

Nos. 09-993, 09-1039, 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 Fifth and Eighth Circuits

**BRIEF FOR DR. CHRISTY GRAVES AS *AMICUS*
CURIAE IN SUPPORT OF RESPONDENTS**

MIKE PAPANTONIO
TROY A. RAFFERTY
LEVIN, PAPANTONIO, THO-
MAS, MITCHELL, RAFFERTY
& PROCTOR, P.A.
316 South Baylen Street
Post Office Box 12308
Pensacola, FL 32591
(850) 435-7163

ERIK S. JAFFE
(Counsel of Record)
ERIK S. JAFFE, P.C.
5101 34th Street, NW
Washington, DC 20008
(202) 237-8165
jaffe@esjpc.com

Counsel for Amicus Curiae
(Additional Counsel on
Inside Cover)

Additional Counsel:

JOHN EDDIE WILLIAMS, JR.
JOHN T. BOUNDAS
WILLIAMS, KHERKHER,
HART, BOUNDAS, LLP
8441 Gulf Freeway,
Suite 600
Houston, TX 77017
(713) 230-2200

TABLE OF CONTENTS

Table of Contents.....	i
Table of Authorities.....	ii
Interest of <i>Amicus Curiae</i>	1
Statement	2
Summary of Argument.....	3
Argument	5
I. The High Risk of Metoclopramide-Induced EPS and TD Was Readily Discoverable by Generic Manufacturers Long Before the FDA Added a Black-Box Warning.....	5
II. The History of Inaction in the Face of Readily Available Evidence of Metoclopramide’s Risks Counsels Against Preemption.	15
Conclusion.....	20

TABLE OF AUTHORITIES

Cases

Buckman Co. v. Plaintiffs’ Legal Comm., 531 U.S. 341 (2000)18

McNeil v. Wyeth, 462 F.3d 364 (CA5 2006).....5

Mensing v. Wyeth, Inc., 588 F.3d 603 (CA8 2009).....5, 11

Wyeth v. Levine, -- U.S. --, 129 S. Ct. 1187 (2009).....17, 18, 19, 20

Statutes

21 U.S.C. § 352(f)(2)19

Regulations

21 C.F.R. § 201.57(e)19

21 C.F.R. § 201.80(e)15

21 C.F.R. § 314.80(b)18

Other Authorities

American Gastroenterological Ass’n
 Institute, *American Gastroenterological Association Medical Position Statement on the Management of Gastroesophageal Reflux Disease*, 135
 GASTROENTEROLOGY 1383 (2008)14

- Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER (June 1981) (<http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm>) 16
- Daniel D. Sewell, Angela B. Kodsi, Michael P. Caligiuri & Dilip V. Jeste, *Metoclopramide and Tardive Dyskinesia*, 36 BIOL. PSYCHIATRY 630 (1994)..... 9
- Douglas Shaffer, Marian Butterfield, Carol Pamer & Ann Corken Mackey, *Tardive Dyskinesia Risks and Metoclopramide Use Before and After U.S. Market Withdrawal of Cisapride*, 44 J. AM. PHARM. ASS'N 661 (Nov./Dec. 2004) 10
- Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research (CDER), FDA, to NDA holders for Reglan (Feb. 26, 2009) (available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf>) 13

- Linda Ganzini, Daniel E. Casey,
William F. Hoffman & Anthony
McCall, *The Prevalence of
Metoclopramide-Induced Tardive
Dyskinesia and Acute
Extrapyramidal Movement Disorders*,
153 ARCH. INTERN. MED. 1469 (June
28, 1993)8, 9, 16
- Lucinda G. Miller & Joseph Jankovic,
*Metoclopramide-Induced Movement
Disorders*, 149 ARCH. INTERN. MED.
2486 (Nov. 1989)7
- Memorandum from Kate Gelperin, *et
al.*, Office of Surveillance and
Epidemiology, CDER, FDA, to Donna
Griebel, Director, Division of
Gastroenterology Products, OND,
CDER, FDA, *Risk of Metoclopramide-
induced Movement Disorders*, June
27, 2008 (OSE RCM # 2008-269).....11, 12, 19
- P. Jay Pasricha, Nonko Pehlivanov,
Aravind Sugumar & Joseph Jankovic,
*Drug Insight: from disturbed motility
to disordered movement – a review of
the clinical benefits and medicolegal
risks of metoclopramide*, 3 NATURE
CLINICAL PRACTICE
GASTROENTEROLOGY & HEPATOLOGY
138 (March 2006)9, 10, 14, 16

