

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**

**BRIEF OF PETITIONERS ACTAVIS INC.
AND ACTAVIS ELIZABETH LLC**

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QUESTION PRESENTED

Are the states preempted under the Supremacy Clause of the Constitution from requiring additional safety information on a generic product label where the brand has not changed its label?

LIST OF PARTIES

Nos. 09-993 and 09-1039 (Eighth Circuit)

A. Defendants-Appellees

PLIVA, Inc.

Teva Pharmaceuticals USA, Inc.

UDL Laboratories, Inc.

Actavis Elizabeth LLC

Wyeth, LLC

B. Plaintiff-Appellant

Gladys Mensing

No. 09-1501 (Fifth Circuit)

A. Defendant-Appellant

Actavis Inc.

B. Plaintiff-Appellee

Julie Demahy

CORPORATE DISCLOSURE STATEMENT

Actavis Group hf is a privately-held Icelandic company, and the parent corporation of Actavis Group PTC, ehf, which is the parent of petitioner Actavis Inc., a Delaware corporation. Petitioner Actavis Elizabeth LLC, a subsidiary of Actavis Inc., is the successor to Purepac Pharmaceutical Co. No publicly held corporation owns ten percent or more of Actavis Inc.'s stock.

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BRIEF OF PETITIONER ACTAVIS

OPINIONS BELOW

The opinion of the Eighth Circuit Court of Appeals is reported at 588 F.3d 603 (8th Cir. 2009) and reprinted in the Joint Appendix (JA ____) at 400-21. The district court's opinion is reported at 562 F. Supp. 2d 1056 (D. Minn. 2008) and reprinted at JA 364-85.

The opinion of the Fifth Circuit Court of Appeals is reported at 593 F.3d 428 (5th Cir. 2010) and reprinted at JA 520-63. The district court's opinion is reported at 586 F. Supp. 2d 642 (E.D. La. 2008) and reprinted at JA 477-519.

JURISDICTION

This Court has jurisdiction under 28 U.S.C. § 1254.

The Court of Appeals for the Eighth Circuit rendered its decision in Nos. 09-0993 and 09-1039 on November 27, 2009. The petitions for writ of certiorari were filed on February 19 and 25, 2010, respectively.

The Court of Appeals for the Fifth Circuit rendered its decision in No. 09-1501 on January 8, 2010. The petition was filed timely on June 7, 2010, following an order extending the deadline.

CONSTITUTIONAL, STATUTORY AND REGULATORY PROVISIONS INVOLVED

The pertinent provisions of the United States Constitution, Article VI, clause 2, 21 U.S.C. § 355 and 21 C.F.R. §§ 314.3, 314.70, 314.94, 314.97 and 314.150 are reproduced in the Appendix to the Petition in 09-1501 at App. 113a-131a.

STATEMENT OF THE CASE

Congress created the modern generic drug industry when it amended the Federal Food, Drug, and Cosmetic Act (FFDCA) in 1984. Pub. L. No. 98-417, 98 Stat. 1585 (1984). In addition to streamlining the approval process for generic drugs, the legislation promoted confidence in their safety and effectiveness by ensuring that generic drugs were exact copies of their brand counterparts. In these consolidated cases, respondents seek to hold petitioners Actavis Inc. and Actavis Elizabeth LLC (collectively Actavis) and three other generic drug companies liable under state law for not adding safety information to the labels of their metoclopramide products.

Following this Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (*Wyeth*), numerous lower courts have held that generic manufacturers may be held liable for failing to add warnings to the labels of their products, contrary to the requirement that their labels duplicate the label of the brand drug. Unlike the brand manufacturer in *Wyeth*, generic manufacturers are prohibited from making

unilateral changes to their labels due to the same labeling requirement in the FFDCA and FDA's regulations. Respondents' state law claims would conflict with federal law by requiring Actavis to violate the same labeling requirement and are therefore preempted.

A. The Regulatory Framework.

1. New drugs.

Under the FFDCA, a new drug may not be marketed until the Food and Drug Administration (FDA) has approved a new drug application (NDA). 21 U.S.C. §§ 331(d), 355(a). Before an NDA is submitted, the manufacturer must conduct a range of preclinical investigations, obtain FDA authorization to conduct human clinical trials designed to establish safety and efficacy, and then conduct those clinical studies. 21 U.S.C. § 355(i); 21 C.F.R. § 312.20. Once all of these studies have been completed, the sponsor must submit an NDA, containing "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective." 21 U.S.C. § 355(b)(1)(A). Because FDA will find a drug safe and effective only under labeled conditions of use, FDA must review the drug label as part of the NDA process. 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d).

After a drug is approved, the brand manufacturer's obligations continue. Manufacturers must maintain records, conduct additional testing as directed, and advise FDA of significant adverse health consequences that are reported following the

drug's introduction to the market. 21 U.S.C. § 355(k)(1); 21 C.F.R. § 314.80.

