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 Eighth Circuit and for the Fifth Circuit

BRIEF FOR RESPONDENTS GLADYS MENSING AND JULIE DEMAHY

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BRIEF FOR RESPONDENTS

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[1] *See Mensing v. Wyeth*, J.A. 400; *Demahy v. Actavis, Inc.*, J.A. 520; *Gaeta v. Perrigo Pharm. Co.*, No. 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011); *Vitatoe v. Mylan Pharm., Inc.*, No. 1:08cv85, 2010 WL 1008788 (N.D. W. Va. Mar. 5, 2010); *Weilbrenner v. Teva Pharm. USA, Inc.*, No. 7:08-CV-23, 2010 WL 924915 (M.D. Ga. Mar. 10, 2010); *Swicegood v. Pliva, Inc.*, No. 1:07-cv-1671, 2010 WL 1138455 (N.D. Ga. Mar. 22, 2010); *Dorsett v. Sandoz, Inc.*, No. CV06-7821, 2010 WL 1174204 (C.D. Cal. Mar. 26, 2010); *Finnicum v. Wyeth, Inc.*, No. 1:09-CV-785 (E.D. Tex. May 25, 2010); *Fulgenzi v. Wyeth, Inc.*, No. 5:09CV1767, 2010 WL 649349 (N.D. Ohio Feb. 19, 2010); *Munroe v. Barr Labs.*, 670 F. Supp. 2d 1299 (N.D. Fla. 2009); *Bartlett v. Mutual Pharm. Co.*, 659 F. Supp. 2d 279 (D.N.H. 2009); *Stacel v. Teva Pharm. USA*, 620 F. Supp. 2d 899 (N.D. Ill. 2009); *Schrock v. Wyeth*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009); *Couick v. Wyeth, Inc.*, No. 3:09-CV-210-RJC-DSC, 2009 WL 4644394 (W.D.N.C. Dec. 7, 2009); *Pustejovsky v. Wyeth*, No. 4:07-CV-103-Y, 2009 WL 3336032 (N.D. Tex. Sept. 4, 2009); *see also In re Budeprion XL Marketing & Sales Litig.*, No. 09-md-2107, 2010 WL 2135625 (E.D. Pa. May 26, 2010) (rejecting preemption defense in consumer fraud class action against generic drug companies); *Kellogg v. Wyeth*, 612 F. Supp. 2d 437 (D. Vt. 2009) (post-*Levine* ruling denying certification for interlocutory appeal of pre-*Levine* ruling denying preemption). Long before *Levine*, the Fourth Circuit reached the same conclusion in *Foster v. American Home Prods. Corp.,* 29 F.3d 165, 170 (4th Cir. 1994).

Levine held that the manufacturer, not the Food and Drug Administration (FDA), bears primary responsibility for ensuring that labeling for its drug adequately warns of the product's risks. This conclusion applies equally to the manufacturers of generic drugs. Under the federal regulatory scheme, the manufacturer of a generic drug shares responsibility with the manufacturer of its brand-name counterpart to ensure that the labeling for both products adequately warns prescribers and protects consumers.

Defendants seek a special immunity from state tort liability for generic drug companies, an immunity that would create an arbitrary and irrational distinction between classes of patients based on the vagaries of pharmacy practice: those whose prescriptions were filled with brand-name products would retain their right to sue, while those whose pharmacies substituted generic drugs would lose that right. Not only would such a regime make no sense, but it would also create a disincentive for consumers to take generic drugs, which is precisely the opposite of what Congress intended when it passed the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act (FDCA) in 1984. Try as they might, Defendants cannot muster any evidence that Congress ever intended such a bizarre result.

Today, seventy percent of prescriptions in this country are filled with generic drugs. And, contrary to Defendants' claims, the fact that a drug has "gone generic" does not mean that it is safe. In reality, as the facts of this case demonstrate, drug risks frequently do not become clear until years after a drug has been on the market. The drug that injured Gladys Mensing and Julie Demahy, for example, had

been available as a generic for more than fifteen years at the time it was first prescribed to them, and it was just two years ago that FDA finally mandated a "black box" warning of the risks of long-term use. If generic drug companies are granted immunity for failing to warn of known risks of their drugs, they will have very little incentive to strengthen their warning labels as new risks emerge, even though federal law mandates that they do so. The inevitable result will be more deaths and injuries that could easily have been prevented—a result that Congress did not intend and this Court should not countenance.

