No. 09-091039 FEB 25 2010

In The
Supreme Court of the United States

ACTAVIS ELIZABETH, LLC,

Petitioner,

v.

GLADYS MENSING,

Respondent.

On Petition For A 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" to the Food, Drug and Cosmetic Act (FDCA)) and its implementing regulations require a generic drug manufacturer to maintain the labeling for a generic the "same as" the labeling for the "brand" or "listed" drug that is its bioequivalent. *See* 21 U.S.C. § 355(j)(2)(A)(iv-v); 21 C.F.R. § 314.94(a)(8).

The question presented is whether the Eighth Circuit Court of Appeals misinterpreted that requirement and the doctrine of conflict preemption when it concluded that generic drug manufacturers could be held liable under state law for failing to strengthen the warnings in the labeling for the generic drug.

LIST OF PARTIES

Pursuant to Rule 14.1(b), the following list identifies parties to the appellate proceeding in the Eighth Circuit Court of Appeals:

A. ***Petitioners****

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

B. ***Respondent***

Gladys Mensing

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* PLIVA, Inc., Teva Pharmaceuticals USA, Inc., and UDL Laboratories, Inc. have filed a separate Petition for Writ of Certiorari.

CORPORATE DISCLOSURE STATEMENT

Actavis Elizabeth, LLC is neither a subsidiary nor affiliate of any publicly owned corporation. Actavis Elizabeth, LLC is not publicly traded.

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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 1-25. The district court's decisions finding that the claims against the generic drug manufacturers were preempted are available at 562 F. Supp. 2d 1056 (D. Minn. 2008), and No. 07-3919 (DWF/SRN), 2008 WL 4724286 (D. Minn. Oct. 30, 2008). The decisions are reprinted at App. 26-49 and 50-64.

JURISDICTION

The Eighth Circuit Court of Appeals rendered its decision on November 27, 2009. (App. 2.) This Court has jurisdiction under 28 U.S.C. § 1254.

STATUTORY PROVISIONS INVOLVED

The pertinent statutory and regulatory provisions are set forth at App. 65-144.

INTRODUCTION

Invoking this Court's decision in *Wyeth v. Levine*, ___ U.S. ___, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009) no fewer than eleven times, the Eighth Circuit Court of Appeals has presented generic drug manufacturers with a stark choice – either be subject to state law

claims that their drug labeling is "inadequate," or "simply stop[ ] selling the product." (App. 18-19.) Given that federal law requires generic drug manufacturers to maintain the labeling of their product the "same as" the brand drug that is its bioequivalent, withdrawal from the market is the only realistic choice. That "choice" threatens to dismantle the generic drug industry contemplated and initiated by the Hatch-Waxman Amendments – an industry that currently produces seven of every ten drug prescriptions filled in the United States[1] and, according to the Commissioner of the FDA, has saved consumers nearly $750 billion over the last decade.[2]

This appeal presents a question of first impression on the proper interpretation of the Hatch-Waxman Amendments and their implementing regulations: Does the duty imposed upon generic drug manufacturers to maintain "the same" labeling as the bioequivalent brand drug conflict with state law duties imposed upon all drug manufacturers to maintain "adequate" warnings and directions for their products? The Eighth Circuit ignored the first prong of that question. It concluded that under this Court's application of conflict preemption in *Wyeth v. Levine*, it did not have to determine what duty federal

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[1] The statistic appears at App. 9, citing Susan Okie, *Multinational Medicines – Ensuring Drug Quality in an Era of Global Manufacturing*, 361 NEW ENG. J. MED. 737, 738 (Aug. 2009).

[2] Natasha Singer, *Generics Face Longer Wait for Approval*, N.Y. TIMES, Feb. 19, 2010, at B3 (quoting FDA Commissioner Margaret A. Hamburg).

law imposes on generic manufacturers. The only question presented was: "Does federal law *forbid* them from taking steps to warn their customers?" (App. 16, emphasis added.) Absent any such specific federal prohibition, the Eighth Circuit concluded, there could be no preemption; if the generic drug manufacturers "did not believe" that they could comply with both state and federal requirements, "they could have simply stopped selling the product." (App. 18-19.) That is a startling assessment of this Court's application of the doctrine of conflict preemption in *Wyeth v. Levine.* The Eighth Circuit's implicit assumption that the Hatch-Waxman Amendments intended to allow states to force generic drug manufacturers out of business is, in fact, the polar opposite of Congress's aim.

This Court held in *Wyeth v. Levine* that: 1) the manufacturer of a brand drug could be liable under state law for marketing a product with inadequate warnings because the Food, Drug and Cosmetic Act (FDCA) and its implementing regulations allow a brand drug manufacturer with "newly acquired information" to strengthen its warnings without the FDA's prior approval, 129 S.Ct. at 1209-10; and 2) the trial court record contained evidence indicating that Wyeth had such information, *id.* at 1210. The Eighth Circuit concluded that since the Hatch-Waxman Amendments are part of the FDCA, and *Wyeth* interprets the FDCA, *Wyeth* precluded any conflict preemption argument presented by generic drug manufacturers. (App. 20-21.)

