No. 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

PETITIONERS' REPLY BRIEF

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LIST OF PARTIES

Petitioners' list of parties was set forth at page ii of its Petition for Writ of Certiorari, and there are no amendments to that statement.

CORPORATE DISCLOSURE STATEMENT

Petitioners' corporate disclosure statement was set forth at page iii of its Petition for Writ of Certiorari, and there are no amendments to that statement.

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Respondent highlights the importance of this Court's review of the decision below. She joins the Eighth Circuit in failing to distinguish the statutes and regulations applicable to generic drugs from those applicable to branded drugs. Respondent makes sweeping statements that the requirements of the Food, Drug, and Cosmetic Act and the FDA regulations thereunder apply equally to generic and branded drug manufacturers. They do not.

This case presents an important issue of federal law that bears directly on the health and well-being of the American public. That issue was not addressed or decided in *Wyeth v. Levine*. In his concurring opinion in *Levine*, Justice Breyer recognized that "it is also possible that state tort law will sometimes interfere with the FDA's desire to create a drug label containing a specific set of cautions and instructions." *Wyeth v. Levine*, 555 U.S. ---, 129 S. Ct. 1187, 1204 (2009) (Breyer, J., concurring). Here, the applicable statutes and regulations reflect FDA's insistence that generic drug labeling match the specific cautions and instructions contained in the branded drug label. Moreover, the Hatch-Waxman Amendments were enacted to lower the cost of prescription drugs. As Justice Breyer also noted, "some have argued that state tort law can sometimes raise prices to the point where those who are sick are unable to obtain the drugs they need." *Id.* Although Congress and FDA both had the vision to eliminate redundancy and place the burden of prescription drug labeling content on the branded drug manufacturer and FDA, rather than the brand manufacturer and five, ten, or even twenty different generics, the Eighth Circuit thought differently. Its decision will

eviscerate Hatch-Waxman, eliminate the efficiencies that allow generic pharmaceuticals to be sold at lower prices, and create the anomalous circumstance for the first time in this country where exactly the same drug sold by many different companies can have labeling with many different warnings, precautions, and instructions for use.

Furthermore, the decisions that have addressed the issue reveal the need for this Court's guidance. Aside from applying *Levine* in an overly-broad manner, lower courts have reached conclusions that are not supported by the statutory and regulatory language.

Finally, the public policy arguments Respondent posits for denial of the petition have no place in this arena. Public policy is for Congress to address. It did so when it enacted the Hatch-Waxman Amendments to provide the American people with the low-cost drugs they need. The issue presented here is whether the Eighth Circuit's decision abrogates the Hatch-Waxman Amendments and thereby defeats Congress's objectives in enacting the legislation.

I. FEDERAL REGULATION OF GENERIC DRUGS IS DISTINCT FROM FEDERAL REGULATION OF BRANDED DRUGS

Respondent notes, as if it were dispositive, that this Court, in *Levine*, said that "the manufacturer bears responsibility for the content of its label at all times" and "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate," and argues those

statements apply with equal force to branded and generic drugs. (Respondent's Brief in Opposition ("Opp."), p. 3.) But, *Levine* did not involve generic drugs and those statements do not explain how a generic drug company fulfills its responsibility regarding the content of its label: Does it ensure that the label remains the "same as" the branded drug's label at all times as required by Hatch-Waxman and FDA regulations or does it ignore Hatch-Waxman and concern itself instead with state-law duties?

No court has squarely answered that question yet. Instead, courts have ignored the central tenets of Hatch-Waxman and applied to generic drugs the statutes and regulations applicable to branded drugs. But, a generic manufacturer does not craft its own labeling; rather Hatch-Waxman requires it to adopt the labeling of the branded drug. As a result, under the requirements of both the statute and FDA's regulations, a generic drug manufacturer's responsibility for its drug labeling at all times is to ensure that it remains the same as the labeling of the branded drug. *See* 21 U.S.C. §355(j).