Defendants' main defense cannot withstand even the mildest scrutiny. They argue that it would have been "impossible" for them to warn consumers of their drug's risks without running afoul of federal regulations. Yet the United States itself has disavowed this theory. Moreover, Defendants themselves concede that they could have told FDA about the mounting evidence that long-term use of their drug causes catastrophic injuries and asked the agency to approve a stronger warning. Ignoring this mounting evidence, Defendants chose to sit back and do nothing. They should not be rewarded with an immunity that would strip consumers of any means of seeking redress for their injuries.

PERTINENT STATUTORY AND REGULATORY PROVISIONS

Pertinent statutory and regulatory provisions are set forth in an Appendix to this brief.[2]

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[2] A number of regulations relevant to this case have been revised or redesignated over the past decade. This brief

STATEMENT OF FACTS

In March 2001, Gladys Mensing's doctor prescribed Reglan to treat her diabetic gastroparesis. J.A. 402. The active ingredient in Reglan is metoclopramide, which is available in both branded and generic forms. *Id.* Pursuant to Minnesota's drug substitution law, Minn. Stat. § 151.21, Ms. Mensing's pharmacist filled her prescriptions with generic metoclopramide. *Id.* The generic metoclopramide was manufactured by, *inter alia*, Defendants Pliva, Inc. (Pliva), Teva Pharmaceuticals USA, Inc. (Teva), UDL Laboratories (UDL), and Actavis Elizabeth LLC (Actavis). *Id.* at 391. Ms. Mensing took metoclopramide, as prescribed, for four years. *Id.* at 402.

Ms. Mensing's long-term use of metoclopramide caused her to develop tardive dyskinesia. *Id.* Tardive dyskinesia is a severe and irreversible neurological disorder, characterized by "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 (5th Cir. 2006).

In 2002, Julie Demahy's doctor prescribed Reglan to treat her gastroesophageal reflux disorder (reflux). J.A. 434, 521. Ms. Demahy's pharmacist filled her prescriptions with generic metoclopramide

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follows the practice of *amicus curiae* United States in citing to the regulations in effect in 2001, the earliest year in which either of the Plaintiffs ingested the Defendants' products, noting subsequent changes where relevant. U.S. Amicus Br. 4 n.2. By contrast, Defendants' briefs cite to a number of revised versions of these same regulations that post-date the events here at issue.

in accordance with Louisiana's substitution statute, La. Admin. Code, Title 46, Part LIII, Chapter 25, § 2511. *Id*. The generic metoclopramide Ms. Demahy ingested was manufactured by Defendant Actavis, Inc. (Actavis). *Id*. Like Ms. Mensing, Ms. Demahy took metoclopramide, as prescribed, for approximately four years. *Id*. As a result of her use of metoclopramide she too developed tardive dyskinesia. *Id*.

Both Plaintiffs sued the manufacturers of the metoclopramide they had ingested. They asserted traditional state-law products liability claims for failure to warn. They alleged that the defendants had provided inadequate warnings regarding the risk of tardive dyskinesia from long-term metoclopramide use and that the absence of adequate warnings of that risk caused their injuries. J.A. 26, 439.[3]

In both cases, the generic drug company defendants moved to dismiss based on federal preemption. J.A. 402, 522.[4] On appeal from the district court rulings,[5] both the Fifth Circuit and the

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[3] Both plaintiffs also sued the manufacturers of brand-name Reglan for misrepresention. Those claims were abandoned or dismissed under state law because the Plaintiffs had never taken Reglan. J.A. 418-21, 478.

[4] To be precise, following the district court's grant of motions to dismiss by Pliva and Actavis in the *Mensing* case, the other generic defendants asserted preemption through motions for summary judgment, but on purely legal, not factual, grounds. J.A. 402-03. Actavis also filed a motion to dismiss in *Demahy*. J.A. 522.