Shortly after the Eighth Circuit decision issued, it was followed by the Fifth Circuit.[3] The same question is currently pending in the Sixth Circuit Court of Appeals.[4] Generic drug manufacturers who "believe" – and rightly so – that federal law prohibits them from making unilateral labeling changes will have little choice but to "simply stop[ ] selling" generic versions of drugs with a past, present, or any whiff of future, litigation history. The prompt resolution of the correct interpretation of the Hatch-Waxman Amendments and their implementing regulations is thus critical to the continued viability of the generic drug industry in the United States.

STATEMENT OF THE CASE

Respondent filed this action in the United States District Court for the District of Minnesota against Petitioner Actavis Elizabeth, LLC ("Actavis"), which manufactures a generic drug (metoclopramide) prescribed for the treatment of diabetic gastroparesis and gastric reflux disease. Respondent alleged that a specific warning in the labeling for metoclopramide explaining that patients may develop tardive dyskinesia (a movement disorder) was "inadequate" under

[3] *Demahy v. Actavis, Inc.*, ___ F.3d ___, 2010 WL 46513 (5th Cir. Jan. 8, 2010).

[4] *Morris v. Wyeth, Inc., et al.* (6th Cir. No. 09-5509); *Wilson v. PLIVA, Inc., et al.* (6th Cir. No. 09-5466); *Smith v. Wyeth, Inc., et al.* (6th Cir. No. 09-5460).

Minnesota law. It is undisputed that metoclopramide's labeling was (and is) identical to the labeling of Reglan®, the brand name drug for which metoclopramide is the bioequivalent. Reglan® was first approved by the FDA in 1980. It is the only drug currently approved for diabetic gastroparesis.

The district court concluded that any judgment against Actavis based upon a state law duty to strengthen the warnings for metoclopramide would conflict with federal law, which requires metoclopramide's labeling to be the "same as" Reglan®'s, and Petitioner's claims were therefore preempted. (App. 46-47.) The Eighth Circuit reversed. (App. 25.)

A. The Regulatory Framework of the Modern Generic Drug Industry Envisioned by Congress.

Up until the 1984 passage of the Hatch-Waxman Amendments, federal regulation of the domestic generic drug industry was uneven, erratic and outdated. Recognizing the acute need for a better system, Congress set about balancing the need "to make available more low cost generic drugs" against the need to encourage "pioneer" drug manufacturers to continue the expensive research and development process required to bring new drugs to market.[5] The

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[5] "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 ("H.R. Rep. No.

(Continued on following page)

result, the Drug Price Competition and Patent Term Restoration Act of 1984, H.R. Rep. No. 98-857(I) (App. 145-54), is comprised of two titles. Title I simplifies the approval process for generic drugs, while Title II extends patent protections for "pioneer" drugs.

The Abbreviated New Drug Application (ANDA) process created in Title I (21 U.S.C. § 355(j)) states that the FDA will approve a generic drug for marketing upon proof that the drug: (1) has the same active ingredients; (2) has the same route of administration, dosage form, and strength; (3) has the same labeling; and (4) is bioequivalent to, the pioneer drug. 21 U.S.C. § 355(j)(2)(A)(i-v) (App. 66-68.) By only requiring generics to prove "bioequivalency" and maintain the same label as the brand drug, Congress envisioned a relatively inexpensive and streamlined approval process. Additional clinical trials would not only be "unnecessary and wasteful because the drug has already been determined to be safe and effective," but would be "unethical," because it would require "that some sick patients take placebos and be denied treatment known to be effective." H.R. Rep. No. 98-857(I) (App. 151.)

857(I)") ("The purpose of . . . the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs. . . .") (App. 146); *Abbreviated New Drug Applications – Final Rule*, 57 Fed. Reg. 17950, 17951 (Apr. 28, 1992) (the Act achieved a "careful balance between promoting competition among brand-name and duplicate or 'generic' drugs and encouraging research and innovation.")

The FDA proceeded to draft regulations to implement Title I of the Hatch-Waxman Amendments, publishing its proposed rules in 1989. 54 Fed. Reg. 28872 (July 10, 1989). Those proposed rules, the FDA's responses to comments on the proposed rules, and the FDA's final rules set forth the requirement that the labeling for the generic drug be *identical* to that of the brand drug at all times, as well as the policy reasons supporting that requirement. On the one hand, *consistent* labeling promotes public confidence in generics: "Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Abbreviated New Drug Application Regulations – Final Rule*, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992). On the other hand, *in*consistent labeling – *i.e.,* allowing generic drug manufacturers to add to or strengthen the brand drug labeling – assumes that additional warnings are required to make the brand drug safe and effective. If that were so, then the drugs would not qualify for ANDA treatment under the Hatch-Waxman Amendments. *Id.* at 17953.