Further, as this Court held in *Wyeth*, when new information about the safety of a drug becomes apparent to the brand manufacturer, the brand manufacturer has the ability and obligation to change its label. 129 S. Ct. at 1196-99; *see also* 21 C.F.R. § 201.80(e). In order to make a labeling change, the brand manufacturer must file a supplemental application with FDA. 21 C.F.R. § 314.70. Although certain changes to a drug's approved labeling require prior approval, others, including changes to "add or strengthen a contraindication, warning, precaution or adverse reaction," may be made through the "Changes Being Effected" (CBE) process as soon as FDA receives the brand's supplemental application; the brand need not await FDA approval. 21 C.F.R. § 314.70(c)(6)(iii)(A), (C).

In 2007, Congress added section 355(o)(4) to the FDCA, which authorizes FDA to require labeling changes if it becomes aware of new safety information that it believes should be included in the labeling of the drug. 21 U.S.C. § 355(o)(4); Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85 § 901(a), 121 Stat. 823, 922-26 (2007). Prior to FDAAA, and during the period that is relevant to these cases, FDA had no authority to require a label change on a brand drug; it could only urge the manufacturer to amend its label.

2. Generic drugs.

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) which streamlined the process by which companies may obtain approval of generic versions of brand drugs once the brand patents have expired. Pub. L. No. 98-417, 98 Stat. 1585 (1984). A principal goal of Hatch-Waxman was to achieve a “careful balance between promoting competition among brand names and ‘generic’ drugs,” which would make safe and effective, low-cost drugs widely available, while “encouraging research and innovation” by extending patent protections for brand drugs.¹

Unlike the brand sponsor, which must submit scientifically valid clinical trials demonstrating safety and efficacy in order to obtain approval, Hatch-Waxman permitted a generic applicant to rely on the safety and effectiveness information that the brand submitted if the generic applicant could demonstrate that its product is the same as the brand’s product. 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.94(a)(3). Part of the justification for Hatch-Waxman was FDA’s conclusion that mandating generics to conduct the full testing required of the brand in order to market a drug was “unnecessary and wasteful,” and that such testing could be “unethical” if patients in clinical trials were given placebos in place of drugs already proven effective.

¹ See Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17950, 17951 (April 28, 1992); H. R. Rep. No. 98-857, pt. 1 at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647.

H.R. Rep. No. 98-857, pt. 1 at 16, *reprinted in* 1984 U.S.C.C.A.N. 2647, 2649.

Under Hatch-Waxman, FDA will approve a generic drug for marketing upon proof that the drug (1) has the same active ingredient(s) as; (2) has the same route of administration, dosage form and strength as; (3) *has the same labeling as*; and (4) is bioequivalent to, the brand drug. 21 U.S.C. § 355(j)(2)(A)(i)-(v) (emphasis added). In other words, the thrust of Hatch-Waxman is that the generic must demonstrate that its product is a copy of the brand in every significant respect, including its labeling, so that once approved the generic version can be substituted for the brand drug without a physician's intervention. *See* FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations*, p. iv (30th ed. 2010).

The generic manufacturer is neither required to conduct the clinical studies needed to obtain approval of the brand product nor expected to master the clinical data that supports the various claims made on the product's label. Instead, the fundamental obligation of the generic manufacturer is to make a product that is a true copy of the brand. That obligation provides the framework for a generic drug manufacturer's regulatory duties.

A generic manufacturer is required to report adverse drug experiences that it "obtain[s] or otherwise receive[s]" from any source, including scientific literature, and to submit new safety information in its annual reports to FDA. *See* 21 C.F.R. § 314.98(a), (c); 21 C.F.R. § 314.80; 21 C.F.R.

§ 314.81(b)(2)(i). Nevertheless, the vast majority of such reports do not go to the generic manufacturer, but instead go directly to FDA or to the brand manufacturer.²

Generic drugs are required to have the same labeling as their brand counterparts. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iii). This means that generic drugs must have the same warnings as the brand. If the brand makes a labeling change, it is the generic manufacturer's responsibility to mirror that change in its own label. *See* FDA, *Guidance for Industry, Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000) (ANDA Labeling Revision Guidance). If the brand does not make a labeling change, however, the generic manufacturer may not make a unilateral change to its own label. Making changes that render the generic label different from the label of the reference listed drug (the brand drug) is prohibited by the regulations that require the generic label to be the same as the brand label *at all times*. If a generic does not maintain the same label as the brand, FDA can remove the generic from the market. 21 C.F.R. § 314.150(b)(10).

² *See* FDA, Center for Drug Evaluation and Research, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports, *Manual of Policies and Procedures* 5240.8 (Nov. 1, 2005) (“Generally, [the Office of Generic Drugs] receives few AERs [adverse event reports] or similar reports.”).

