Nos. 09-993, 09-1039, and 09-1501

IN THE
Supreme Court of the United States

PLIVA, INC., ET AL.,
Petitioners,
v.
GLADYS MENSING,
Respondent.

ACTAVIS ELIZABETH LLC,
Petitioner,
v.
GLADYS MENSING,
Respondent.

ACTAVIS INC.,
Petitioner,
v.
JULIE DEMAHY,
Respondent.

On Writs of Certiorari to the United States Courts of Appeals for the Eighth Circuit and for the Fifth Circuit

REPLY BRIEF OF PETITIONERS ACTAVIS INC. AND ACTAVIS ELIZABETH LLC

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INTRODUCTION

Mensing and Demahy brought textbook failure-to-warn claims under Minnesota and Louisiana law. Each alleged that, prior to her injuries, the generic drug defendants had new information about the risks of metoclopramide, had a duty to warn physicians about these risks, should have issued new warnings, failed to do so, and proximately caused plaintiff's injuries. Although the United States has filed a brief supporting Mensing and Demahy, the government agrees with petitioners that "an ANDA holder may not unilaterally change its approved labeling." Brief for the United States as *Amicus Curiae* Supporting Respondents ("US Br.__") 16. Thus, the application of established conflict preemption principles to plaintiffs' direct failure-to-warn claims leads to one conclusion: plaintiffs' claims are preempted.

Perhaps realizing that their traditional direct failure-to-warn claims are preempted, respondents now advance a new theory that the generic manufacturers had a duty to warn respondents' physicians by the indirect means of notifying FDA, which then could have requested that the brand manufacturer add a new warning to the label, at which time a generic manufacturer could legally add a warning to its own label. While this novel theory has attracted much attention, particularly among the *amici*, it merely serves to distract from what should be the central focus of these proceedings: that the Court rule that the direct failure-to-warn claims that respondents actually pled are preempted. The *Demahy* decision held that generic drug

manufacturers can unilaterally change their labels under the Federal, Food, Drug and Cosmetic Act ("FFDCA") regulations, while the *Mensing* court declined to decide the issue. To date, one other Circuit and numerous district courts have incorrectly held that generic manufacturers may unilaterally amend their labels. It is imperative that the Court correct this misreading of the statute and regulations.

Preemption issues related to respondents' new failure-to-ask theory are not ready for review, and in any event, because the complaints do not allege a claim other than a direct failure-to-warn claim, they should be dismissed. State courts have not yet identified a state law basis for the new claims proposed by plaintiffs, defined the elements of any such claim, or considered where the burden of proof should lie. The Court should allow them to do so in the first instance, after a plaintiff has actually alleged such a claim.

The almost uniform, erroneous rulings by the lower courts as to whether a direct failure-to-warn claim against a generic manufacturer is preempted are due to a misreading of this Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009). But the lower courts are also misreading *Wyeth*'s statements regarding the burden of proof on whether FDA would have agreed to a label change where it would be an element of the plaintiff's claims. In fact, *Wyeth* has no application to the allocation of the burden of proof in such a situation, and the lower courts should be permitted to decide this question in a case where any

new legal claim that is permitted under state law is appropriately alleged and prosecuted.

I. Plaintiffs' Failure-to-Warn Claims Are Preempted.

A. Federal Law Prohibited a Generic Manufacturer From Adding a New Warning to Its Drug Label Until the Brand Manufacturer Had Changed Its Label.

As the United States demonstrates in its brief, plaintiffs' claims that the generic manufacturers may be held liable for not adding a warning to the metoclopramide label are preempted because the generic manufacturers could not independently have added a warning to the label of a generic drug without violating federal law. US Br. 15-17. This is also clear from the plain meaning of the FFDCA and FDA's regulations, and from the Agency's consistent and longstanding interpretation of the applicable statutory and regulatory provisions. Actavis Br. 18-24.

Plaintiffs claim that generic defendants could have changed their label through FDA's Changes Being Effected ("CBE") regulation, which permits a brand manufacturer to make changes to its label as soon as it submits a supplemental application to FDA. To support this argument, plaintiffs rely on *Wyeth,* where this Court held that "it has remained a central premise of federal drug regulation that the manufacturer [Wyeth] bears responsibility for the content of its label at all times," including both

"crafting an adequate label and . . . ensuring that its warnings remain adequate." 129 S. Ct. at 1197-98.