Robert B. Stewart, James J. Cerda, Mary T. Moore & William E. Hale, <i>Metoclopramide: An Analysis of Inappropriate Long-Term Use in the Elderly,</i> 26 ANN. OF PHARMACOTHERAPY 977 (July/Aug. 1992)	7
---	---

INTEREST OF *AMICUS CURIAE*¹

Amicus curiae Dr. Christy Graves practices internal medicine in Louisiana and was respondent Julie Demahy's treating physician. Following a diagnosis of gastroesophageal reflux disorder and initial prescription of metoclopramide by Ms. Demahy's gastroenterologist, Dr. Graves continued to prescribe metoclopramide to Ms. Demahy. Because the labeling materials for metoclopramide warned only of a very small risk from the drug of adverse neurological reactions such as extrapyramidal symptoms ("EPS") and tardive dyskinesia ("TD"), Dr. Graves prescribed the drug to Ms. Demahy for approximately four years. Ms. Demahy eventually developed TD. Had Dr. Graves been informed that the product labeling and warnings were grossly inaccurate and that the risk for EPS and TD with long-term use was roughly 100 times higher than stated on the package insert, she would not have prescribed metoclopramide for such an extended period and would have been more alert to the early signs of EPS and TD and sought alternative treatment options.

Dr. Graves is interested in this case because of her personal experience with the harm that inadequate drug label warnings caused for one of her own patients, her direct knowledge of how misleading warnings can affect treatment decisions and lead to treat-

¹ No counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *amicus* or her counsel, make a monetary contribution intended to fund the preparation or submission of this brief. This brief is submitted pursuant to the blanket consent letters from all parties, on file with this Court.

ment choices having far worse risk-benefit profiles than expected, and her desire to ensure that doctors now and in the future have accurate and current information in the drug labeling on which they rely when making treatment decisions.

STATEMENT

In attempting to avoid responsibility for the content of their drug labels, the generic manufacturer petitioners in these cases argue that updating the warnings contained in the labels is the sole responsibility of the brand-name manufacturer and that they are only required to match the labeling of that manufacturer, not seek updates on their own. Actavis Br. at 7, 16, 19-20; PLIVA Br. at 12-13, 37-38.

They claim variously that requiring generic manufacturers to monitor the market and medical evidence for adverse effects from their drugs and alert the FDA to emergent risks is too costly and burdensome for them, is beyond their competence, and would impose a burden on the FDA. Actavis Br. at 20 n. 13, PLIVA Br. at 4, 30, 37-38.

Each of those claims is undermined by the history of metoclopramide, the extensive medical evidence that emerged during the 1980s and 1990s regarding the higher-than-warned risks of neurological side-effects associated with metoclopramide use, and the FDA's eventual and late-coming unilateral actions to strengthen the warnings for metoclopramide once it became aware of such evidence.

SUMMARY OF ARGUMENT

From 1985 through 2009, the warnings in the labeling for metoclopramide asserted that it carried a low risk – only 0.2% or 1 in 500 – of a class of neurological side effects called extrapyramidal symptoms (“EPS”), including a severe side-effect called tardive dyskinesia (“TD”). Extensive evidence in the medical literature, however, showed that warning to be a gross underestimate. The actual risk of EPS and TD, particularly with long-term use of metoclopramide, was in fact at least 100 times higher.