3. FDA's actions on metoclopramide.

FDA approved the NDA for metoclopramide tablets, Reglan®, on December 30, 1980 for the treatment of diabetic gastroparesis.³ It is the only drug currently approved by the FDA for this condition. Michael Camilleri, *Diabetic Gastroparesis*, 356 N. Eng. J. Med. 820, 827 (2007). In 1984, the Agency approved Reglan® tablets for the treatment of gastroesophageal reflux (GER), and the approved labeling included that indication in 1985. That labeling stated that treatment with the drug for longer than 12 weeks “has not been evaluated and cannot be recommended.” In addition, the following three paragraphs describing tardive dyskinesia, a movement disorder, were added:

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase

³ The 1980 label identified movement disorders as a possible side effect. See Physicians' Desk Reference at 1566 (36th ed. 1982).

with the duration of treatment and total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.⁴

In 2004, the labeling for metoclopramide was again revised. Although the section on tardive dyskinesia remained the same, the following sentence was added to the “Indications and Usage” section:

⁴ See Physician’s Desk Reference at 1660 (39th ed. 1985); Physician’s Desk Reference at 1635 (41st ed. 1987).

The use of metoclopramide tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.⁵

The next change relating to tardive dyskinesia was made in March 2009, when FDA, based on “new safety information,” and using the new labeling authority granted by FDAAA, issued a letter requiring that all holders of applications for brand metoclopramide products make changes to their respective labels regarding the tardive dyskinesia warnings, including the addition of a black box warning.⁶ All ANDA holders for those products were required to adopt the new labeling requirements, but not until the brand labels were changed. *See* ANDA Labeling Revision Guidance at 4-5. The labeling changes requested by FDA in March 2009 were submitted in supplemental applications and approved by FDA on June 30, 2009.⁷

⁵ 2004 Reglan® Label, Indications and Usage at 6, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17854s0471bl.pdf (last visited Jan. 23, 2011).

⁶ *See* Risk Evaluation and Mitigation Strategies (REMS) Letters to Sponsor/Applicants Requesting Label Changes, *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm148710.htm> (last visited Jan. 23, 2011).

⁷ *See* Letter from FDA to Alaven Pharmaceuticals, LLC, June 30, 2009, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2009/017854s051,021793s004ltr.pdf (last visited Jan. 23, 2011).

There were only three differences between the 2004 and 2009 labels. First, the black box warning was added. Second, the last sentence of the warning contained a new statement that directly linked use beyond 12 weeks to a risk of tardive dyskinesia. Third, the last statement in the first paragraph of the warnings section added a statement about the prevalence of the disease – *i.e.*, that one published study reported a 20% prevalence level for patients treated for at least three months. In November 2010, however, FDA withdrew that sentence, substituting a statement that 20% of those using the drug do so for more than 12 weeks.⁸

Although no changes were made to the metoclopramide label between 2004 and 2009, FDA extensively reviewed information regarding the safety of metoclopramide during that period in connection with a new drug application submitted by Pozen Inc., for a combination product. During that review, both FDA and an advisory committee examined safety issues related to long-term metoclopramide use and tardive dyskinesia. For example, in a May 18, 2004 memo by Eric Bastings M.D., the Neurology Team Leader in the Center for Drug Evaluation and Research, Dr. Bastings acknowledged concerns regarding extrapyramidal adverse events known to be caused by metoclopramide, and cited medical literature noting that movement disorder specialists believed that to prevent persistent movement disorders, long-term use should be avoided. Dkt. Entry 78, *Mensing v.*

⁸ 2010 Reglan® Label, Warnings at 5, *available at*: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/017854s0551bl.pdf (last visited Jan. 23, 2011).

Wyeth, Inc., 07-cv-3919 (D. Minn.) (Exh. FF to Second Clark Affidavit at 6-8). On May 5, 2005, Mary Ross Southworth, Pharm.D., a Safety Evaluator in the Division of Drug Risk Evaluation in FDA's Center for Drug Evaluation and Research, also issued a memo concluding that data demonstrated that the occurrence of irreversible movement disorders is largely a risk associated with chronic use of metoclopramide. Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (D. Minn.) (Exh. GG to Second Clark Affidavit at 3, 27).

FDA also conducted a study of the outpatient prescribing and drug-use patterns for metoclopramide as well as the duration of therapy for the drug. The study found that there had been a substantial increase in the number of prescriptions dispensed for patients using metoclopramide for a longer than recommended duration. Specifically, data showed that about 10% of the study population used metoclopramide for more than six months. Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (D. Minn.) (Exh. HH to Second Clark Affidavit at 22).