[5] The appeal in *Demahy* was interlocutory, from a ruling denying the motion to dismiss. J.A. 518.

Eighth Circuit rejected the preemption defense, guided by this Court's *Levine* decision. J.A. 415-18, 562-63.

Regulatory History of Metoclopramide

Metoclopramide is a prokinetic gastrointestinal drug that enhances contractions of the esophagus, stomach, and intestines. It acts by blocking the body's dopamine receptors, thereby impeding the transfer of signals between nerves. As a "dopamine antagonist," metoclopramide can adversely affect the body's extrapyramidal system which controls fine motor skills. Tardive dyskinesia is a particularly severe form of such extrapyramidal symptoms (EPS). *See McNeil*, 462 F.3d at 366.

Reglan was first approved by FDA in 1980 as treatment "for two to eight weeks . . . for the relief of symptoms associated with acute and recurrent diabetic gastric stress." *See Physician's Desk Reference*, at 1566 (36th ed. 1982). In 1984 an indication for "short-term (4 to 12 weeks) therapy" for reflux was added. *Physician's Desk Reference*, at 1660 (39th ed. 1985); *see also Physician's Desk Reference*, at 1635 (41st ed. 1987). The following year, generic drug manufacturers, including the Defendants, began to obtain approval for generic versions of metoclopramide.[6]

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[6] Reglan was approved pursuant to a "New Drug Application" (NDA) under 1962 Food, Drug and Cosmetics Act § 505(b), 21 U.S.C. § 355(b) (FDCA), while the Defendants' metoclopramide products were approved through an "Abbreviated NDA" (ANDA) under 1984 FDCA § 505(j), 21 U.S.C. § 355(j), enacted as part of the Drug Price Competition & Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (Hatch Waxman Amendments).

Although Reglan/metoclopramide was approved only for short-term use, many doctors prescribed the drug for longer periods because reflux and gastroparesis are chronic conditions. *See McNeil*, 462 F.3d at 369 (Wyeth's own data showed that 84 percent of patients were using Reglan long-term; 32 percent of patients in one study had been taking metoclopramide for more than one year); *see also* Reglan Label, *Warnings* at 5 (2010) (20 percent of patients using metoclopramide do so for more than 12 weeks).[7] Both Plaintiffs allege that manufacturers of generic metoclopramide were aware of this widespread long-term use but took no steps to discourage the practice.[8]

During all times relevant to these cases, the labels for Reglan and generic metoclopramide repeatedly asserted that the risk of EPS, including tardive dyskinesia, was quite low. The "Clinical Pharmacology" section of the label stated: "Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal symptoms, although these are comparatively rare (See WARNINGS)." Mensing 8th Cir. Opening Br. App. 260a. The "Warnings" section of the label elaborated:

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[7] *Available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/017854s055lbl.pdf (last visited Feb. 17, 2011).

[8] A drug is misbranded if its label "fails to reveal" material facts "with respect to consequences which may result from . . . customary or usual . . . use" of the drug, which includes common "off-label" uses. 21 U.S.C. §§ 321(n) and 352(a) .

> Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg`/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at higher dosages.

Id. at 261a.[9]

The "Adverse Reactions" section of the label reiterated this characterization:

> **Extrapyramidal Reactions (EPS)**
>
> Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day.

Id.[10]

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[9] The "Warnings" section identified tardive dyskinesia, as one of the EPS that may develop in patients treated with metoclopramide, but implied that tardive dyskinesia will occur far less frequently than the far more readily treatable acute dystonic reactions, which the label identified as the "primar[y]" "manifest[ation]" of EPS. *Id.*

[10] Again, tardive dyskinesia was identified as a possible adverse reaction, but one that will occur in far fewer patients than the 1 in 500 who will experience acute dystonic reactions. *Id.*