As this Court also pointed out, "prior to 2007, FDA lacked the authority to order manufacturers to revise their labels." *Id* at 1198. In other words, during the timeframe pertinent to this case, brand manufacturers had control over the label of their pharmaceutical products. In contrast to the law applicable to brands established in *Wyeth,* the Hatch-Waxman Act and FDA regulations require that the generic product have the same labeling as the brand. Actavis Br. 18-24. As a result, prior to 2007 brand drug manufacturers effectively controlled the labeling of generic drugs.

Thus FDA's regulations require that each abbreviated drug application, amendment and supplement contain "[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)(iii); *see* Actavis Br. 18-19, 21. The regulations are very clear that any change made in a supplement, pursuant to the CBE regulation or otherwise, is therefore subject to the same labeling requirement, *i.e.*, the labeling in the supplement must also mirror the brand label. Actavis Br. 19. FDA guidance also states that a generic manufacturer must "ensur[e] that the labeling contained in its application is the same as the currently approved labeling of the [brand]." *See* FDA, *Guidance for Industry, Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000); *see* Actavis Br. 21-22.

Apparently recognizing that the argument that they persuaded the Fifth Circuit to adopt in *Demahy* is fatally flawed, in this Court, respondents have advanced a new, and incorrect, rationale for the same outcome, namely that FDA's regulations, 21 C.F.R. § 314.94(a)(8)(iv), permit differences in generic labeling "to comply with current FDA labeling guidelines or other guidance." *See* Opp. Br. 33-34. To support this argument, respondents cite the preamble to that regulation in which FDA stated that the exception encompasses differences in proposed labeling because "important new information about the safe use of a drug product" requires a labeling change. Opp. Br. 34 (*quoting* 54 Fed. Reg. 28872, 28884 (July 10, 1989)).

Respondents' argument is inconsistent with statements FDA made when it issued the regulation and with statements that the United States has made on behalf of FDA to this Court. In the preamble to the regulations, FDA stated that the exception to same labeling applies when "for example, the agency *may require* a change in the labeling to make available important new information about the safe use of a drug product." Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989) (emphasis added). As the United States notes, "[t]here was no such action on FDA's initiative in the period relevant to these cases." US Br. 16 n.7. Moreover, in the preamble to the final rule, in FDA's discussion of this exact provision, the Agency explicitly rejected a comment that sought a revision that would have permitted ANDA applicants to deviate from the labeling for the reference listed drug

to add contraindications, warnings and other safety related information. Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17950, 17961 (April 28, 1992).

As explained above, the plain and only meaning of FDA's regulations is that at all times the labeling of generic drugs must be the same as the brand. If, however, there were any ambiguity in the Agency's regulations, which have the force of law, then the Agency's consistent and longstanding interpretation of those regulations would be entitled to deference. *See* Actavis Br. 22. Even if FDA had not repeatedly taken that position, its position in the legal briefs filed with this Court, which is consistent with the regulatory text, is, by itself, entitled to deference. *Chase Bank USA, N.A. v. McCoy*, 131 S. Ct. 871, 880-81 (2011).

B. Federal Law Prohibited a Generic Manufacturer From Sending New Warning Information to Physicians Until the Brand Manufacturer Had Changed Its Label.

The United States also correctly rejects plaintiffs' argument that the generic manufacturers could have issued a Dear Healthcare Professional (DHCP) letter with additional warnings. US Br. 18-19. FDA has defined DHCP letters as "correspondence . . . intended to alert . . . health care providers . . . about important new information regarding a human drug or biologic." FDA, *Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of*

Important Safety Information at 1 (Draft, November 2010). As the Fifth Circuit, the Eighth Circuit, *and* the United States all correctly have concluded, the generic drug manufacturers could not have lawfully included a warning in a DHCP letter that was different from the warning on the brand label. JA 553, 413; US Br. 18-19.