Respondent asserts that 21 C.F.R. §201.57(e) applies to branded and generic drug manufacturers alike and requires them "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.'" (Opp., p. 4.) However, that ignores the regulations specifically applicable to generic drugs. A branded drug manufacturer must, as part of an NDA, submit "proposed text of the labeling * * *

and * * * statements describing the reasons for omitting a section or subsection of the labeling format in 201.57," whereas a generic manufacture must, as part of an ANDA, submit "[a] statement that the applicant's proposed labeling * * * is the same as the labeling of the reference listed drug." *Compare* 21 C.F.R. §314.50 *with* 21 C.F.R. §314.94. Thus, FDA's regulations explicitly do *not* refer a generic drug manufacturer to §201.57 for the format or content of its labeling.

Respondent further contends that both branded and generic drug manufacturers may use one of two procedures to change labeling. (Opp., p. 5.) The first procedure – the prior approval supplement ("PAS") (21 C.F.R. §314.70(b)) – is the one the Eighth Circuit relied on to conclude that claims against generic drug manufacturers are not preempted. However, Respondent provides no more support than did the Eighth Circuit for the idea that "proposing" a label change will satisfy any state-imposed duty to provide adequate warnings.

The second procedure – the changes being effected ("CBE") supplement (21 C.F.R. §314.70(c)) – was not addressed by the Eighth Circuit in light of its conclusion that generic drug manufacturers could propose a label change through the PAS process, or propose that FDA send a "Dear Doctor" letter. App.14a. Respondent contends that generic drug manufacturers may use the CBE provisions to change label language in advance of changes to the branded drug labeling because 21 C.F.R. §314.97 "instructs generic drug companies to follow those procedures 'regarding the submission of supplemental applications and other changes to an

approved abbreviated application.'" (Opp., pp. 5-6.) But that ignores other regulations specifically applicable to generic drugs; notably one that requires an original ANDA, any amendment, and any supplement to include "a copy of the currently-approved labeling for the listed drug," and "[a] statement that the applicant's proposed labeling is the same as the labeling of the reference listed drug." 21 C.F.R. §314.94(a)(8)(ii), (iii). FDA reminded generic drug manufacturers that they are not free to use the CBE provision to change label language in advance of changes to the branded drug's label in promulgating the regulations implementing Hatch-Waxman. *See* 57 Fed. Reg. at 17955 (reminding ANDA applicants that "labeling for an ANDA product must, *** correspond to that for the [branded] drug"), App. 105a.

II. GENERIC DRUG MANUFACTURERS AND BRANDED DRUG MANUFACTURERS ARE NOT SIMILARLY SITUATED

Respondent states that "[i]t is not necessary for a drug company to conduct new clinical studies in order to conclude that 'reasonable evidence' supports an additional warning" because a "new warning may be justified by adverse drug experience reports." (Opp., p. 4.) Respondent then states that all drug manufacturers are required to collect adverse event information and report the information to FDA. (Opp., pp. 4-5.) Respondent has chosen her words very carefully. Yes, "a drug company" may be able to discern the need for new or additional warnings based on adverse event reports if that "drug company" has the background information necessary to assess the reported

adverse events. Generic drug manufacturers do not. That real world fact was recognized at the time Hatch-Waxman was enacted:

> [T]he difference between the handling of adverse reactions by a generic company and a major research-based company – I think you have to understand and you do understand that the nature of the business is different. The generic companies are production oriented, the research-based companies are research oriented and if I were in a generic firm collecting adverse experience I would bundle it all together and send it in. I would send everything for fear of not wanting to omit anything.
>
> ***
>
> A generic firm wanting to obey the law and our regulations, lacking the research base that an innovator firm has, would send everything in. Our concern is that we would be inundated with reports with no attempt to self-sort them. It would impose a burden on us to sort them out.