This information about the risks of tardive dyskinesia and other EPS was first added to the Reglan/metoclopramide label in 1985. *Physician's Desk Reference*, at 1660 (39th ed. 1985); *Physician's Desk Reference*, at 1635 (41st ed. 1987). The labeling bore the same language regarding these risks until 2009.[11]

In the years between FDA approval of generic metoclopramide and Plaintiffs' use of the product, a number of studies in the medical literature concluded that the risk of tardive dyskinesia and other EPS associated with metoclopramide use was likely far greater than the 0.2 percent risk reflected on the label. *See McNeil*, 462 F.3d at 370 n.5 (citing studies from 1989, 1993, and 1994). Moreover, prior to mid-2003, at least 87 cases of metoclopramide-associated tardive dyskinesia had been reported to FDA's Adverse Event Reporting System (AERS), most involving long-term use of the product. Douglas Shaffer, *et al.*, *Tardive Dyskinesia Risks and Metoclopramide Use Before and After U.S. Market Withdrawal of Cisapride*, 44 J. Am. Pharm. Ass'n 661, 663 (2004).[12] Adverse event reports submitted to the AERS are publicly available and could have been

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[11] In 2004, FDA did approve the addition of a sentence to the "Indications and Usage" section of the label: "Therapy should not exceed 12 weeks in duration." Reglan Label, *Indications and Usage*, at 6 (2004), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17854s047lbl.pdf.

[12] The authors note that only a small percentage of adverse drug events are spontaneously reported, *id.* at 664 (reporting rates between 1 and 13 percent), so the actual number of cases of metoclopramide-associated tardive dyskinesia would have been far higher.

obtained by the Defendants. 21 C.F.R. § 314.430(e)(4).

Despite the mounting evidence that the risk of tardive dyskinesia was far greater than reflected on the label, no manufacturer ever proposed to FDA that the warnings on the Reglan and generic metoclopramide labels be revised to reflect that greater risk. Nor did any manufacturer of metoclopramide alert health care professionals or patients that metoclopramide's labeling did not adequately convey the risk of tardive dyskinesia associated with long-term use. J.A. 406.

Finally, in 2009, FDA, 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), ordered manufacturers of Reglan and generic metoclopramide to add a "Boxed Warning" to their labels about the increased risk of tardive dyskinesia from long-term metoclopramide use. A Boxed Warning is the strongest warning prescribed by the federal regulations, short of contraindicating the use altogether. 21 C.F.R. § 201.57(e).

The Boxed Warning stated, *inter alia*, "Chronic treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible . . . . 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) (hereinafter "Korvick letter");[13] *see also* Letter from Gary Buehler, CDER, FDA, to ANDA holders for Reglan, 2 (Feb. 26, 2009) (hereinafter "Buehler letter").[14] The FDA also ordered the manufacturers to add information in the warning section of the label that a published study had found tardive dyskinesia occurring in 20 percent of the patients treated for at least three months, *id.*, a hundred times greater than the 0.2 percent risk previously identified on the label.

At the same time it ordered these changes, FDA issued a MedWatch Safety Alert to health care professionals and a news release regarding the risk of tardive dyskinesia associated with long-term metoclopramide use. *See* FDA, *Metoclopramide-Containing Drugs* (Feb. 26, 2009).[15] The FDA took these steps because it "want[ed] patients and health care professionals to know about this risk so they can make informed decisions about treatment." FDA, *News Release* (Feb. 26, 2009).[16]

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[13] *Available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf.

[14] *Available at* http://www.fda.gov/ downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111378.pdf.

[15] *Available at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm106942.htm.

[16] *Available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149533.htm.

Federal Regulation of Drug Safety

The Drug Approval Process

All prescription drugs sold in this country require FDA approval before they may be marketed. The core objective of FDA approval process is to ensure that drugs are both safe and effective. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000). Manufacturers of new drugs must submit an NDA that demonstrates such safety and effectiveness through the results of clinical trials. 21 U.S.C. §§ 355(b), (d). NDA applicants must also propose labeling for the drug, which must identify, *inter alia*, appropriate use of the product, contraindications, warnings, precautions, and adverse reactions. 21 C.F.R. § 201.56. In particular, the drug's label must bear "such adequate warnings against use . . . where its use may be dangerous . . . as are necessary for the protection of users." 21 U.S.C. § 352(f)(2) (App. 1a).