B. Proceedings Below.

Petitioners manufacture metoclopramide, a generic form of Reglan®. According to the allegations of their complaints, respondents Gladys Mensing and Julie Demahy were each prescribed metoclopramide for several years, contrary to labeling stating that treatment should not exceed 12 weeks. Respondents

each developed tardive dyskinesia, which they attribute to long-term use of metoclopramide.⁹

1. Mensing

Mensing filed suit in the federal court in Minnesota in 2007. Mensing's 203-paragraph First Amended Complaint, which also named as defendants the manufacturer of Reglan[®] (Wyeth, Inc.), and other manufacturers of metoclopramide, alleged numerous causes of action under Minnesota law. The court granted Actavis's motion to dismiss Mensing's complaint. According to the court, "a generic drug manufacturer cannot unilaterally change its label without prior FDA approval," and "it would be impossible for [the generic manufacturers] to abide by both state and federal laws." JA 382-83. The court held that this conflict would also stand as an obstacle to the accomplishment of the full purposes and objectives of Hatch-Waxman, a key purpose of which is to increase the availability of safe and effective, low-cost generic drugs and to relax the generic approval and labeling process. JA 383.

The court also rejected the argument that the generic defendants could have sought to strengthen their warnings through the prior approval supplement process. JA 383-84. Finally, the court recognized that generic drug manufacturers are not permitted to send "Dear Doctor" letters as a means of providing additional or different warnings. JA 384.

⁹ Mensing was prescribed metoclopramide from 2001 to 2005 and Demahy was prescribed the drug from 2002 to 2007. JA 21-22, 434-35. Neither discontinued the use of metoclopramide after FDA added the warning against long-term use in 2004.

Again, the 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. JA 384. 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 and objectives of the Act.” JA 384.

The Eighth Circuit reversed in a decision that relied heavily on *Wyeth*. JA 400-21. The court discussed whether a generic manufacturer can change its label before the brand has made such a change, but then stated that “[i]n this case we need not decide whether generic manufacturers may unilaterally enhance a label warning” 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.” JA 409-10. The court also held that “the generic manufacturers could have suggested that the FDA send out a warning letter to health care professionals.” JA 413.

2. Demahy

Demahy filed suit in state court in Louisiana, and, after the case was removed, the district court denied Actavis’s motion to dismiss Demahy’s complaint. JA 477-519. Following Actavis’s interlocutory appeal, the Fifth Circuit affirmed. JA 520-63. While acknowledging that Hatch-Waxman required that Actavis’s product have the same label as Reglan® at the time it was approved, the Fifth

Circuit held that if there were new safety information, Actavis could have changed its label after approval and that therefore Demahy's claims were not preempted. The court rejected Demahy's contention that Actavis could have communicated directly with physicians about the risks associated with prolonged use of metoclopramide without FDA approval, although it held that "generic manufacturers . . . [could] suggest that FDA send such letters on their behalf." JA 553.¹⁰

SUMMARY OF THE ARGUMENT

Respondents' state law failure-to-warn claims against Actavis run headlong into core federal conflict preemption principles. A classic conflict exists when compliance with state and federal law is impossible, as it is here. Actavis could not have unilaterally changed its warning label, as respondents' state law claims would require, and simultaneously complied with federal law labeling requirements applicable to generic manufacturers. Respondents' claims are therefore preempted.

The FDCA and FDA's implementing regulations require that a generic drug be a true copy of the brand drug in all significant respects, including labeling. 21 U.S.C. § 355(j)(2)(A). FDA's regulations also state that this identical labeling requirement applies to ANDAs, 21 C.F.R. § 314.94, which are defined to include the original application and any supplements thereto, including a supplement filed under the CBE regulation. 21

¹⁰ There are currently more than 1,000 metoclopramide cases pending in the federal and state courts.

C.F.R. § 314.3. Although FDA permits a brand manufacturer to make unilateral changes to its warning labels without prior approval by the Agency, 21 C.F.R. § 314.70(c)(6)(iii)(A), (C), generic manufacturers may use the CBE regulation only to parrot warning language that a brand manufacturer already has added to its label under that same regulation.

That generic manufacturers cannot use the CBE regulation to deviate from the brand label is entirely consistent with this Court's decision in *Wyeth*, a case involving a brand manufacturer to whom the generic labeling restrictions did not apply. In that case, this Court held that plaintiff's state law claims were not preempted because the brand manufacturer could have used the CBE regulation to make a unilateral change to its warning label. That option is foreclosed to generic manufacturers.

The other option available to brand manufacturers to warn healthcare professionals – a “Dear Doctor” letter – is similarly unavailable to generic manufacturers, since the FDCA and the Agency's regulations treat such letters as labeling. The only state law claims alleged in respondents' complaints are respondents' failure-to-warn claims, and they are preempted.

The Fifth and Eighth Circuits, however, raised the specter of a hypothetical state law claim for failing to “take steps” to propose a label change to FDA. Respondents have not identified how such a theory could fit into the state failure-to-warn claims that they asserted in their complaints, nor have they

identified any law in either Minnesota or Louisiana supporting the viability of such a claim.

At every juncture, from the gateway of preemption to respondents' ability to prove that Actavis failed to "take steps," to the essential element of causation, respondents would face roadblocks. If respondents are arguing that generic manufacturers have the same duty to gather safety data and perform studies as the brand, that claim would be preempted as contrary to the underlying goals of Hatch-Waxman.

