the requirement that a generic drug's labeling must be the "same as" that of the listed drug, both before and after approval, is repeated again and again throughout every document – the Hatch-Waxman provision, FDA regulations, FDA Federal Register documents, FDA guidance documents – that addresses the issue since the ANDA provisions were enacted. By

contrast, no statutory or regulatory provision authorizes a generic manufacturer to change label language where there has been no change to the labeling of the listed drug.

3. Procedures for Changes to Label Warnings

Once an application is approved, the drug can be marketed only under the provisions of the application as approved – including the approved labeling language. As a result, if the manufacturer wants to make any change to an approved application, it is required to submit a supplemental application that is subject to the same review and approval process as the initial application. *See* 21 U.S.C. §301 *et seq.*; Drugs; Statement of Ingredients; Prescription-Drug Advertisements, 28 Fed. Reg. 6375, 6380 (June 20, 1963) (regulation regarding submission of supplemental applications for NDAs "for any change beyond the variations provided for in the application ... that may alter the conditions of use, the labeling ....").

Since 1965, FDA, using its enforcement authority, has permitted branded drug manufacturers to revise product labeling to "add" or "strengthen" a "contraindication, warning, precaution, or adverse reaction" without prior FDA approval under the "changes being effected" ("CBE") provision of FDA's regulations. *See* Supplemental New-Drug Applications ("1965 Regulation"), 30 Fed. Reg. 993, 993- 94 (Jan. 30, 1965); *see also* 21 C.F.R. §314.70(c)(6)(iii)(A). CBE supplements to "add" or "strengthen" warnings are permitted only where the NDA holder becomes

aware of newly discovered safety information and there is sufficient evidence of a causal association with the drug. *See* New Drug and Antibiotic Regulation – Proposed Rule ("1982 Proposed Rule"), 47 Fed. Reg. 46622 (Oct. 19, 1982); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices – Proposed Rule ("2008 Proposed Rule"), 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008). FDA explained that "some information, although still the subject of a supplement, would no longer require agency preclearance. These supplements would describe changes placed into effect to correct concerns about newly discovered risks from the use of the drug." 1982 Proposed Rule, 47 Fed. Reg. at 46623. However, FDA stated, in both the proposed and final rule, that the CBE procedure was a limited exception to the requirement of prior approval for labeling changes. *Id.* at 46635; New Drug and Antibiotic Regulation – Final Rule, 50 Fed. Reg. 7452 (Feb. 22, 1985). CBE supplements must be submitted to FDA for ultimate approval. *See* 21 C.F.R. §314.70(c), App. 73a. FDA can accept, modify, or reject any change made via a CBE supplement and may order the manufacturer to cease distribution of the drug. *Id.*, App. 80a.

When FDA adopted the regulations implementing Hatch-Waxman, FDA included a provision that requires generic drug manufacturers to "comply with the requirements of §§314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application." 21 C.F.R. §314.97, App. 89a. However, in doing so, FDA made clear that generic manufacturers could not use the CBE

provisions to alter labeling that would make the generic drug's labeling different from or inconsistent with the branded drug's labeling.

> Section 314.70 -- Supplements and Other Changes to an Approved Application
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> FDA received no comments on this provision, but has amended the provision to adopt references to statutory, rather than regulatory, provisions or to explain what information should be provided. However, the agency wishes to remind ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug.

ANDA Regs, 57 Fed. Reg. 17955, App. 105a. "Paragraph 4" referred to by FDA specifically rejected the suggestion that ANDA manufacturers be permitted to alter warnings. *See id.* at 17953, App.103a.

FDA reaffirmed in a proposed rule issued on January 16, 2008, that §314.70 does not permit generic drug manufacturers to change their labeling where there has been no change to the branded drug's labeling. *See* 2008 Proposed Rule, 73 Fed. Reg. 2848. Section 314.70 was amended to codify FDA's longstanding view on when the labeling of a drug approved under an NDA may be changed in advance of agency approval. *Id.* at 2849. FDA explained that the amendment applies

only to supplemental NDAs because "CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic manufacturer is required to conform to the approved labeling for the listed drug." *Id.*, n.1.[3]