Under the Hatch-Waxman Amendments, once a brand-name drug loses patent protection, another company may seek approval for a generic version of that drug through a process known as an abbreviated NDA or ANDA. 21 U.S.C. § 355(j). Because ANDA approval is based on the brand-name or "reference listed" drug (RLD), the proposed labeling for the generic drug must generally be the same as that for the RLD. 21 C.F.R. § 314.94(a)(8)(iv) (App. 15a). However, the proposed ANDA labeling is also subject to the statutory requirement that it bear "adequate warnings." 21 U.S.C. § 352(f)(2). In order to resolve any tension between these two requirements, FDA has instructed drug companies applying for an ANDA that, "if an ANDA applicant

believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. 17950, 17961, cmt. 40 (Apr. 28, 1992).

Manufacturers' Post-Approval Obligations

Because pre-marketing clinical trials of branded drugs are typically quite small, involving only carefully selected patients taking the drug for limited periods of time, many serious risks associated with a drug are not discovered until a larger and more diverse population has been exposed to the drug and the drug has been on the market for a number of years. Karen E. Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medicines*, 287 JAMA 2215 (May 1, 2002) (finding that half of all black box warnings on drugs introduced after 1975 were added after the drug had been on the market for seven or more years). Often, as in this case, risks do not fully emerge until long after generic drugs have entered the market and captured a large percentage of sales. For this reason, FDA imposes numerous post-approval obligations on manufacturers of both brand-name and generic drugs to ensure products remain safe and effective as labeled. 21 U.S.C. § 355(k).

All drug manufacturers must conduct regular pharmacovigilance to stay current on information regarding their products and ensure that their products remain safe and effective as labeled. *See* 21 U.S.C. § 355(k). They must "promptly review all adverse drug experience information obtained . . . from any source, . . . including reports in the scientific literature" and submit adverse event

reports to FDA. 21 C.F.R. §§ 314.80 (App. 11a) (NDA holders) and 314.98(a) (App. 18a) (ANDA holders). Each year, they must report to FDA a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and they must describe to FDA "the actions the applicant has taken or intends to take as a result of this new information." 21 C.F.R. §§ 314.81(b)(2)(i) (App. 13a) (NDA holders) and 314.98(c) (ANDA holders).

Most importantly, both the RLD holder and generic drug manufacturers are subject to the requirement that their approved "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. § 201.57(e).[17]

A drug company does not need to conduct extensive clinical research to support a new warning; "reasonable evidence of an association of a serious hazard with a drug" can come from adverse event reports or from studies in the medical literature, such as the published studies and adverse event reports discussed above, *supra*, p. 9, which had linked long-term metoclopramide use with tardive dyskinesia. *Levine*, 129 S. Ct. at 1197; J.A. 558-60. The FDA itself relied on published studies when it

[17] In 2006, FDA issued amended labeling regulations for prescription drugs. 71 Fed. Reg. 3922 (Jan. 24, 2006). That rulemaking redesignated § 201.57(e) as 21 C.F.R. § 201.80(e) and it remains the regulatory standard for drugs labeled under the old rules, such as metoclopramide. 71 Fed. Reg. at 3988, 3996. A virtually identical requirement applies to drugs labeled under the new regulation. 21 C.F.R. § 201.57(c)(6). 71 Fed. Reg. at 3,990.

mandated the black-box warning for metoclopramide in 2009. *See* Korvick letter at 1-2; Buehler letter at 1-2.

Procedures for Updating Warnings of Drug Risks

A number of procedures are available to generic-drug manufacturers to update the warnings on drug labels to account for new evidence of a serious hazard associated with a drug and to notify health care professionals of these risks.