(Statement of Mark Novitch, M.D., Deputy Commissioner, FDA, App.120a; *see also id.* at App. 118-119a (testifying "[b]ecause the innovator [branded] manufacturer is familiar with the

preapproval testing, it is in a good position to evaluate the [post-marketing] adverse reactions," and "[i]f adverse reactions reports were received by firms unfamiliar with the clinical trials, and, because of the nature of their business, lacking ties with the research community, we are concerned about the adequacy of the reports we would receive").)

And, yes, both branded and generic manufacturers have reporting requirements. But, those requirements differ. A branded manufacturer must conduct post-marketing surveillance that encompasses review and analysis of all reported adverse events – an analysis based on the knowledge obtained through the clinical trials conducted to obtain approval of the drug. *See* 21 C.F.R. §314.80, App.81a. In contrast, generic manufacturers, who do not have the underlying scientific data, are required only to report to FDA those adverse events reported to them. *See* 21 C.F.R. §314.98, App.90a.

Respondent's reliance on FDA's change to metoclopramide labeling in 2009 to assert that reports in the medical literature alone can provide support for a labeling change is misleading. (Opp., p. 5) First, as was true of the Eighth Circuit, Respondent ignores the fact that while FDA cited only three pieces of literature in its correspondence mandating the change, 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.

Second, FDA did not send letters to all metoclopramide manufacturers as Respondent implies.[1] Those letters were addressed only to the manufacturer of the branded metoclopramide product and those manufacturers marketing generic versions of metoclopramide for which the branded drug upon which they are based is no longer on the market. All other manufacturers of generic metoclopramide were not advised to, and did not, change their label language until the label of branded drug upon which their drug products were based was changed and approved by FDA.

III. THE LOWER COURTS NEED THIS COURT'S GUIDANCE

Respondent argues review is unwarranted because no conflict exists among the Circuit Courts of Appeal.[2] However, only two appellate courts have ruled on preemption as to generic drug

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[1] As required under the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), FDA communicated only with the metoclopramide brand-name manufacturer and the manufacturers selling generic metoclopramide for which the branded product upon which they are based was no longer on the market. *See* 21 U.S.C. §355-1(a)(2). In enacting the FDAAA, Congress followed the existing practice of having the branded labels change before changes are made to generic labeling so that their labels will be the "same as" the branded counterparts.

[2] Contrary to Respondent's suggestion (Opp. pp. 8-9), *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994), did not decide the preemption issue posed here. In fact, the generic drug manufacturer was not a defendant in *Foster* when the court issued the cited decision. The language Respondent quotes is pure dicta.

manufacturers – the court below, and the Fifth Circuit in *Demahy v. Actavis*, 593 F.3d 428 (5th Cir. 2010). Five appeals currently are pending before federal Circuit Courts of Appeal from district court decisions that, like the district court here, found plaintiff's claims against the generic manufacturers *were preempted*.[3] *See Morris v. Wyeth, Inc.*, 6th Cir. Case No. 09-5509; *Smith v. Wyeth, Inc.*, 6th Cir. Case No. 09-5460; *Wilson v. Pliva, Inc.*, 6th Cir. Case No. 09-5466; and *Gaeta v. Perrigo Pharmaceuticals Co.*, 9th Cir. Case No. 09 15001. In each case, the district court specifically ruled that *Levine* did not affect its conclusion that plaintiff's claims were preempted.[4]

In addition, hundreds, if not thousands, of cases involving this question are pending in federal and state courts around the country.

We already have shown that the Eighth Circuit's decision is badly flawed. The same is true of the Fifth Circuit's decision in *Demahy*. It ruled that, "while Congress plainly intended for a generic drug manufacturer to submit labeling identical to – or, the "same as" – the brand name drug when seeking ANDA approval," the statutory scheme "is silent as to the manufacturer's obligations after the ANDA is granted." *Demahy*, 593 F.3d at 436. That conclusion ignores the fact that the "same as"

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[3] The fifth case, pending in the Fifth Circuit, addresses the recent decision in *Demahy* and asks the court to reconsider that decision. *See Pustejovsky v. Pliva, Inc.*, 5th Cir. Case No. 09-10983.