In their opposition, respondents incorrectly state that FDA has asserted (in the certiorari brief filed by the United States) that the Fifth and Eighth Circuits' conclusions that generic manufacturers could not unilaterally issue DHCP letters were erroneous. Opp. Br. 36 n.30. In fact, the FDA stated that a letter that warns about risks of a product constitutes labeling and must conform to the sameness provisions applicable to labeling. US Cert. Br. 17-18. Respondents also argue that DHCP letters are not subject to the same labeling requirement because they constitute promotional labeling. Opp. Br. 36-37. But FDA regulations define labeling broadly to include "[b]rochures, booklets, mailing pieces . . . letters . . . containing drug information supplied by the manufacturer." 21 C.F.R. § 202.1(*l*)(2); *see also* 21 U.S.C. § 321(m). This obviously includes promotional materials. As the United States notes, the DHCP letter that plaintiffs envision would have been subject to 21 C.F.R § 201.100(d), which requires it to be "consistent with and not contrary to [the drug's] approved . . . labeling." US Br. 18-19.

Further, FDA defines promotional labeling as materials "used to help sell prescription drugs." FDA, *Drug Advertising: A Glossary of Terms*, *available at*

www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm (last visited Mar. 22, 2011). DHCP letters are intended to alert health care providers about important new information. Under no reasonable interpretation can DHCP letters be characterized as promotional labeling.

Even if the Court does not find the statutory and regulatory provisions clear on their face, as discussed above, FDA's interpretation of those requirements is entitled to deference.

C. Arguments That Plaintiffs Will Be Deprived of One Potential Defendant and/or That the Statutes Create an Anomaly Are Not Grounds for Finding That There Is No Preemption.

Plaintiffs accuse the generic drug manufacturers of seeking a special immunity that would deprive plaintiffs of any remedy, and creating arbitrary distinctions between classes of patients "based on the vagaries of pharmacy practice." Opp. Br. 2, 51-52. The real issue, however, is whether a generic drug manufacturer may be sued under state law for failing to do something that it is forbidden to do under federal law. Under the Supremacy Clause, the States may not enact laws that are inconsistent with the laws of Congress, and since this Court's decision in *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521-23 (1992), this principle applies to jury verdicts. Thus, even if a ruling on preemption in this case deprived injured patients who take generic

drugs of any remedy, or Hatch-Waxman's "same as" language creates an anomalous distinction between patients prescribed brand or generic drugs, that outcome would not be a basis for finding no preemption where there is a conflict between federal and state law.

Moreover, plaintiffs are incorrect that a holding of preemption in this case would deprive injured patients of any remedy. While "off-label prescribing" is not a violation of federal law, that fact does not absolve physicians from state law claims for prescribing metoclopramide for unapproved long-term use. *See, e.g., Sherrill v. Souder*, 325 S.W.3d 584 (Tenn. 2010) (malpractice claim for long-term prescription of Reglan). The metoclopramide label has explicitly warned that the risk of developing tardive dyskinesia "increase[s] with the duration of treatment," and that treatment for more than 12 weeks "has not been evaluated and cannot be recommended" since 1985. *See* Actavis Br. 8-9. In 2004, while both plaintiffs were using the drug, FDA approved a label change indicating: "Therapy should not exceed 12 weeks in duration." *Id.* at 10. In the face of such a specific warning, Dr. Graves, an *amicus* who treated Mrs. Demahy, prescribed the drug for 4 years. *See Amicus Curiae* Brief of Dr. Christy Graves at 1.[1]

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[1] The linchpin of Dr. Graves' argument is that during all relevant periods "the warnings in the labeling for metoclopramide asserted that it carried a low risk – only 0.2% or 1 in 500 – of [EPS which includes] tardive dyskinesia" although "[t]he actual risk . . . was in fact at least 100 times higher." Graves Br. 3. Dr. Graves is apparently unaware that

II. These Consolidated Cases Are Not an Appropriate Vehicle for Deciding, in the Abstract, Whether a Possible State Law Claim That Generic Manufacturers Must Ask FDA To Support a Label Change Is Preempted.

Respondents and the United States seek a ruling on whether a claim of liability for failure to ask FDA to support a change in the brand and generic label is preempted. Because this claim was not adequately pleaded below, the complaints should be dismissed. In any event, this case is not an appropriate vehicle for a ruling on any potential preemption issue related to this new claim, because it was never defined below, because respondents have cited no authority finding a failure to warn where the defendant has no direct control over its warning, and because it is unclear whether plaintiffs could ever prevail on such a speculative claim.