In addition, respondents would fare no better in their efforts to prove the causation element of a "take steps" claim. They would have the burden of proving not only that Actavis had new and significant safety information to share with FDA, but also that FDA would have agreed that a labeling change was appropriate, that it would have proceeded to ask the brand to change its label, and that the brand would have agreed. Each link in this chain would be pure speculation.

Respondents' cases should be dismissed.

ARGUMENT**I. STATE LAW CLAIMS BASED ON THE GENERIC DRUG MANUFACTURER'S FAILURE TO CHANGE WARNINGS ON THE LABEL OF ITS GENERIC DRUG OR TO NOTIFY HEALTHCARE PROFESSIONALS OF NEW SAFETY INFORMATION ARE PREEMPTED.****A. Generic manufacturers may not unilaterally add safety information to the labels of their generic drugs.**

The FDCA and FDA's implementing regulations require a generic drug to have the same label as the brand. Under Hatch-Waxman:

An abbreviated application shall contain . . . information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug.¹¹

21 U.S.C. § 355(j)(2)(A). FDA's regulations also require that each ANDA contain "[a] statement that the applicant's proposed labeling . . . is the same as the labeling of the reference listed drug." 21 C.F.R.

¹¹ The statute defines "listed drug" as a drug "which has been approved for safety and effectiveness under subsection [355](c)," which is the section applicable to approval of NDAs. 21 U.S.C. § 355(j)(7); *see also id.* at § 355(j)(2)(A)(i).

§ 314.94(a)(8)(iii).¹² The regulations further define “abbreviated application” as including all amendments and supplements to an application. 21 C.F.R. § 314.3(b).

That definition of “abbreviated application” is central to this case and was not even cited by the Fifth Circuit in *Demahy*. It declares that an “[a]bbreviated application means the application described under § 314.94 [the section that spells out the content of ANDAs], *including all amendments and supplements to the application.*” 21 C.F.R. § 314.3(b) (emphasis added). The term “abbreviated application” includes abbreviated new drug applications. *Id.*

Thus, the same labeling requirement set out in 21 U.S.C. § 355(j)(2)(A)(v) and 21 C.F.R. § 314.94 applies to the original ANDA, and to amendments and supplements to that ANDA. 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.

A generic drug manufacturer may invoke the CBE regulation, but only to conform the generic drug’s label to a change already made by the brand. The FDA regulations unequivocally prohibit the generic manufacturer from adding a warning to its label if that addition would make the generic label

¹² The statute and regulations permit certain differences in labeling that are not applicable here. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

different from the brand. In fact, FDA may “withdraw approval of [an] abbreviated new drug application . . . if the agency finds [t]hat the labeling . . . is no longer consistent with that for the [brand] drug.” 21 C.F.R. § 314.150(b)(10).

When it issued the proposed rule implementing Hatch-Waxman, FDA stated that it “will not accept ANDA’s for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug.” Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989).¹³

¹³ FDA’s decision recognized the control that the brand manufacturers have over the proprietary, scientific information that drives label changes. The generic manufacturers, by contrast, receive a small percentage of the total AERs and do not have the same access to the scientific, safety history of any particular drug. As a result, the brand manufacturer, which is in a superior scientific position to most generics, is in the best position to analyze the safety data and to determine whether a label change is necessary. In addition, the effect of requiring generic manufacturers to maintain the same label as the brand is that the generic manufacturers also must have the same label as each other. For any given brand name drug, there can be multiple generic versions. There are, for example, six approved therapeutically equivalent versions for each strength of Reglan® tablets. See Reglan® Therapeutic Equivalents, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Generics> (last visited Jan. 23, 2011) (search for “Reglan,” click on NDA No. 17854, then click on “therapeutic equivalents”). If each generic manufacturer for a particular brand name drug were able to make unilateral changes to its label, the result could be a variety of different warnings among the generic versions of a drug, not to mention the fact that all of those generic labels would deviate from the brand.

Two of the comments to the proposed regulation urged FDA to revise the proposal “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.” Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17950, 17961 (April 28, 1992). FDA responded that it “disagree[d] with the comments.” *Id.* According to the Agency, “the ANDA product’s labeling must be the same as the listed drug product’s labeling because the listed drug product is the basis for ANDA approval.” *Id.* The Agency went on to explain 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.*

This consistent labeling requirement applies at all times. Thus, if the brand drug changes its labeling after a generic is on the market, the generic must revise its label. *See* ANDA Labeling Revision Guidance at 4; *see also* 21 C.F.R. §§ 314.3, 314.94(a)(8)(iv). In fact, even if FDA requires labeling changes for the brand, as it did when it revised the prescription drug label format, the generic must wait until the brand changes its label before making the changes. *See* Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, Final Rule, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006); *see also* Proposed Rule, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000). If a generic does not maintain the same

label as the brand, FDA can remove the generic from the market. 21 C.F.R. § 314.150(b)(10).