Such information was readily available to generic manufacturers through published medical reports and studies and through the FDA’s publicly available database of reported adverse drug reactions. No extensive studies were required; no post-market clinical testing, and no pre-existing experience with clinical trials from before metoclopramide was approved. All the generic manufacturers needed to do was monitor the medical literature for articles on their own drug and periodically check the FDA database for new reports relating to metoclopramide.

Had the generic manufacturers taken those steps they readily would have found and easily understood the evidence described in this brief and been able to take appropriate action – whether attempting to issue a non-misleading warning or requesting from the FDA a strengthened warning for all metoclopramide labels. Such minimal efforts are a far cry from the purported difficulties petitioners claim attend post-market monitoring, would not have meaningfully added to the costs of generic metoclopramide, would have averted untold suffering among patients, and

likely would have lowered the overall cost of health care by avoiding the medical and legal costs of metoclopramide-induced EPS and TD.

The readily available evidence of a higher risk of EPS and TD from metoclopramide has several implications for the preemption theories asserted by petitioners. At a minimum it demonstrates that the post-market monitoring needed to remain abreast of the heightened risks of metoclopramide-induced EPS and TD was fairly straight-forward and not unduly burdensome. Satisfying their state-law duty to warn thus would not conflict with the various other goals of federal law and policy regarding generics, and in fact would be consistent with the more fundamental federal concern regarding accurate safety information in drug labeling. The history demonstrates that generic manufacturers were not incapable of monitoring post-market safety information, and cannot simply pass the buck to the brand manufacturer by claiming a lack of expertise or context.

The FDA's response to the evidence of heightened risks from metoclopramide also undermines petitioners' claims that this case requires an intrusive inquiry into the FDA's decision-making processes or that it requires impermissible second-guessing and speculation. When the FDA finally considered the evidence of metoclopramide-induced TD in 2008-2009, it acted decisively and urgently to add a black-box warning to the product. It did so based on much of the same information that had been available for more than a decade. There is little need to speculate regarding the FDA's reaction to that same information had generic manufacturers submitted it earlier

in connection with a proposed labeling change. The suits in these cases thus pose no threat to the FDA or federal law and complement, rather than obstruct, their functions.

ARGUMENT

I. **The High Risk of Metoclopramide-Induced EPS and TD Was Readily Discoverable by Generic Manufacturers Long Before the FDA Added a Black-Box Warning.**

As described in Respondents' Brief, at 6, metoclopramide or Reglan® is a drug approved for short-term use in treating recurrent diabetic gastric stress and gastric reflux. It is a dopamine antagonist – blocking the dopamine receptors that receive signals between nerves. *Id.* Like other drugs of its class, it can have adverse effects on the body's nervous system, in particular the body's extrapyramidal system, which controls fine motor movement. Such adverse neurological effects are known as extrapyramidal symptoms ("EPS") and involve a loss of control over various fine motor movements. A particularly severe form of EPS is tardive dyskinesia ("TD"), which involves "grotesque involuntary movements of the mouth, tongue, lips, and extremities, involuntary chewing movements, and a general sense of agitation." *McNeil v. Wyeth*, 462 F.3d 364, 366 (CA5 2006).

Metoclopramide was originally approved by the FDA in 1980 and sold under the brand name Reglan®. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 606 (CA8 2009). Generic versions of metoclopramide began receiving FDA approval in 1985. *Id.* The ap-

proved uses for metoclopramide were for relatively short durations – between 2 and 12 weeks. Resp. Br. at 6 (citing Reglan label published in the Physician’s Desk Reference from the early to mid-1980s).

Since 1985 and throughout the time period relevant to this case, the labeling for branded and generic metoclopramide advised of a low risk of EPS of all kinds – only 1 in 500, or 0.2%. Resp. Br. at 7-8 (quoting label warnings). The incidence of TD was not separately described on the label, but because it is a mere subset of EPS, the label necessarily suggested an even lower incidence of TD than of EPS generally.