A. Plaintiffs' Current "Failure-to-Ask" Theory Was Not Pleaded by Plaintiffs, Nor Was That Claim Defined by the Courts Below.

The theory of liability now advanced by plaintiffs has morphed considerably from a classic failure-to-warn claim. While plaintiffs now assert that generic drug manufacturers are liable for failing

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the initial statement on the 2009 label that the prevalence of tardive dyskinesia is 20% was withdrawn as an error, and that today the 0.2% figure which she disputes remains on the label. *See* pp. 15-17, *infra*.

to ask FDA to support a label change, in their complaints, the plaintiffs asserted simply that generic drug defendants' failure to warn physicians of new information about the risks of metoclopramide caused plaintiffs' injuries. Since plaintiffs' direct failure-to-warn claims are preempted and since they did not plead their new failure-to-ask claims in their complaints, this Court should direct that all plaintiffs' claims be dismissed.

In the courts below, neither plaintiffs nor the courts discussed how plaintiffs' new claims would fit into applicable state law, including, for example, whether such claims could be brought as product liability failure-to-warn claims, as general negligence claims or under some other legal theory. And when the purported state law duty is analyzed in the context of metoclopramide's regulatory record, it becomes clear that the abstract preemption positions advocated by plaintiffs are seriously flawed. This Court therefore should limit its decision to the claims and record presented, which require dismissal.[2]

Plaintiffs' complaints in the district courts articulated classic direct failure-to-warn claims. The complaints are grounded on the assumption that a generic drug manufacturer had control over its labeling and could unilaterally make a change. The complaints do not assert that the generic drug

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[2] If the Court reaches the issue of whether this new "take steps" claim is preempted, Actavis agrees with PLIVA that the claim is preempted because it is dependent upon speculation regarding Agency actions and unduly interferes with FDA's chosen means and methods for carrying out the "same as" mandate of Hatch-Waxman.

manufacturers should have asked FDA to support a label change or, more precisely, urged the brand manufacturer to change its label. For example, Mensing alleged in her First Amended Complaint that "[t]his case involves DEFENDANTS' failure to warn doctors and patients of information within its knowledge or possession," JA 182 (¶ 41); "DEFENDANTS failed to use reasonable care to modify the package insert," JA 195 (¶ 93); "[Defendants] failed to promptly respond to and adequately warn about these risks," JA 199 (¶ 114); *see also* JA 193 (¶ 85), JA 204-05 (¶ 133).[3] Demahy's complaint similarly presumed the generic manufacturers' control over the label: "Defendants had a duty and obligation to disclose to plaintiff and her physicians the true facts concerning Reglan and/or metoclopramide." JA 441 (¶ 33).[4]

In their briefs to the district court, plaintiffs for the first time floated an argument that the generic drug manufacturers should have suggested a label change to FDA. That argument was made in response to the defendants' preemption arguments,

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[3] Indeed, in the sections of her complaint that identify the specific causes of action, Mensing made the allegations against all defendants, which included both the brand manufacturer and several generic manufacturers, with no acknowledgement of the fact that they were differently situated with regard to their ability to effect a label change. JA 198-219.

[4] Demahy's complaint does assert that Actavis "failed to fully, truthfully and accurately disclose Reglan and/or metoclopramide data to the FDA." JA 437-38 (¶ 20). The complaint does not identify what "data" was not disclosed and how these failures create a cause of action under Louisiana products liability law.

and was not described as a separate theory of state law liability. Moreover, plaintiffs did not identify the source of that duty. The scope of this newly-asserted duty also has been uncertain throughout the litigation. While plaintiffs assert in this Court that their remaining theories are still the standard, *Wyeth*-like failure-to-warn claims that were asserted in their complaints (Opp. Br. 21, 44), the claims now being advanced are in fact profoundly different, as both lower courts implicitly recognized.[5]

In a typical failure-to-warn case, the issues – as plaintiffs note – are (a) whether the warning was inadequate and, if so, (b) whether the absence of an adequate warning caused plaintiff's injury. Opp. Br. 41-44. The underlying assumption in these typical cases, however, is that the defendant had control over its label and could have added a warning upon learning of the new information that warranted the change. Here the generic drug manufacturers did