Under the FFDCA, the Agency has the authority to “promulgate regulations for the efficient enforcement” of the Act. 21 U.S.C. § 371(a). 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. There can be no question here that those regulations are consistent with the plain meaning, and that they are a permissible interpretation of, the Act. *See Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-44 (1984). In addition, the Agency’s regulations preempt state failure-to-warn claims which would require a generic manufacturer to unilaterally change its label. *See Hillsborough County v. Automated Med. Labs.*, 471 U.S. 707, 713 (1985); *Fidelity Fed. Sav. & Loan v. de la Cuesta*, 458 U.S. 141, 153-54 (1982). If, however, there were any ambiguity in the Agency’s regulations, which have the force of a law, then the Agency’s consistent and longstanding interpretation of those regulations would be entitled to deference. *See Auer v. Robbins*, 519 U.S. 452, 462-63 (1997); *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994).

In concluding that the generic manufacturer may change its label even though the brand has not, the Fifth Circuit read the CBE regulation as if it exists alone instead of as part of a larger regulatory scheme. FDA regulations must be read together and in a manner that allows a manufacturer to comply with all of the requirements. *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631-

632 (1973). If the relevant regulations are read together, then they plainly require the labeling for an ANDA product to correspond to that for the brand reference drug.

The Fifth Circuit cited an FDA regulation, 21 C.F.R. § 314.97, which states that a generic drug applicant must comply with the CBE regulation, 21 C.F.R. § 314.70, to support its assertion that a generic manufacturer may unilaterally add warning information to its label. JA 545-46. The court, however, neglected to discuss the definition of “abbreviated application,” 21 C.F.R. § 314.3, which, when read together with the requirement that an ANDA’s labeling be the same as the labeling on the brand reference product at all times, 21 C.F.R. § 314.94(a)(8)(iii), prohibits the filing of a supplement under the CBE regulation with a warning or other provision that differs from the brand. There is no inconsistency between 21 C.F.R. § 314.97 and the same labeling regulations (sections 314.3 and 314.94(a)(8)(iii)), and the only way to read the provisions in harmony is to read the same labeling regulations as a limitation on section 314.97. While section 314.97 requires a generic drug manufacturer to use the CBE regulation to change its label to match a change in the brand label, the Fifth Circuit was wrong in concluding that it provides any authority for the generic manufacturer to unilaterally change its label.

Petitioner’s position on the unavailability of the CBE regulation to make unilateral label changes is unequivocally supported by FDA. Brief for the United States as Amicus Curiae, filed in Nos. 09-993

and 09-1039 on November 2, 2010 (US Cert. Br.). The United States declares that “[t]he holder of an approved ANDA is not free to change its approved labeling at will.” US Cert. Br. 12. In fact, the United States directs the Court’s attention to the same regulations, guidance documents and preamble language cited above and notes that FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling. U.S. Cert. Br. 13-14.

B. Generic manufacturers may not unilaterally send “Dear Healthcare Professional” letters that contain warnings about their drugs that are different from those of the branded drug.

“Dear Healthcare Professional” (DHCP) letters may be sent by manufacturers to the healthcare professionals who prescribe their drugs. These letters may address many topics, including warnings and safety-related information. *See* FDA, Center for Drug Evaluation & Research, NDAs: “Dear Health Care Professional” Letters, *Manual of Policies & Procedures* 6020.10 (July 2, 2003); *see also* 21 C.F.R. § 200.5 (containing formatting and content restrictions for DHCP letters). The type of DHCP letters on which respondents’ failure-to-warn claims are grounded would have provided healthcare professionals with different warnings for petitioners’ products. The Eighth Circuit, the Fifth Circuit, and the Solicitor General correctly concluded that petitioners could not have lawfully made a unilateral

change to their warning label through a DHCP letter. JA 413, 553; US Cert. Br. 17-18.

The potential conflict caused by DHCP letters of this nature is twofold. First, labeling is defined broadly under the FFDCA and includes such letters. 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(l)(2) (“[b]rochures, booklets, mailing pieces . . . letters . . . containing drug information supplied by the manufacturer are . . . labeling”). If a generic manufacturer acts unilaterally to change its label through a DHCP letter containing a new warning, it will have violated the statutory and regulatory requirements discussed in Section I.A above that mandate its labeling mirror that of the brand.

Second, FDA may withdraw approval of an ANDA if “the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular.” 21 C.F.R. §§ 314.150(b)(3), (10); *see also* 21 U.S.C. § 321(n) (defining drug as “misbranded” if its labeling is false or misleading). If petitioner had sent a DCHP letter changing the warnings for its product, the letter would have rendered its labeling misleading. As the United States explained, “an ANDA holder’s letter warning about risks seemingly unique to its product could mislead consumers and providers into believing that the generic drug and RLD were not therapeutic equivalents.” US Cert. Br. 17-18.