[4] The *Gaeta* Court issued a detailed decision explaining why *Levine* was not controlling in denying a motion that it reconsider its decision in light of *Levine*.

requirement in §355(j) applies to much more than labeling. Section 355(j) provides:

> (2)(A) An abbreviated application for a new drug shall contain —
>
> ****
>
> information to show that the ***active ingredient*** of the new drug ***is*** the ***same as*** that of the listed drug;
>
> ****
>
> (iii) information to show that the ***route of administration***, the ***dosage form***, and the ***strength*** of the new drug ***are*** the ***same as*** those of the listed drug
>
> ****
>
> (v) information to show that the ***labeling*** proposed for the new drug ***is*** the ***same as*** the labeling approved for the listed drug ****

21 U.S.C. §355(j) (emphasis added), App. 65a-67a.

If the Fifth Circuit is correct that generic drug labeling must remain the same only through initial approval, then the same must be true for the other provisions in §355(j), meaning that generic drug manufacturers would be permitted after approval to change the active ingredient, dosage form, route of administration, and strength of their

drugs. Generic drugs would be duplicates of the branded product only at the time of initial approval. Congress cannot possibly have intended that result.

Similarly, the Fifth Circuit failed to appreciate that FDA's regulations contain defined terms. For instance, it concluded that FDA's regulations such as 21 C.F.R. §314.94 do not address post-approval modifications at all. *Demahy* at 436. It also concluded that the CBE provision "does not, on its face, distinguish between generic and name brand drug manufacturers * * * [but] provides that 'the holder of an approved application' – not just an approved new drug application – 'may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change.'" *Id.* at 440. The court's conclusions appear to be based on its assumption of the meaning of the terms "applicant" and "application." Those terms are defined:

> "Abbreviated application" means the application described under §314.94, ***including all amendments and supplements*** to the application.
>
> "Applicant" means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain FDA approval of a new drug or an antibiotic drug and any person who owns an approved application or abbreviated application.

> "Application" means the application described under §314.50, ***including all amendments and supplements*** to the application.

21 C.F.R. §314.3 (emphasis added), App. 72a.

Accordingly, §314.94, when read in light of the definitions, requires an ANDA, any amendment to an ANDA, and any supplement to an ANDA to include "a copy of the currently approved labeling for the listed drug," and "[a] statement that the applicant's proposed labeling is the same as the labeling of the reference listed drug," 21 C.F.R. §314.94 (a)(8)(i), (iii), App. 86a. And, that requirement applies to the "applicant" – the person submitting an original ANDA, an amendment, or a supplement and any person who owns an approved ANDA. The regulations cited by the Fifth Circuit do address "post-approval modifications," and the "holder of an approved application" in §314.70 applies to NDA holders.

In short, the lower courts are confused over the proper application of *Levine* and over the proper interpretation of the applicable statutes and regulations as well.

IV. PETITIONERS SEEK PROTECTION FROM CONFLICTING OBLIGATIONS

Respondent is incorrect in contending that petitioners seek "a special shield against tort liability that is not available" to manufacturers of name-brand drugs. (Opp., p. 11.) What

Petitioners seek is protection from conflicting obligations. The federal statutes that essentially created the generic drug industry require generic drug labeling to be the "same as" the labeling of the branded drug. The Eighth Circuit, however, requires labeling changes to comply with state law duties. To avoid liability, generic drug manufacturers either must remove their products from the market or recreate themselves, at substantial cost, to become research-based companies with the resources and knowledge necessary to evaluate and substantiate labeling changes. Both results – one depriving the consuming public of low-cost generic drugs and the other leading to dramatic increases in the costs of generic drugs – are contrary to Congress's purposes and objectives in enacting Hatch-Waxman.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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