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[5] The United States also attempts to assist respondents in defining the take steps claim by stating that, even though no formal process was available for generic drug companies to revise their labels, a generic drug company could direct their proposals to the Office of Generic Drugs. US Br. 20-21. In fact, FDA has no process in place that specially addresses the evaluation of a request by the generic manufacturer to add a warning to its label. The internal guidance that the United States cites (*MAPP* 5200.6) outlines procedures for issuing and tracking consults in the Office of Generic Drugs. The fact that one of the 40 listed reasons for requesting a consult that appears on the form is "labeling revision" is not instructive. There is nothing to indicate that the revisions referred to have anything to do with warnings or that they should be initiated by the ANDA applicant as opposed to being done to conform to the brand reference listed drug.

not have such control; the brand manufacturer did. At most, the generic manufacturer could petition FDA to ask the brand manufacturer to make the label change, which, even if ultimately agreed to, might not have been made for a substantial period of time. Plaintiffs have cited no authority finding a failure-to-warn claim where the defendant does not have any direct control over its warning. None of the district or appellate courts below explained how the claim that plaintiffs now assert is actually viable under the law of either state.

B. Liability Under Plaintiffs' Current Theory Would Be Purely Speculative.

1. Any Hypothetical Duty to Seek a Label Change Is Inconsistent With the Regulatory Record for Metoclopramide.

The United States suggests that a hypothetical state law "failure-to-ask" claim could be based on a federal duty imposed on manufacturers of generic drugs to suggest or propose warnings to FDA (US Br. 26), while acknowledging that "[s]ituations where an ANDA holder alone has a basis to believe stronger warnings should be added to its drug's approved labeling have not been known to arise frequently" (*Id*. 20-21). In fact, we are not aware of a single instance where this has ever occurred and none has been identified by the government. The regulatory record here dramatically confirms that generics had

no information unknown to FDA on the key risk issue.

Here, plaintiffs assert that the risk of tardive dyskinesia is much higher than the label indicates. But the fact that the risk of tardive dyskinesia increases when the drug is used beyond its indicated usage of 12 weeks was well known to FDA and is contained throughout the record in the 2005 *Pozen* hearings that were before the *Mensing* court.[6] Indeed, based on its own 2002 to 2004 study of metoclopramide usage, FDA was aware of the exact percentages of use beyond 12 weeks and of the increased risk caused by that fact.[7] Nevertheless, FDA did not order a label change until long after the plaintiffs in these two cases stopped using the drug.

Plaintiffs state that in connection with the 2009 label change FDA "ordered the manufacturers to add information in the warning section of the label

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[6] *See* Actavis Br. 11-12.

[7] *See* Memorandum from Sigal Kaplan, June 10, 2005, Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (Exh. HH to Second Clark Affidavit at 2-4). This data was submitted for publication in 2006: Sigal Kaplan, Judy A. Staffa & Gerald J. Dal Pan, *Duration of Therapy With Metoclopramide: A Prescription Claims Data Study*, 16 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 878, 879 (2007). Plaintiffs cite to the studies mentioned in *McNeil v. Wyeth*, 462 F.3d 364 (5th Cir. 2006) as demonstrating the inadequacy of the warning. Opp. 9. All of these articles were specifically referred to in a May 18, 2004 memorandum by Dr. Eric Bastings during the *Pozen* review. *See* Memorandum of Eric Bastings, May 18, 2004, Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (Exh. FF to Second Clark Affidavit at 7-12); *see also* Memorandum from Mary Ross Southworth, May 5, 2005, Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (Exh. GG to Second Clark Affidavit at 4-5).

that a published study had found tardive dyskinesia occurring in 20 percent of the patients treated for at least three months . . . a hundred times greater than the 0.2 percent risk previously identified on the label." Opp. Br. 11. This is highly misleading because it mixes apples and oranges in two different ways. First, the 0.2% risk number is not for tardive dyskinesia but for extrapyramidal symptoms (EPS), a larger grouping of movement disorders, which includes tardive dyskinesia. Second, the 20% figure is a prevalence estimate and the 0.2% in an incidence figure.[8] But even more importantly, FDA has retracted the 20% prevalence reference, stating that "[i]nadvertent editing has resulted in inaccuracies regarding the representation of the data reviewed." Letter from FDA to Alaven Pharmaceuticals, LLC, July 20, 2010 (Addendum at 1a). As a result, the metoclopramide label no longer contains the 20% prevalence statement.