The identical-labeling requirement is not limited to ANDA applications for marketing approval. FDA regulations, guidance documents, and commentary require generic drug manufacturers to maintain the labeling of the generic the same as the brand drug after approval, including the required submission of a revised label once the generic manufacturer is informed by the FDA of a change to the labeling of

the brand drug.[6] Most recently, in its publication of a proposed revision to the "Changes Being Effected" ("CBE") regulation (the regulation this Court analyzed in *Wyeth v. Levine*), the FDA reminded drug manufacturers that "CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. § 355(j)." *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices – Proposed Rule*, 73 Fed. Reg. 2848, 2849 n.1 (Jan. 16, 2008).

B. Is Reflected in the Operations of Domestic Generic Drug Manufacturers.

The resources and capabilities of generic drug manufacturers reflect the streamlined regulatory system the FDA created to implement the Hatch-Waxman Amendments. Generic drug manufacturers do not have the resources to, and do not attempt to, conduct clinical trials or draft the labeling necessary for a drug to be deemed safe and effective when used in accordance with its approved labeling. Instead, they identify brand drugs that have been deemed

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[6] *See, e.g.*, Division of Generic Drugs, Policy and Procedure Guide, "Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling" 1 (Aug. 21, 1989); Center for Drug Evaluation and Research, Guidance Document, "Revising ANDA Labeling Following Revision of the RLD Labeling" 5-6 (May 2000); Center for Drug Evaluation and Research, Guidance Document, "Changes to an Approved NDA or ANDA" 20 (April 2004); 57 Fed. Reg. at 17961.

"safe and effective" when used according to their labeling for many years, and whose patent protections are about to expire. They analyze costs to replicate the drug, potential manufacturing difficulties, the company's ability to maintain sound quality control, and whether sufficient demand exists to sustain a generic competitor.

Once the decision is made to go forward, a generic drug manufacturer's FDA submission could not, and does not seek to, "re-prove" the drug's safety and efficacy when used with approved labeling. The focus of the ANDA is proof of bioequivalence – identity in active ingredients, route of administration, dosage form, strength, and labeling. Following the FDA's approval of an ANDA, generic drug manufacturers carry out the two categories of post-market duties imposed upon them by the FDA[7]: 1) they submit to the FDA reports on every complaint meeting the agency's reporting requirements, regardless of the source (consumers, pharmacies, or plaintiffs' attorneys), and "whether or not considered drug related"[8]; and 2) they monitor the labeling for the brand drug counterpart and propose a parallel change, through a CBE, *if and when* the brand drug label changes.

Even if they had the power and authority to make unilateral labeling changes to reflect "newly

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[7] *See* 21 C.F.R. § 314.98 (App. 144); 21 C.F.R. § 201.57. (App. 70.)

[8] 21 C.F.R. § 314.80(a) (App. 115.)

acquired information," *see Wyeth*, 129 S.Ct. at 1209-10, generic drug manufacturers would have no resources, clinical experience, or historical information upon which to make such a judgment. They neither conduct clinical trials, nor employ medical literature reviewers, and are not privy to the years of labeling discussions that occurred between the FDA and the brand drug manufacturer during the patent life of the drug. Lacking such context, any generic-proposed change would both lack scientific substantiation and risk rehashing already-settled label discussions.

REASONS FOR GRANTING THE WRIT

This Court should grant certiorari because the reasoning of the Eighth Circuit threatens to dismantle the very industry intended by Congress when it passed the Hatch-Waxman Amendments, and frustrate the congressional design of Hatch-Waxman to make low-cost generic drugs widely available. And it does so without any comprehensive analysis of the statute, its purpose, or its regulations, relying instead on broad statements from this Court's decision in *Wyeth v. Levine* that have no application to the distinctly different generic drug industry and market. This Court should grant certiorari because manufacturers like Actavis will be forced to cease manufacturing low-cost, competitive generic drugs if they are exposed to millions upon millions of dollars of tort

liability based on a state law "duty" that they cannot fulfill under the current federal regulatory scheme.