First, a generic drug manufacturer may fulfill its obligations under § 201.57(e) by contacting FDA's Office of Generic Drugs (OGD) to express its concern about the need for stronger warnings on both the brand-name and generic products. Brief of the United States as Amicus Curiae 15-17. After adopting its final rule implementing the Hatch-Waxman Amendments, FDA advised ANDA holders: "After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17961 cmt. 40. Such a communication from a generic drug company to the OGD triggers a "substantive evaluation" of the need for additional warnings under FDA operating procedures. U.S. Amicus Br. 15-17 (citing Center for Drug Evaluation & Research, *Manual of Policies & Procedures* 5200.6 (May 9, 2001) (MAPP)).

Alternatively, any drug manufacturer can seek a labeling change by filing a "supplemental application" to its NDA or ANDA in accordance with

21 C.F.R. § 314.70 (App. 8a); *see also* 21 C.F.R. § 314.97 (App. 17a) (making § 314.70 applicable to ANDA holders). There are two kinds of supplemental applications under § 314.70: 1) a prior approval supplement (PAS) which requires FDA approval before proposed changes can be implemented, 21 C.F.R. § 314.70(b); and 2) a "Changes Being Effected" supplement (CBE), under which a manufacturer may implement the proposed change at the same time as the supplement application is submitted to FDA, 21 C.F.R. § 314.70(c).[18]

A drug manufacturer may use either supplement process to obtain FDA approval for a new warning. In general, drug manufacturers use the PAS process, and obtain prior agency approval, for changes to a drug's approved labeling. 21 C.F.R. §§ 314.70(b) and (b)(3). However, FDA regulations expressly permit a change in the approved labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" to be made through a CBE supplement. 21 C.F.R. §§ 314.70(c) and (c)(2)(i).

The CBE process developed out of the PAS process in 1965 so certain kinds of labeling changes are "placed into effect at the earliest possible time." The FDA will "take no action against a drug or applicant solely because" it had added a new

[18] Every time a drug manufacturer, brand-name or generic, submits a supplement application, it must certify to FDA that it will "update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling." FDA, Form 356h (Oct. 2005), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

warning to its approved labeling "prior to his receipt of a written notice of approval of the supplemental new-drug application." 30 Fed. Reg. 993-94 (Jan. 30, 1965). The agency adopted this policy of non-enforcement, which eventually became CBE, "in the interest of drug safety." *Id.* The FDA retains authority to reject labeling changes made through the CBE process. *Levine*, 129 S. Ct. at 1198.

A drug manufacturer can also request a labeling change through a Citizen Petition. 21 C.F.R. § 10.30 (App. 2a). The Citizen Petition process authorizes any person to request that FDA take formal agency action, including actions related to the safety of a prescription drug.[19] The Citizen Petition initiates an agency review of the proposed action. Both brand-name and generic drug companies frequently utilize the Citizen's Petition process.[20]

Besides changing approved labeling, drug manufacturers can ensure warning information is

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[19] *See, e.g.,* Letter from Janet Woodcock, M.D., Director, CDER, FDA, to James P. Reichmann (Feb. 17, 2011) (granting requested change in labeling for terbutaline regarding pregnancy risk), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/UCM243797.pdf; Letter from Steven K. Galson, M.D., M.P.H., Acting Director, CDER, FDA, to Sidney M. Wolfe, M.D., *et al.* (Aug. 9, 2005) (granting request to remove Meridia (sibutramine) from market due to safety risks), *available at* http://www.fda.gov/ohrms/dockets/dockets/02p0120/02p-0120-pdn0001-vol1.pdf.

[20] *See* FDA, Chronological Lists of Petitions and Advisory Opinions 2006-2008 (listing numerous petitions filed by drug companies), *available at* http://www.fda.gov/RegulatoryInformation/Dockets/UCM090522.htm, /UCM090519.htm, and /UCM090358.htm (last visited Feb. 22, 2011).