FDA's regulations also permit changes in approved applications through a prior approval supplement. *See* 21 C.F.R. §314.70(b), Appx. 73a. However, the prior approval supplement provision also does not provide a mechanism for a generic drug manufacturer to change its labeling where there has been no change to the listed drug's labeling. *See* 21 C.F.R. §314.94, Appx. 84a. *See also* Guidance for Industry, Providing Regulatory Submissions in Electronic Format — ANDAs, Center for Drug Evaluation and Research, June 2002, ("Electronic Format Guidance"), p. 6 (applying to "electronic submission of abbreviated new drug applications (ANDAs) and *supplements* and *amendments* to those applications" and advising ANDA holders that "you must provide a statement that your proposed labeling is the same as the labeling of the reference listed drug except for differences explained in the annotated comparison of labeling (21 C.F.R. §314.94(a)(8)(iii))"). Under FDA's regulations, every supplemental ANDA a generic drug manufacturer submits involving labeling must include a statement that the labeling being submitted for the

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[3]FDA issued its Final Rule on August 22, 2008. See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices – Final Rule, 73 Fed. Reg. 49603 (Aug. 22, 2008).

generic drug "is the same as" the then-current approved labeling for the branded drug.

B. PROCEEDINGS BELOW

1. The District Court Proceedings

Respondent's state-law claims against Petitioners were premised on an alleged failure to adequately warn of the purported risks of long-term metoclopramide use. The district court had jurisdiction under 28 U.S.C. §1332.

PLIVA and Actavis sought dismissal of Respondent's claims on the ground that the Hatch-Waxman Amendments preempted them. After reviewing the FDCA, the Hatch-Waxman Amendments, the legislative history, and FDA's regulations, documents, and responses to comments during rulemaking, the district court concluded that "a generic drug manufacturer cannot unilaterally change its label without prior FDA approval." App. 45a. The court held that a unilateral change would directly conflict with the federal law requiring that their labels be the same as those of the listed drugs and that, "under these circumstances, it would be impossible for [the generic manufacturers] to abide by both state and federal laws." App. 45a. The court ruled that

> [i]f Plaintiff's claims were not preempted, [the generic defendants] would be forced to choose between complying with the federal law while being exposed to state tort liability, or

> unilaterally adding a heightened warning to their labels at the risk of exposing themselves to federal liability. This conflict would stand as an obstacle to the accomplishment and full purposes and objectives of the Hatch-Waxman Act, a key purpose of which is to increase the availability of low-cost generic drugs and to relax the generic approval and labeling process.

App. 45-46a.

The district court also rejected the argument that the generic defendants could have sought to strengthen their warnings through the prior approval supplement process. App. 46a. The district court noted that a generic drug manufacturer may seek to add safety information to drug labeling only by providing information scientifically substantiating the change, which generic manufacturers do not possess. The court concluded that the outcome of any such request would be mere speculation. App. 46a.

Finally, the district court recognized that generic drug manufacturers are not permitted to send "Dear Doctor" letters as a means of providing additional or different warnings. App. 47a. Again, the district court concluded that enforcing a state-law duty that would require generic drug manufacturers to send "Dear Doctor" letters would directly conflict with the statutory scheme. App. 47a. Further, the court concluded that "speculation over what the FDA might have done if [the generic defendants] had requested such a letter would

stand as an obstacle to the accomplishment and execution of the full purposes of the Act." App. 47a.

Adhering to its ruling, the District Court subsequently granted motions to dismiss filed by the other generic drug manufacturers named in the suit. App. 49a.

2. The Appeal to the Eighth Circuit Court of Appeals

The Eighth Circuit reversed. The court concluded that generic drug manufacturers are subject to the requirement in 21 C.F.R. §201.57(e) that their labeling "shall be revised as soon as there is reasonable evidence of an association of a serious hazard with a drug." App. 11a. According to the court, "§201.57(e) does not permit generic manufacturers passively to accept the inadequacy of their drug's label as they market and profit from it." App. 12a.

Relying on FDA's responses to comments during the rulemaking stage, the court determined that, at a minimum, generic drug manufacturers should alert FDA to any new safety hazard associated with their products. App. 12a. As a result, the court ruled that it was not impossible for generic drug manufacturers to comply with both federal and state law because no provision in the FDCA or the Hatch-Waxman Amendments forbids them from "proposing a label change through the prior approval process," App. 13a, or suggesting FDA send out warning letters to healthcare professionals, App. 14a.