Instead of analyzing the purpose of the Hatch-Waxman Amendments, the Eighth Circuit concludes that they "must be considered part and parcel of the FDCA," and this Court's interpretation of the FDCA in *Wyeth v. Levine* is therefore controlling. (App. 20.) Based on that premise, the Eighth Circuit cites numerous broad statements in *Wyeth* to support its conclusion that preemption is inapplicable to a state law claim in a product liability action involving pharmaceuticals. They include *Wyeth*'s: 1) presumption against conflict preemption (App. 8); 2) recitation of the "central premise" of federal drug regulation as being "that the manufacturer bears responsibility for the content of its label at all times" (App. 9); 3) conclusion that the FDCA and implementing regulations charge manufacturers "both with crafting an adequate label and with ensuring that its warnings remain adequate" (App. 9); 4) reference to congressional "silence" in the FDCA on whether state-law suits pose an obstacle to its objectives (App. 8-9); and 5) dismissal of agency interpretations other than views that have been formalized in a promulgated regulation (App. 12 n.4.)

Nor is this wholesale adoption of *Wyeth* into the regulatory system for generic drugs limited to broad principles. The Eighth Circuit decision, for example, adopts *Wyeth*'s specific requirement of "clear evidence" that the FDA "would not have approved" a labeling change submitted by a drug manufacturer before a

state law claim can be preempted and applies it to generics. (App. 17.) But *Wyeth*'s "clear evidence" requirement makes no sense if generic drug manufacturers are only permitted to submit proposed labeling changes *after* a brand drug's label change has been approved by the FDA, and the submission must be identical to the approved change.

Equally misplaced are the Eighth Circuit's transplanted conclusions from *Wyeth* that the FDA is unlikely to threaten an enforcement action against a generic drug manufacturer that unilaterally enhances its label warnings (App. 17 n.6); that adverse experience reports provide sufficient information to trigger a duty for generic drug manufacturers to make unilateral labeling changes (App. 19-20); and that state law jury verdicts "motivat[e]" generic drug manufacturers to provide "adequate" warnings. (App. 20-21.) The FDA *would* pursue enforcement against a generic drug manufacturer that has violated the agency's policy decision to maintain *consistent* labeling of generics vis-à-vis brand drugs; generic drug manufacturers *do not* have the background clinical information or resources to analyze the significance of scattered adverse event reports; and state law jury verdicts would not change the structural and regulatory differences that require generic drug manufacturers to maintain their labeling the "same as" that of brand drugs. The *only* way a generic drug manufacturer could bring its labeling into compliance with the alleged state law duty would be to change

the very labeling that federal law says must be *identical* to the brand drug.

Finally the Eighth Circuit justifies its refusal to analyze the federal duties imposed upon generic manufacturers by concluding that "we need not decide whether generic manufacturers may unilaterally enhance a label warning through the CBE procedure" because "the generic defendants could have at least *proposed* a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers if approved." (App. 11-12, footnote omitted, emphasis in original.) A "proposal" that Actavis forwarded to FDA, however, would not make the labeling for metoclopramide any more adequate under Minnesota common law. Only a *change* in the labeling would satisfy the state law duty. Concluding that Actavis could "propose" a label change therefore does not avoid the conflict.[9]

Neither *Wyeth*'s broad anti-preemption statements nor its specific holdings abrogate the Supremacy

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[9] The Eighth Circuit decision implicitly recognizes the inadequacy of its own "propose a label change" resolution of the conflict between state and federal law. The Court concludes that "[t]he regulatory framework makes clear that a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug." (App. 12.) Instead of specifying the "steps" a generic manufacturer *can* take to "warn" physicians or consumers, the Court simply suggests that generic defendants are "not compelled to market metoclopramide" and can "stop[ ] selling the product" if they "believe" federal and state duties conflict. (App. 18-19.)

Clause, U.S. CONST. art. VI, cl. 2, or the doctrine of conflict preemption, and cannot substitute for the case-specific analysis applied in *Geier v. Am. Honda Motor Co.*, 529 U.S. 861 (2000); *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141 (1982), and other preemption cases. The Hatch-Waxman Amendments and implementing regulations create and regulate a distinct industry and must be analyzed as such. That industry poses conflict preemption questions vastly different from those posed in *Wyeth v. Levine*. Absent further guidance from this Court, courts will continue to ignore those important distinctions and continue to thwart and frustrate the objectives of Congress.

CONCLUSION

When federal courts allow state court juries to penalize generic drug manufacturers for not unilaterally changing the labeling of a generic drug, they thwart a federal policy decision to require consistent labeling for brand and their bioequivalent generic drugs, so as to promote confidence in the drug approval system. When those same courts advise generic drug manufacturers to "stop making" a low-cost generic if they do not wish to be subject to the same post-marketing duties and obligations as brand drug manufacturers, they invite the dismantling of an industry that has saved, and continues to save, billions of dollars for millions of Americans. Because this Court has yet to interpret the Hatch-Waxman

Amendments and promulgating regulations, and because the Eighth Circuit's interpretation of *Wyeth v. Levine* exposes a critical need for clarification of that decision, Petitioner respectfully urges this Court to grant certiorari and reverse.

Respectfully submitted,

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