* * *

In *Wyeth*, this Court held that “it is not impossible for Wyeth to comply with its state and

federal law obligations.” 129 S. Ct. at 1204. Those obligations could be reconciled because “[t]he CBE regulation permitted Wyeth to unilaterally strengthen its warning.” *Id.* at 1199. But generic manufacturers do *not* have the ability to unilaterally change their labeling, either through a CBE supplement or a DHCP letter. It is legally impossible for them to satisfy a jury-imposed duty to add warnings that differ from the warnings on the brand label.

II. RESPONDENTS AND THE LOWER COURTS HAVE NOT IDENTIFIED A STATE LAW CLAIM THAT PREVENTS DISMISSAL, AND ANY SUCH CLAIM WOULD BE BASED ON SPECULATION.

As demonstrated above, respondents’ state law claims that Actavis should have strengthened the labeling of its metoclopramide product or directly warned healthcare professionals are preempted. The *Mensing* court’s conclusion that it did not need to decide whether a generic manufacturer could unilaterally change its label because, “a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug,” JA 410, does not support a different result.¹⁴ Nor

¹⁴ In fashioning a speculative “take steps” claim, the Eighth Circuit expressed a concern that otherwise “injured parties like *Mensing*” would be left with “no legal remedy.” JA 418. This concern was misplaced. Any lack of legal remedy would not be due to the success of petitioner’s preemption arguments, but to a strategic decision by respondents. Respondents could have alleged state law claims against their physicians who prescribed metoclopramide beyond the treatment period permitted by the

does either court's conclusion that Actavis could have asked FDA to distribute a DHCP letter. None of the courts below identified any basis in Minnesota or Louisiana law for such a claim. In their complaints, neither plaintiff identified any state cause of action that could be the basis of a "take steps" claim.

If the Eighth Circuit is suggesting that plaintiffs could hold the generic companies liable for their alleged injuries based on the generic companies' failure to perform the kind of pharmacological due diligence and other duties required of brand manufacturers, their claims would be preempted. As the Solicitor General has explained, "imposing on a generic manufacturer a state law duty not to market its product without developing for itself knowledge as comprehensive as FDA's or the NDA holder's could pose preemption questions." US Cert. Br. 22.

Although the Eighth Circuit concluded that federal regulations required a generic company to "take steps to warn its customers when it learns that it may be marketing an unsafe drug" by notifying FDA, neither it nor the respondents have explained how such a federal obligation could fit into the state failure-to-warn claims that plaintiffs asserted in their complaints nor have they identified any law in either Minnesota or Louisiana indicating such a claim would be viable.¹⁵

label, but they elected not to do so, instead pursuing only claims against the generic manufacturers.

¹⁵ Respondents did state in their briefs below that Actavis could have proposed a label change to FDA through the prior

Respondents' failure to plead a claim based on a generic manufacturer's alleged failure to "take steps" to request a label change or otherwise present safety information to the FDA is understandable for another reason. Even if not preempted, and even if theoretically permitted under state law, such a claim has no path for establishing the essential element of causation.

Any claim that might be asserted by Mensing or Demahy based on an alleged duty to "propose" a labeling change to FDA, "suggest" that FDA issue a "Dear Doctor" letter, or "take steps" to warn by providing FDA information, would face daunting challenges. Every tort claim requires proof of causation (*see, e.g.*, Restatement (Third) of Torts: Liability for Physical and Emotional Harm §§ 18 comment c, 26, 28(a)), and any attempt by Mensing to assert the Eighth Circuit's proposed "take steps" claim would thus require her to prove that Actavis's failure to provide additional information to FDA "caused" her injury.

This Court's discussion of causation in *Wyeth* is not to the contrary. The issue in *Wyeth* was proof of preemption as a legal defense to liability, not proof of causation as a necessary element of a prima facie case of tort liability. Since in *Wyeth* the defendant would be arguing that it would be "impossible for it to comply with both federal and state requirements,"

approval supplement process. *See* Mensing Opp. to Mot. to Dismiss at 32 (District Court Dkt. Entry 71); Demahy Opp. to Mot. to Dismiss at 8-9 (District Court Dkt. Entry 29); Mensing Reply Br. at 11 (Eighth Circuit, filed May 18, 2009). These arguments were not tied to a state law claim.

the Court held that such a defense should not be accepted “absent clear evidence that the FDA would not have approved a change” to the drug’s label that had already been made by the manufacturer. 129 S.Ct. at 1198. Because the issue was whether FDA would have made a specific decision to veto a label change that satisfied state law obligations, the burden of proof was on the defendant.

Theoretical “take steps” liability presents an entirely different scenario. If the state law duty is to propose a label change or otherwise “take steps,” liability for compensation involves proof that fulfillment of the duty would have prevented the injury. State law, not federal law, imposes the burden of demonstrating what FDA would have done on the plaintiff. Indeed, for a claim that arose before September 2007 (the time period applicable to both *Mensing* and *Demahy*), proving a causal link between the act or omission of a generic drug manufacturer and an injury that could have been avoided by a warning involves both proving that FDA would have been persuaded that additional warnings were appropriate and – since FDA could not at that time order a label change on its own authority – persuading the brand manufacturer (who controlled the label) to change it.