The court also held that allowing state-law failure-to-warn claims to proceed will not obstruct Congress's purposes in enacting Hatch-Waxman. App. 18a. Although acknowledging the primary purpose of the Amendments was to provide for low-cost generic drugs and acknowledging that labeling changes must be scientifically substantiated, the court concluded that generic drug manufacturers need not acquire information to support label changes through their own clinical studies, but, instead, could merely reference studies published elsewhere or rely on reports of adverse drug experiences they received. App. 18a.

REASONS FOR GRANTING THE PETITION

A. THE DECISION BELOW IS UNREALISTIC AND DEFEATS THE PURPOSE OF THE HATCH-WAXMAN AMENDMENTS

Due to the overwhelming evidence in the legislative history, FDA regulations, Federal Register documents, and other FDA documents, the Eighth Circuit acknowledged that "generic labels must be substantively identical to the name brand label even after they enter the market." App. 10a. However, the court then skirted the preemptive effect of the requirement that generic drug labeling be the "same as" the labeling of the listed drug by concluding that generic drug manufacturers can comply with both federal and state law by "proposing a label change through the prior approval process," or proposing that FDA send a "Dear Doctor" letter to provide additional or different warnings. App. 14a. That conclusion is

inadequate as a matter of law, is based on view of real-world facts that is wrong, and threatens to frustrate the fundamental purpose of the Hatch-Waxman Amendments.

The conclusion is inadequate as a matter of law because the court gave no support for the idea that "proposing a label change" would satisfy any state-imposed duty of providing adequate warnings for the product. A plaintiff claiming to have been harmed due to inadequate warnings will contend (with obvious force) that a manufacturer who had proposed a label change to clarify or enhance warnings should have stopped selling the product pending FDA's review of the proposal – a result that would take the generic drug off the market, which in some instances may be on the day after the generic drug was first approved.

Furthermore, the Eighth Circuit's theoretical mechanism of "proposing a label change" directly implicates the obstruction prong of implied preemption. The Eighth Circuit acknowledged that the primary purpose of Hatch-Waxman was to provide for low-cost generic drugs and that labeling changes must be scientifically substantiated. The reality is that, to obtain the scientific substantiation required to support a proposed label change, a generic manufacturer would essentially be required, post-approval, to conduct the clinical studies that Congress exempted them from conducting.[4] The Eighth Circuit thought that

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[4] Generic companies are actually required only to establish that the generic drug is bioequivalent to its branded counterpart. *See* 21 U.S.C. §355(j).

generic drug manufacturers could merely reference studies published elsewhere or rely on adverse event reports they received to support a label change, but that conclusion obviously was based on the court's assumption that FDA did no more than rely on a few studies published elsewhere when it mandated a change to metoclopramide labeling, the product at issue in this case, in early 2009. The court did not consider the fact that FDA has in its possession all the original clinical data, all the world literature regarding metoclopramide, and 29 years of data from the adverse events reported to it from all sources since the listed drug was approved. Nor did the Eighth Circuit have before it certain facts regarding FDA's review of metoclopramide that took place in the years before FDA issued the required label change. In addition, the court's conclusion did not acknowledge that, even after generic versions of products enter the market, the majority of adverse events continue to be reported directly to FDA or the branded drug manufacturer.

Unlike the branded manufacturer and FDA, generic manufacturers never accumulate the universe of data regarding a particular drug product. They cannot merely review literature or a handful of adverse event reports and discern a need for strengthened warnings. That would require a knowledge base equal to that of the branded drug manufacturer and FDA – a knowledge base that can be acquired only at a cost that would bring the generic drug price up to the listed drug's price.

FDA has acknowledged the fundamental differences in the knowledge base of the branded manufacturer and the generic manufacturer by

imposing different post-marketing surveillance responsibilities on them. Following a branded drug's introduction to market, its manufacturer must conduct post-marketing surveillance that encompasses review and analysis of all reported adverse events – an analysis that is conducted against the backdrop of knowledge obtained through the clinical trials conducted to obtain approval in the first place. *See* 21 C.F.R. §314.80, App. 81a. In contrast, generic manufacturers, who do not have the underlying scientific data to perform a meaningful analysis of reported adverse events, are required only to report to FDA those adverse events reported to them. *See* 21 C.F.R. §314.98, App. 90a.