By 2001 and 2002, however, when respondents began taking generic metoclopramide, it was well known that the drug was routinely prescribed for longer periods than the label suggested.² And, during the more than 20 years between the initial approval of metoclopramide and when respondents began taking it, a substantial quantity of publicly available evidence accumulated that the risks of EPS and TD were much higher than claimed on the label.

² Resp. Br. at 7; Robert B. Stewart, James J. Cerda, Mary T. Moore & William E. Hale, *Metoclopramide: An Analysis of Inappropriate Long-Term Use in the Elderly*, 26 ANN. OF PHARMACOTHERAPY 977, 978 (July/Aug. 1992) (“long-term treatment with [metoclopramide] has become more common”); P. Jay Pasricha, Nonko Pehlivanov, Aravind Sugumar & Joseph Jankovic, *Drug Insight: from disturbed motility to disordered movement – a review of the clinical benefits and medicolegal risks of metoclopramide*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY 138, 141 (March 2006) (“Despite the recommendation for short-term use (4-12 weeks), metoclopramide is frequently prescribed for chronic use.”).

In 1989, for example, a published review of 16 cases of metoclopramide-related movement disorders, noted that there were “[a]t least 1031 patients with metoclopramide-induced movement disorders” described in the medical literature. Lucinda G. Miller & Joseph Jankovic, *Metoclopramide-Induced Movement Disorders*, 149 ARCH. INTERN. MED. 2486, 2489 (Nov. 1989). The authors observed that “[d]espite the manufacturer’s estimate of only 0.2% frequency of metoclopramide-induced movement disorders, the actual prevalence is probably greater.□” *Id.* (footnote omitted)

In 1992, another published analysis noted the increased long-term use of metoclopramide and the resulting increased incidence of TD. Robert B. Stewart, James J. Cerda, Mary T. Moore & William E. Hale, *Metoclopramide: An Analysis of Inappropriate Long-Term Use in the Elderly*, 26 ANN. OF PHARMACOTHERAPY 977, 978 (July/Aug. 1992) (“TD originally was thought to be a very rare adverse effect of metoclopramide treatment, particularly as the drug is usually intended for short-term therapy.□ However, as long-term treatment with this drug has become more common, the incidence of TD has increased.”) (footnote omitted).

In 1993, researchers set out to quantify the incidence of EPS and TD caused by metoclopramide. They initially observed that merely looking to the incidence reports filed with the FDA was inadequate because many adverse reactions are simply not reported. Linda Ganzini, Daniel E. Casey, William F. Hoffman & Anthony McCall, *The Prevalence of Metoclopramide-Induced Tardive Dyskinesia and Acute*

Extrapyramidal Movement Disorders, 153 ARCH. INTERN. MED. 1469, 1471 (June 28, 1993) (“adverse drug reaction registries underestimate the true incidence of EPS because of substantial underreporting.”) (footnote omitted). Such underreporting and the lack of studies on the true rate of metoclopramide-induced TD was a problem in their view:

Despite the absence of prevalence studies, the manufacturer’s product labeling reports the incidence of all metoclopramide-induced EPS at 0.2%.[□] Our clinical experience suggests that the true prevalence of metoclopramide-induced EPS is substantially higher than reported by the manufacturer.

Id. (footnote omitted).

To remedy the deficiency in the data on metoclopramide-induced EPS, the authors thus conducted their own controlled prevalence study of patients taking metoclopramide. That study found that 29% of patients taking metoclopramide had TD as compared to 17% of the control group. *Id.* at 1472. The incidence of another EPS – parkinsonism – was likewise considerably higher for patients taking metoclopramide: 31% as compared to 7.8% for the control group. *Id.* at 1473; *see also id.* (the “results indicate that the prevalence and severity of EPS, including tardive dyskinesia, drug-induced parkinsonism, and subjective akathasia, were significantly increased in a group of chronically ill, older, metoclopramide-treated men”).