To meet that burden, *Mensing* would have had to prove not only that Actavis had new information that it did not present to FDA (not alleged here), but also that FDA would have urged the brand manufacturer to change its label based on the “new” information – a matter of pure speculation. Expert testimony about what FDA would have done if asked

to change the label on a drug or to warn healthcare professionals about a drug is inherently speculative and cannot meet the standards for admissibility and reliability under Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993). Indeed, courts have generally excluded expert testimony about what actions FDA might have taken with respect to regulation of its products.¹⁶ Thus, not only is it likely that the plaintiffs in the instant cases would have difficulty proving “take steps” claims, had they been alleged, any plaintiff is likely to be barred from asserting a claim that a generic manufacturer should have requested FDA

¹⁶ For example, in *Bartlett v. Mutual Pharmaceutical Co.*, No. 08-cv-358, 2010 WL 2889114, at *14 (D.N.H. July 22, 2010), a product liability case where the plaintiff had argued that Mutual, a generic drug company, should have unilaterally changed its label, the court excluded “speculation as to what FDA might have done in hypothetical circumstances.” (citation omitted). Numerous other trial courts have excluded testimony about whether FDA would have taken a particular action as speculative. *In re Trasylol Prods. Liab. Litig.-MDL-1928*, 2010 WL 4259332, at *8, 12 (S.D. Fla. Oct. 21, 2010) (excluding as “speculation” testimony regarding what FDA “would have done in hypothetical circumstances”); *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1053-54 (D. Minn. 2007) (excluding as “speculation” testimony that particular statements by a drug company “likely played a role in the Agency’s allowing the clinical investigation program to go forward”); *Twin Cities Bakery Workers Health & Welfare Fund v. Biovail Corp.*, 2005 WL 3675999, at *3-5 (D.D.C. Mar. 31, 2005) (excluding testimony as “too speculative” that FDA would have approved a drug but for misuse of a patent), *aff’d*, *Meijer, Inc. v. Biovail Corp.*, 533 F.3d 857, 863 (D.C. Cir. 2008); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 550 n.62 (S.D.N.Y. 2004) (excluding expert testimony that amounted to “speculation as to what FDA might have done in hypothetical circumstances”).

take regulatory action on the grounds that evidence essential to such a claim is pure speculation.¹⁷

Finally, even if a path could be identified for proving causation in a “take steps” claim, the regulatory record for metoclopramide highlights the weakness of any such claim. That record demonstrates that the FDA was fully apprised of all the issues related to metoclopramide and the risks of tardive dyskinesia. FDA not only oversaw the various metoclopramide labeling changes through 2004, but in 2004 and 2005 FDA closely scrutinized the safety of metoclopramide and it could have requested additional labeling changes if it had concluded that those changes were warranted. FDA’s active consideration of an extensive record concerning the safety of metoclopramide demonstrates that for this product FDA was in a position to take action if the Agency had believed that such action was necessary.

The record is also devoid of evidence that Actavis had any information about the use of metoclopramide and the risk of tardive dyskinesia that was unknown to FDA. In 2004 and 2005, FDA reviewed a new drug application (NDA 21-645) submitted by Pozen Inc. for a combination metoclopramide product. During the review of this application, both FDA and an advisory committee thoroughly examined safety issues related to long-term metoclopramide use and tardive dyskinesia. FDA looked at all AERs as well as published articles

¹⁷ The same analysis would apply to an argument that Actavis should have asked FDA to direct generic manufacturers to send out DHCP letters.

that studied the safety of metoclopramide. The Agency conducted an internal review and found that the data demonstrated that the occurrence of irreversible movement disorders is largely a risk associated with chronic use of metoclopramide and that the cases from the AER database correlated well with what had been reported in the literature. *See* pp.11-12, *supra*.

In preparation for an advisory committee review of the Pozen application, FDA also conducted a review of the outpatient prescribing and drug use patterns for metoclopramide in the United States as well as the duration of therapy for the drug. That study found that there had been a substantial increase in the number of prescriptions dispensed for metoclopramide along with a longer than recommended duration of use. *See* p.12, *supra*.

Despite FDA's thorough review of issues related to the use of metoclopramide and tardive dyskinesia, including its review of metoclopramide AERs related to movement disorders, and despite its understanding that metoclopramide was being used for periods of time beyond the labeled recommendations, FDA did not require manufacturers to revisit metoclopramide labeling until 2009, after it had gained new authority to order a change in drug labels, which occurred after both Mensing and Demahy had stopped using the drug. There is no information that Actavis could have added to the extensive information that FDA reviewed during this period of time and thus no steps that Actavis could have taken that would have changed FDA's course of action.

Simply put, respondents did not allege a take steps claim; neither they nor the courts below identified such a claim in state law; and, in any event, respondents could not prove such a claim.

CONCLUSION

The decisions below should be reversed and remanded with directions to dismiss all claims.

Respectfully submitted,

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