With this statement removed, the only changes remaining from the 2009 order are the black box itself and a new statement linking use beyond 12

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[8] Incidence measures how many people develop a disease in a given time frame (*i.e.* the number of new cases that develop in a year) and prevalence measures what percentage of the population has a disease. The most recent medical literature on these measures in relation to tardive dyskinesia comes from the Mayo Clinic and concludes that the risk (incidence) of tardive dyskinesia from metoclopramide is likely to be less than 1%. A.S. Rao & M. Camilleri, *Review Article: Metoclopramide and Tardive Dyskinesia*, 31 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 11, 14-16 (2010). That low level is confirmed by the Shaffer study cited by plaintiffs, which reported 87 adverse reaction reports from 1992 to 2003 but which reported 50,000,000 prescriptions during that time. *See* Opp. 9.

weeks to the risk of tardive dyskinesia, although the label had previously stated that "[b]oth the risk of developing [tardive dyskinesia] and the likelihood that it will become irreversible are believed to increase with the duration of treatment and total cumulative dose." *See* Actavis Br. at 8-11. The statement about the risk of EPS, including tardive dyskinesia, being 0.2%, to which plaintiffs so strenuously object, has remained on the label throughout. Significantly, plaintiffs have never suggested that the 2009 label was insufficient; instead the claim is that the generic manufacturers should have requested FDA to make the 2009 changes earlier.

There is no basis for the plaintiffs' claim that the generic manufacturers had a duty to request FDA to amend the warning on metoclopramide to state that the risk of tardive dyskinesia was 20%. In fact, when FDA considered that issue in 2009, it made an explicit decision not to place such information on the metoclopramide label. If this is plaintiffs' claim, as they apparently contend in this Court, then the claim is preempted as having been explicitly rejected by FDA. *Wyeth,* 129 S. Ct. at 1198-99.

2. The Court Should Allow the State Courts to Decide Burden of Proof and Other Issues Regarding Any Failure-to-Ask Claim.

Both the Fifth and Eighth Circuits relied on this Court's statements in *Wyeth* about the burden that defendant Wyeth would bear in asserting a

preemption defense if it were to attempt to demonstrate that FDA would not have accepted the label change that plaintiffs advocated. JA 414, 555-56. Neither court recognized that whether the question of FDA action arises as part of the basic element of plaintiff's claim (as it could if the claim were that the generic manufacturer had a duty to ask FDA to support a label change) or a part of a preemption defense will affect which party has the burden of proof. Given the history of lower courts misinterpreting the meaning of *Wyeth* on the conflict preemption issue and on this issue, it is critical that the Court clarify that nothing in *Wyeth* affects the authority of state courts to define the elements of any claim that plaintiffs might be permitted to bring, including the allocation of the burden of proof.

Wyeth v. Levine was a classic failure-to-warn case, in which the drug manufacturer had the authority to make unilateral changes to its label and, this Court concluded, the record developed at trial indicated that the manufacturer had new information justifying such a revision. The one situation where the Court recognized that there could be preemption is where the defendant could show that FDA would have rejected a stronger warning label, but because preemption is a defense this Court concluded that there would be no preemption "absent clear evidence that the FDA would not have approved the change to [the] label" of the drug at issue there. 129 S. Ct. at 1198.

It is important, however, that this Court make it clear to the lower courts that its statements about the burden of proof in *Wyeth* have no applicability to

liability cases that may be brought against generic manufacturers that cannot make a label change. If the courts below allow plaintiffs to bring a claim for failing to ask FDA to support a label change, then those courts should be free to decide whether under state law plaintiffs should have the burden of demonstrating not only that the generic manufacturers had a duty to provide additional information to FDA, but that FDA and the brand manufacturers would have acted on that information. Unless this Court makes it clear that its statements about the burden of proving FDA action in the context of a preemption defense have no applicability here, there is a distinct risk that the lower courts will incorrectly apply the Court's statements regarding the burden of proof in *Wyeth* just as they almost uniformly and incorrectly have held that this Court's holding about the ability of a brand to unilaterally change its label applies in actions against generic manufacturers.[9]

C. The United States' New "Misbranding" Argument, Like Respondents' "Take Steps" Argument, Is Not Sufficiently Developed to Guide a Preemption Determination.