The authors raised as plain a red-flag as can be imagined, concluding that their “data clearly suggest that both the prevalence and severity of metoclopra-

mid-induced acute EPS and tardive dyskinesia have been underestimated and underrecognized and are approximately *100 times more prevalent than previously reported.*” *Id.* (emphasis added).

Another controlled study published by a different group of researchers in 1994 reached similar conclusions, finding that the incidence of TD in metoclopramide-treated patients was 27%, as compared to 12% in the control group. Daniel D. Sewell, Angela B. Kodsi, Michael P. Caligiuri & Dilip V. Jeste, *Metoclopramide and Tardive Dyskinesia*, 36 *BIOL. PSYCHIATRY* 630, 631 (1994).

These studies and the numerous published reports of metoclopramide-induced EPS and TD cited by the authors were more than enough to raise serious concerns that the labeling for metoclopramide was inaccurate and misleading.

Indeed, in a review of the literature twelve years later, the Ganzini and Sewell studies continued to be cited as evidence that EPS “probably occur more frequently than is realized.” P. Jay Pasricha, Nonko Pehlivanov, Aravind Sugumar & Joseph Jankovic, *Drug Insight: from disturbed motility to disordered movement – a review of the clinical benefits and medicolegal risks of metoclopramide*, 3 *NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY* 138, 143-44 (March 2006).

The Pasricha review also discussed a further source of information that was readily available to generic metoclopramide manufacturers throughout the period relevant to this case: the FDA’s database of reported adverse drug reactions, the Adverse Event Reporting System or ‘AERS.’ “Between 1968 and

2003, the Adverse Event Reporting System database of the medwatch program maintained by the FDA contained 87 cases of tardive dyskinesia” in patients taking metoclopramide *Id.* at 142. “Permanent disability was reported in nearly 25% of cases.” *Id.* at 143; *see also* Douglas Shaffer, Marian Butterfield, Carol Pamer & Ann Corken Mackey, *Tardive Dyskinesia Risks and Metoclopramide Use Before and After U.S. Market Withdrawal of Cisapride*, 44 J. AM. PHARM. ASS’N 661, 663 (Nov./Dec. 2004) (noting at least 87 cases of metoclopramide-associated tardive dyskinesia reported to AERS prior to mid-2003, most involving long-term use of the product).

Having reviewed both published reports and AERS information that was equally available to generic manufacturers, the Pasricha article described the 0.2% EPS frequency estimate as “probably a gross underestimation” due to the likely failure to include the elderly in the prospective clinical trials, difficulty recognizing the early signs of EPS, and the short length of the studies compared with the longer exposure likely to trigger EPS. Pasricha, *et al.*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY at 143. And the authors noted the “consistent finding * * * that elderly women are at the highest risk of developing tardive dyskinesia.” *Id.*

Despite the readily available evidence of greater risks from metoclopramide than disclosed in the labeling, there is no evidence that any of the petitioners informed the FDA of the inadequacy of the labeling or sought to strengthen the warnings.

Indeed, it was not until 2009 that the FDA, on its own initiative took action to strengthen the warnings

for metoclopramide. As the Eighth Circuit described below in *Mensing*: “Acting on its own initiative pursuant to the Food and Drug Administration Amendments Act of 2007, Pub.L. No. 110-85, 121 Stat. 823 (FDAAA), the FDA ordered manufacturers of Reglan and generic metoclopramide on February 26, 2009 to add a boxed warning to their labels about the increased risks of tardive dyskinesia from long term metoclopramide usage.” 588 F.3d at 607.

In FDA’s 2008 internal report describing its reasons for adding stronger warnings for metoclopramide, the FDA cited the 1993 Ganzini study as well as the review of the literature by Pasricha, *et al.*, described above, both of which noted a higher incidence of TD than disclosed in the product labeling. Memorandum from Kate Gelperin, *et al.*, Office of Surveillance and Epidemiology, CDER, FDA, to Donna Griebel, Director, Division of Gastroenterology Products, OND, CDER, FDA, *Risk of Metoclopramide-induced Movement Disorders*, June 27, 2008, at 5 (OSE RCM # 2008-269) (“Gelperin Report”). The report also noted two other studies looking at patients with movement disorders or taking drugs for Parkinson’s or similar conditions and noted the high percentage of such patients that had a high rate of previous metoclopramide use, suggesting that a substantial percentage of EPS and TD cases were being caused by metoclopramide. *Id.* at 6.