Finally, the decision below places generic drug manufacturers in the untenable position of having to amass that knowledge base by the day after their drugs are approved. Under the Court of Appeals' view, the day after its ANDA is approved, a generic drug manufacturer becomes responsible under state law for information Congress exempted it from acquiring the day before. That cannot possibly be what Congress intended in the Hatch-Waxman Amendments.

B. THE COURT SHOULD GRANT REVIEW BECAUSE THE EIGHTH CIRCUIT'S APPLICATION OF THIS COURT'S DECISION IN *WYETH V. LEVINE* IS OVERLY-BROAD

The Eighth Circuit relied heavily for its result on this Court's decision in *Wyeth v. Levine.* That case, however, did not involve the statutory

provisions applicable to generic drugs and thus the Court did not consider the congressional objectives of the Hatch-Waxman Amendments or decide whether state-law claims against generic drug manufacturers are preempted. *Levine* stressed a branded drug manufacturer's ability to change labeling prior to obtaining FDA approval through the CBE provisions, but the district court in this case held that those provisions are not available to a generic manufacturer and the Court of Appeals pretermitted that issue by holding that a generic manufacturer could, in any case, propose a label change to the FDA.

The Court of Appeals found it significant that the Court in *Levine* ruled that "manufacturers, not the FDA, bear primary responsibility for their drug labeling." *Levine*, 129 S. Ct. at 1202. But this Court was not considering the statutes and regulations governing generic drugs, under which manufacturers are required only to assure that their drugs are bioequivalent to the branded drugs and to adopt the labeling, verbatim (with exceptions not applicable here), of the branded drug. Under those statutes and regulations, the generic manufacturer fulfills its responsibility for its drug labeling by ensuring that it remains the same as the labeling of the branded drug.

Moreover, in *Levine* the branded manufacturer argued that state tort claims "interfere with 'Congress's purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives.'" *Id.* at 1199. Here, however, the question is whether state tort law interferes with Congress's

purpose of making low-cost generic drugs available to the public – a question not raised or addressed in *Levine*.

In short, both the "impossibility preemption" and the "obstacle preemption" issues in *Levine* and in this case are markedly different, and the court below erred in giving *Levine* virtually controlling effect here.[5] If *Levine* was dispositive of the issue, preemption in pharmaceutical litigation would have been laid to rest – fully and completely. Yet, this Court recognized that its decision in *Levine* did not completely foreclose preemption of claims even against manufacturers of branded pharmaceutical products. As Justice Stevens stated, "we recognize that some state-law claims might well frustrate the achievement of congressional objectives...." *Levine, Id.* at 1204. Accordingly, review is warranted to clarify the breadth of *Levine* and to guide the lower courts in cases against generic drug manufacturers.

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[5] Other courts also have read *Levine* broadly. *See, e.g., Demahy v. Wyeth*, 2010 U.S. App. LEXIS 430 (5th Cir., Jan. 8, 2010); *Kellogg v. Wyeth*, 612 F. Supp. 2d 421 (D. Vt., 2009); *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla., 2009); and *Stacel v. Teva Pharms.*, USA, 2009 U.S. Dist. LEXIS 21079 (N.D. Ill., Mar. 16, 2009).

Two other courts, however, have concluded that *Levine* does not govern in cases involving generic drug manufacturers. *See Gaeta v. Perrigo Pharms. Co.*, 2009 U.S. Dist. LEXIS 115752 (N.D. Cal., Nov. 24, 2009) (holding state law preempted); *Morris v. Wyeth, Inc.*, 582 F. Supp. 2d 861 (W.D. Ky., Oct. 24, 2008) (same), motion for reconsideration denied Order, Case No. 3:07-CV-378-R, Feb. 20, 2009, Notice regarding *Levine* March 5, 2009 (ruling that *Levine* did not alter the conclusion).

CONCLUSION

The Eighth Circuit's decision essentially returns the regulation of generic drugs to that which existed before Hatch-Waxman was enacted. The Court should grant this petition for a writ of certiorari to correct the Eighth Circuit's error.

Respectfully submitted,

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