communicated directly to health care providers through "Dear Health Care Professional" (DHCP) letters. 21 C.F.R. § 200.5 (App. 5a). A drug manufacturer can request that FDA send out a DHCP letter[21] or it can issue one itself. Drug companies typically consult with FDA before sending their own DHCP letter, although the FDCA and FDA regulations do not prohibit drug companies from sending such correspondence unilaterally. U.S. Amicus Br. 17; *see also* 44 Fed. Reg. 37434, 37447 cmt. 63 (Jun. 26, 1979) ("the issuance of letters . . . warning health care professionals [about] possibly harmful adverse effects associated with the use of the drug . . . is not prohibited by these regulations"). DHCP letters are considered labeling under the Act, 21 U.S.C. § 321(m); nevertheless, because FDA classifies such letters as "promotional labeling," they are not subject to the "sameness" requirement applicable to "approved labeling." 21 C.F.R. § 201.100(d)(1).[22]

Thus, a number of procedures are available to generic drug companies to meet their obligations under 21 C.F.R. § 201.57(e) (App. 6a) to update their drugs' labeling with new warnings and to provide doctors with adequate warning regarding emerging risks of their drugs. As the Fifth Circuit emphasized, each of these procedures

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[21] *See, e.g.*, 21 U.S.C. § 355-1(i)(2) (establishing this process as a part of a risk evaluation and mitigation strategy under FDA Amendments Act of 2007).

[22] DHCP letters must contain a "true statement" about product risks, 21 C.F.R. § 201.100(d)(1), and must not be otherwise false or misleading. 21 U.S.C. § 352(a).

> shares the same fundamental attributes: the manufacturer bears primary responsibility for maintaining its label consistent with safe and effective use of its product; when reports indicate that a label requires revision, the manufacturer must alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science. . . . The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. *Who* prompts the FDA to consider necessary changes to that shared label is immaterial.

J.A. 554 (emphasis in original).

The Critical Role of Generic Drug Manufacturers in Ensuring Drug Safety

The generic drug industry has thrived under the regulatory regime established by Congress in the Hatch-Waxman Amendments. Today, over seventy percent of prescriptions are filled with generic drugs. Susan Okie, *Multinational Medicines—Ensuring Drug Quality in an Era of Global Manufacturing*, 361 New Eng. J. Med. 737, 738 (2009). Every state has enacted a drug substitution law that permits or requires pharmacies to fill a prescription written for a brand-name drug with its generic equivalent, absent a specific physician's instruction or consumer objection. Thomas P. Christensen, *et al.*, *Drug*

Product Selection: Legal Issues, 41 J. Am. Pharm. Ass'n 868, 869 (2001).

Because of their lower cost, generic drugs quickly capture the vast majority of sales of that product. Congressional Budget Office, *Effects of Using Generic Drugs on Medicare's Prescription Drug Spending*, at 7 (2010) (Over 90 percent of prescriptions for "multiple-source" drugs [available in branded and generic forms] are filled by generics.).[23] Unable to compete on price, RLD holders often actually or effectively abandon the market. GPhA, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 7 (2010) (32 percent of unique drug molecules with active sales are sold only as generics).[24] Wyeth, the manufacturer of Reglan, sold its NDA rights to a smaller company, Schwarz Pharma, Inc., Decl. of Jeff Siefert in Supp. of Schwarz Pharma Mot. for Summ. J. at 2, *Mensing v. Wyeth, Inc.*, 562 07-CV-3919 (D. Minn. 2008), ECF No. 99, and that company decided not to pay to continue publishing the Reglan label in the *Physician's Desk Reference*, presumably on account of declining sales. *See Physician's Desk Reference* (57th ed. 2003). If generic drug manufacturers did not share in responsibility for ensuring the adequacy of drug warnings, there would often be no one left "minding the store."

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[23] *Available at* http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf.

[24] *Available at* http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf.

SUMMARY OF ARGUMENT

In *Wyeth v. Levine*, --- U.S. ----, 129 S. Ct. 1187 (2009), this Court held that federal law does not preempt state inadequate warning claims brought against prescription-drug manufacturers, "absent clear evidence that the FDA would not have approved" a stronger warning for a drug. *Id.* at 1198. At the core of the ruling was the Court's conclusion that

> it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.

Id. at 1197-98.