In addition, the FDA identified 80 adverse event reports between 2001 and 2008 in its AERS database involving metoclopramide-associated TD. *Id.* 9. And it noted the article by Shaffer, *et al.*, identifying 87 cases of metoclopramide related TD through 2003.

Id. at 10. The report recognized that the AERS data likely underrepresented the occurrence of TD due to underreporting. *Id.*

In its discussion section, the FDA report noted that its review of the literature suggested that “the risks would appear to outweigh the clinical benefit of metoclopramide in chronic conditions such as GERD [gastroesophageal reflux disease] where effective drug therapies with better safety profiles are available.” *Id.* at 13. It concluded that “[f]rom a regulatory and public health perspective, heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed.” *Id.* at 14.

The report recommended a boxed warning – the strongest type available – as well as a public health advisory in order to emphasize the dangers of long-term metoclopramide use. *Id.* at 14. The resulting 2009 warnings required by the FDA significantly strengthened the label discussion of TD and noted the 100-times greater risk identified in the literature. The boxed warning itself stated, *inter alia*, that

Chronic treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. The elderly, especially elderly women, are most likely to develop this condition. * * *. Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.

See Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research (CDER), FDA, to NDA holders for Reglan, 2 (Feb. 26, 2009).³ The required revision to the Warnings section of the label identified the much higher incidence of TD when used long-term and the greater risk to elderly women, stating:

Although the risk of tardive dyskinesia (TD) with metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 3 months.

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 with the duration of treatment and the total cumulative dose.

Id. at 3.

What is most notable about the FDA's action is that it was based on information that had been available for years, yet had not been adequately brought to the FDA's attention by petitioners or others. Indeed, the TD incidence data cited by FDA was the same 1992 Ganzini study discussed above and the 2006 Pasricha review of the literature citing that same study and another from 1993. All of that information and

³ The letter requiring the change can be found online at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf>.

more easily could have been identified by petitioners in these cases and brought to the FDA's attention more than a decade earlier and well before respondents began taking metoclopramide.

The failure to revise the warnings for metoclopramide earlier is especially tragic given the limited medical benefits of the drug and hence the importance to doctors of accurate risk information in determining whether the limited benefits are worth the risks. In reviewing the literature on metoclopramide, Pasricha, *et al.*, noted that “the drug is seldom capable of producing dramatic clinical improvement when administered chronically.” Pasricha, *et al.*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY at 145. He further observed that “[i]n many cases, an alternative drug or a shorter duration of treatment could probably have adequately controlled the gastrointestinal symptom.” *Id.* at 141. Indeed, due to the high risks and limited utility of metoclopramide, the American Gastroenterological Association gave metoclopramide a grade of “D” (on the A, B, C, D scale) for use in treatment of GERD, recommending against its use based on “fair evidence that it is ineffective or harms outweigh benefits.” American Gastroenterological Ass'n Institute, *American Gastroenterological Association Medical Position Statement on the Management of Gastroesophageal Reflux Disease*, 135 GASTROENTEROLOGY 1383, 1384 (2008).

II. The History of Inaction in the Face of Readily Available Evidence of Metoclopramide's Risks Counsels Against Preemption.

The fact that substantial evidence of the risks of metoclopramide-induced EPS and TD was publicly available for nearly two decades before the FDA was forced to unilaterally act on that information strongly counsels against preemption in this case. Generic manufacturers have a state-law duty to warn their customers of the genuine risks of their products, and the label for metoclopramide was woefully inadequate for decades. Respondents are not required by federal law to sit idly by in the face of evidence that their labels are misleading, and should not be given a free pass by claiming that providing accurate safety information is too burdensome for them and is the exclusive obligation of the brand-name manufacturer.