As previously noted, plaintiffs' cases should be dismissed because the only failure-to-warn claims alleged in their complaints are preempted. Plaintiffs

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[9] The Solicitor General agrees that the burden of proof issue is an issue of state law which should not be resolved by this Court. US Br. 32.

claim that the generic manufacturers have "imagined" that, in the absence of the ability to use the CBE regulation, liability is now being premised on a "take steps" claim, rather than a straightforward inadequate warning claim where the ability of the defendant to make a label change is not part of the plaintiffs' case-in-chief. Opp. 44. But the take steps claim that defendants refer to comes directly from both plaintiffs' briefs and the *Mensing* decision. In the Courts of Appeal, both Mensing and Demahy stated that "failure even to seek such approval [through the PAS process] was negligent and actionable." Appellant's Opening Br., *Mensing*, 2008 WL 5707474, at 30-31 (filed Feb. 20, 2008); Br. of Appellee, *Demahy*, 2009 WL 6297313, at 28-29 (filed Mar. 30, 2009); *see also* JA 402, 416. These latter claims sound in negligence for failure of a duty to seek a change from FDA, not for a failure to warn.

The uncertainties surrounding the nature and scope of plaintiffs' new claim, and how preemption principles might properly apply to them, are illustrated by the new argument that has been raised for the first time in the *amicus* brief filed by the United States. The government suggests that a federal duty on the part of generics to ask FDA to adopt stronger warnings arises from the need to reconcile the FFDCA's misbranding provision and the "same as" labeling requirement for generics in Hatch-Waxman. US Br. 25-29. There are several flaws in the United States' argument.

First, the government asserts that generic manufacturers are "obligated . . . to seek to revise their labeling" because commentary in the Federal

Register instructs generic manufacturers to "contact" FDA with "new safety information," but concedes that instances in which a generic manufacturer might possess such information would be so infrequent and factually "unique" that FDA has not promulgated any regulation to implement that "contact." US Br. 20-21.

Second, based on that tenuous foothold, the government "[f]ocus[es] the preemption inquiry on the standard in 21 C.F.R. § 201.57(e)" – the regulation that imposes a duty on drug manufacturers to revise their labeling "as soon as there is reasonable evidence of an association of a serious hazard with a drug." US Br. 27. Again, the government does not cite to any regulation which a generic manufacturer could use to revise its labeling even if it possessed such information. Nor does the government offer any example of a generic manufacturer's "compliance" with this federal "duty." That is because the theoretical process described is not the way the generic industry operates under Hatch-Waxman.

Hatch-Waxman was superimposed on an existing system in which FDA and the brand manufacturer constituted the sources of knowledge about a drug – the hubs that received, evaluated and acted upon information that they themselves created (*i.e.*, through clinical studies) or that they received from numerous spokes – physicians, pharmacists, consumers, etc. (*i.e.*, adverse event reports). None of the spokes had the authority to change drug labeling, and no state law holds such information sources liable for "inadequate" warnings. Hatch-Waxman

and its implementing regulations place generics in the same position, imposing a duty on generics to forward similar information to FDA, while maintaining the generic drug label the "same as" the brand drug label.

The system envisioned by Hatch-Waxman works, as amply demonstrated in the regulatory record described above. *See* Section II.B.1. All of the information that plaintiffs claim should have led to a labeling change prior to 2009 was considered by FDA at the *Pozen* hearings in 2005. The government does not argue to the contrary.

Instead, the government justifies the imposition of label revision responsibilities on generic manufacturers because otherwise generic drugs could have inadequate warnings but not be "misbranded." US Br. 29. That argument places the entire generic industry in an untenable position by essentially classifying generic drugs as "misbranded" in hindsight, based on a jury verdict that a label that the generic manufacturer had no power to change was "inadequate." Even if the manufacturer were to "propose" a change, its drug would *still* be misbranded until such time as FDA (which does not consult with a generic manufacturer regarding labeling changes) requires the brand manufacturer to make a change to its labeling. The government's qualification that "[a] misbranding determination in a private tort suit would not, of course, bind FDA in the exercise of its regulatory authority" (US Br. 32, n.16) provides cold comfort to a generic manufacturer exposed to state court liability based on jury

conclusions that its drug was "misbranded" due to inadequate labeling it had no power to change.