Review of publicly available information is not unduly burdensome. As the previous section demonstrates, the evidence of EPS and TD from long-term metoclopramide was readily and publicly available and would have been relatively simple for generic manufacturers to discover and analyze. Such evidence more than amply signaled that a stronger warning was necessary and that the existing warning was inadequate. Indeed, the evidence easily satisfies the requirement that a drug's "labeling shall be revised 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." 21 C.F.R. § 201.80(e).

Contrary to the assertions by petitioners, PLIVA Br. at 37-38, such analysis would not have been par-

ticularly difficult, required no burdensome clinical studies, required no extensive knowledge of prior clinical studies performed by the brand manufacturer, and would have raised numerous red flags regarding EPS and TD. Articles in the medical literature were quite explicit in drawing the obvious and indisputable conclusion that the risks reported on the labeling were grossly understated. *See Ganzini, et al.*, 153 ARCH. INTERN. MED. at 1471, 1473 (“the true prevalence of metoclopramide-induced EPS is substantially higher than reported by the manufacturer”; “both the prevalence and severity of metoclopramide-induced acute EPS and tardive dyskinesia have been underestimated and underrecognized and are approximately 100 times more prevalent than previously reported”); Pasricha, *et al.*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY at 143, 145 (0.2% EPS frequency estimate as “probably a gross underestimation”; “the risk of developing tardive dyskinesia seems to be grossly underestimated in the package insert”).⁴

The FDA’s publicly available AERS database likewise contained publicly available information that

⁴ Tellingly and tragically, it was the failure of manufacturers to do even the most basic review of the scientific literature that was one of the factors in the 1937 Sulfanilamide disaster. *See* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER (June 1981) (<http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm>) (“Even a review of the current existing scientific literature would have shown that other studies--such as those reported in several medical journals--had indicated that diethylene glycol was toxic and could cause kidney damage or failure.”). That disaster, of course, led to the adoption of the FDCA.

required no extraordinary measures to access and analyze. Had respondents merely reviewed the reports in AERS, it would have discovered 87 instances of metoclopramide-related EPS through 2003. That number certainly would have raised a red flag, and is far more than the 20 adverse events noted by this court in *Wyeth v. Levine*, -- U.S. --, 129 S. Ct. 1187, 1193 (2009).

Petitioners' claim that generic manufacturers receive only limited numbers of adverse event reports and hence cannot place them in context, PLIVA Br. at 38, gets it only half right. While it is true that few adverse event reports are submitted directly to the generic manufacturers, it is simply not true that they are incapable of putting such reports in context. All respondents had to do was look to the database itself and *read* the other reports, regardless of who submitted them. Despite any imbalance in the source of reports to the AERS database, there is no imbalance whatsoever in access to all the reports. The only reason generic manufacturers would lack context for their reports would be if they simply refused even to look at the other reports on the database. The notion that generic manufacturers would turn such a blind eye to the consequences of the drug they sell, feigning ignorance and relying on the brand manufacturers to do their work for them, is precisely why it is important to have state law tort remedies.

The subsequent FDA response to evidence regarding EPS and TD obviates causation concerns. As described in Part I, the evidence available to respondents for years was largely the same evidence relied upon by FDA more than a decade later when it finally

considered the issue and in 2009 ordered a black-box warning concerning the risks of EPS and TD from long-term metoclopramide use. Given the FDA's actual response to such evidence, there is no need to speculate about what it would have done if the generic manufacturers had raised the same evidence and concerns earlier. FDA would have done *what it in fact did* – add a warning.