The government's new argument simply echoes the *Mensing* court's suggestion that generic drug manufacturers either be subject to state law claims that their drug labeling is "inadequate," or "simply stop[] selling the product." JA 416. As the United States recognizes elsewhere in its brief, the more logical way to interpret regulations promulgated for brand manufacturers is to give force to Hatch-Waxman's mandate for uniform labeling (labeling the "same as" brand drugs). *See, e.g.*, US Br. at 15-16 & n.8 (noting that as applied to an ANDA holder, the CBE regulation must be interpreted to mean that generic manufacturers may unilaterally change their labeling to make it uniform with a brand drug's labeling – not to add or change warning language).

Further, while the United States argues that plaintiffs' new claims against generic drug manufacturers are not categorically preempted, it has acknowledged the merits of the argument for impossibility preemption in cases where the label is not misbranded and a state court finds liability against the generic manufacturer (US Br. 29) and that certain kinds of claims, such as an alleged failure of a generic drug manufacturer to develop its own clinical trials, could be preempted. US Cert. Br. 21-22; US Br. 28 n.14. And, as we point out above, if the heart of plaintiffs' claim is that the generic manufacturers should have requested a warning declaring that the prevalence of tardive dyskinesia is 20% (*see* Opp. 6-11), as plaintiffs argue in this Court,

then FDA has already explicitly rejected that warning. Hence even plaintiffs' take steps case would be preempted. *Wyeth,* 129 S. Ct. at 1198-99. This Court should thus decline to consider the United States' argument in the abstract.

The variety of potential approaches and results simply highlights that these consolidated cases – with all their uncertainties and hypothetical claims – do not present a viable vehicle for determining the boundaries of preemption. The preemption inquiry should be considered when a concrete case presents it.

CONCLUSION

The claims that plaintiffs pleaded and pursued – that Actavis allegedly breached a duty to provide plaintiffs' physicians with new information on risks associated with the long-term use of metoclopramide – are in direct conflict with the "same as" labeling requirement of Hatch-Waxman and are preempted. The decisions below should be reversed and remanded with directions to dismiss all claims.

Respectfully submitted,

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March 23, 2011

APPENDIX

[LOGO]
Department Of Health And Human Services

Food and Drug Administration
Silver Spring MD 20993

PRIOR APPROVAL SUPPLEMENT REQUEST

NDA 17854
NDA 21793

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Manager, Regulatory Affairs and Drug Safety
2260 Northwest Parkway, Suite D
Marietta, GA 30067

Dear Ms. Alonso:

Please refer to your new drug application (NDA) for Reglan (metoclopramide) Tablets and Reglan ODT (metoclopramide orally disintegrating tablets) 5 mg, 10 mg.

We have reassessed the statements regarding Tardive Dyskinesia in the Warnings and Precautions Section of the prescribing information. Inadvertent editing has resulted in inaccuracies regarding the representation of the data reviewed.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

> **Tardive Dyskinesia (see Boxed Warnings)**
>
> Treatment with metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or

extremities. The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. An analysis of utilization patterns showed that about 20% of patients who used metoclopramide took it for longer than 12 weeks. Treatment with metoclopramide for longer than the recommended 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

Although the risk of developing TD in the general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Both the risk of developing TD and the likelihood that TD will become irreversible increase with duration of treatment and total cumulative dose.

Metoclopramide should be discontinued in patients who develop signs or symptoms of TD. There is no known effective treatment for established cases of TD, although in some patients, TD may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn.

Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. Therefore, metoclopramide should not be used for the symptomatic control of TD.

We request that you submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most re-

cently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

The supplement should be submitted within 30 days.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/ Number	Submission Type/ Number	Submitter Name	Product Name
NDA-21793	GI-1	Alaven Pharmaceutical LLC	Reglan RPT (Metoclopramide) *5/10* MG TABS
NDA-17854	GI-1	Alaven Pharmaceutical LLC	Reglan

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
07/20/2010