Petitioners' reliance on *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2000), is inapposite, particularly in light of the actual history of metoclopramide. Given FDA's "explicit actions" in response to the same information petitioners should have provided earlier, there is no need for "speculation as to the FDA's behavior in a counterfactual situation" and no need for "second guessing the FDA's decisionmaking or overburdening its personnel." *Id.* at 354 (Stevens, J., joined by Thomas, J., concurring in the judgment). Because we already know the FDA's response to the late-acquired, but long-available, evidence of higher EPS and TD rates than disclosed on the label, this is indeed a "different case" than *Buckman* and does not raise the same type of concerns underlying *Buckman*. *Id.*

This case is instead more comparable to *Wyeth v. Levine*, where this Court viewed state-law failure-to-warn suits as "complementary," rather than antagonistic, to FDA's mission. -- U.S. at --, 129 S. Ct. at 1202. Indeed, far from discouraging generic manufacturers from bringing safety concerns to its attention, FDA regulations in fact *require* manufacturers to report on such concerns. *See* 21 C.F.R. § 314.80(b) (requiring manufacturers to "promptly review all ad-

verse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information received from * * * postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers” and submit reports and follow-up information to the FDA). And FDA regulations provide that a drug whose label lacks an adequate warning of a serious risk is misbranded. *See* 21 U.S.C. § 352(f)(2); 21 C.F.R. § 201.57(e) That obligation squarely rebuts the notion that FDA will be burdened with *unwanted* safety information and concerns as a result of state-law duties to warn. Rather, the FDA has an interest, if not an affirmative duty, to address misbranded drugs. And the history of metoclopramide reflects that the FDA in fact acts on that interest, subject to its inherent limitations. Indeed, earlier efforts to improve the warnings on metoclopramide would undoubtedly been welcomed by the FDA. When the FDA finally got to the issue of long-term use of metoclopramide on its own, it concluded that “heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed.” Gelperin Report at 14.

As in *Wyeth*, state law incentives to keep safety information in product labels current and accurate constitute “an additional, and important, layer of consumer protection that complements FDA regulation” and supplements FDA’s “limited resources to monitor the 11,000 drugs on the market.” -- U.S. at --, 129 S. Ct. at 1202. Ultimately, however, grounding preemption on uncertain concerns over how FDA will handle increased information and efforts by generic

manufacturers to keep their labels current and accurate, or what effect it will have on the cost of generic drugs, is a poor basis for preemption. Those concerns are not founded on any direct conflict with statutory or regulatory provisions, but rather an amorphous notion of “obstacle” preemption based on overly simplified views of the objects and purposes of federal law. But, as Justice Thomas has noted, federal law rarely has a single purpose, and elevating one purpose above the other is not a proper basis for preempting state law. *Wyeth*, -- U.S. at --, 129 S. Ct. at 1215-17 (Thomas, J., concurring in the judgment).

Petitioners would have this Court elevate cost and convenience above safety as the sole “object” of federal law regarding generic drugs. But federal law seeks to advance both goals, and conspicuously lacks an express preemption provision. Petitioners’ efforts to preempt state law based on their – or this Court’s – view as to which goal is more important and whether state-law claims might be an obstacle to that goal improperly invade the States’ traditional authority over health and safety and should be rejected.

CONCLUSION

For the reasons above, this Court should affirm the decisions below.

Respectfully submitted,

ERIK S. JAFFE
(Counsel of Record)
ERIK S. JAFFE, P.C.
5101 34th Street, N.W.
Washington, D.C. 20008
(202) 237-8165
jaffe@esjpc.com

MIKE PAPANTONIO
TROY A. RAFFERTY
LEVIN, PAPANTONIO, THOMAS,
MITCHELL, RAFFERTY &
PROCTOR, P.A.
316 South Baylen Street
Post Office Box 12308
Pensacola, FL 32591
(850) 435-7163

JOHN EDDIE WILLIAMS, JR.
JOHN T. BOUNDAS
WILLIAMS, KHERKHER, HART,
BOUNDAS, LLP
8441 Gulf Freeway Suite 600
Houston, TX 77017
(713) 230-2200

Counsel for Amicus Curiae

Dated: March 2, 2011