These consolidated cases, before this Court on appeals from rulings on motions to dismiss for failure to state a claim, raise the issue whether federal law preempts the same state inadequate warning claims brought against manufacturers of generic drugs as a matter of law. Both the Fifth and the Eighth Circuit Courts of Appeals, guided by this Court's decision in *Levine*, ruled that it did not.

Congress did not intend to preempt state-law tort claims against generic drug companies. Congress's decision not to include an express preemption provision in the Hatch-Waxman Amendments, coupled with the absence of any federal remedy for persons injured by inadequately labeled drugs, demonstrates that Congress intended

to preserve state tort remedies as a complementary form of consumer protection.

Defendants' bid for conflict preemption on impossibility grounds is belied by the governing regulatory framework and by their own concessions. For defendants to prevail on this defense at this early procedural stage (*i.e.*, on motions to dismiss), they would have to demonstrate that it was impossible for them to have provided adequate warnings for their drug. But federal law, like state law, requires drug companies to provide adequate warnings about the dangers posed by their products and FDA regulations include a variety of procedural mechanisms through which Defendants could have sought FDA approval for stronger warnings. Defendants now concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide or to issue a DHCP letter about the risks associated with long-term use, but they chose not to do so.

Having made this concession, Defendants can only establish their impossibility preemption defense through "clear evidence that the FDA would not have approved a change" in warnings. *Levine*, at 1198. Defendants have not even attempted to make this showing and all evidence is to the contrary: when, in 2009, FDA learned on its own of the true risks associated with Reglan and metoclopramide, the agency ordered a new "Boxed Warning" for the drug. Equally as important, whether FDA would have denied approval for a stronger warning if Defendants had requested one is an issue of fact, inappropriate for resolution on a motion to dismiss.

Based on the disputed assumption that any warning change would have required prior agency approval, Defendants argue that it is Plaintiffs' burden to prove that FDA would have approved a warning change. But this argument mischaracterizes state law: to establish their claims for inadequate warning, Plaintiffs need only establish that Defendants sold metoclopramide with inadequate warnings regarding its risks, and that the absence of such adequate warnings caused their injuries. The burden of proving that FDA would have prohibited a stronger warning remains on Defendants as a necessary element of their impossibility preemption defense.

Defendants' argument for switching the burden of proof rests on a "fundamental misunderstanding" of *Levine*. Defendants contend that *Levine* turned on manufacturers' ability to warn "unilaterally" by virtue of the CBE process, and they argue that if their ability to warn is subject to prior FDA approval, then the Plaintiffs' claims are impliedly preempted. But *Levine* rested on the drug manufacturer's responsibility under federal law to maintain adequate warnings regarding its product's risks, not on the availability of one particular procedure for updating those warnings, the CBE process, which was not disputed. As this Court recognized, regardless of the process a manufacturer employs, FDA always retains the authority to approve or reject a labeling change. A preemptive conflict between state and federal law will only arise where a defendant can prove that FDA would have rejected a labeling change that state law requires.

Nor are the Plaintiffs' claims preempted on the ground that they obstruct statutory or regulatory

purposes. State tort remedies for inadequate warnings complement the federal regulatory scheme for generic drugs by helping to ensure that generic drugs remain safe as well as inexpensive. Drug risks often do not emerge until years after generic drugs have entered the market and captured the vast majority of sales and FDA lacks the resources to monitor the safety of all available drugs on its own. By providing incentives for generic drug manufacturers to pay attention to publicly available adverse event reports and scientific literature regarding the products they sell, and to go to FDA when such information reveals the need for additional warnings, state tort law plays a critical role in ensuring drug safety. By contrast, a ruling in favor of preemption would eliminate these incentives, increase health care costs, and undermine confidence in the safety and therapeutic equivalence of generic drugs. It would also leave Plaintiffs without remedy for their injuries.

Finally, Plaintiffs' claims are not preempted under the reasoning of either *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981), or *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). Pliva's argument that they are is again based on the false premise that Plaintiffs' claims are something other than traditional black-letter inadequate warning claims under state law. Moreover, neither case stands for the sweeping proposition for which Pliva cites it. *ArkLa Gas* was a narrow holding about the exclusive authority of the Federal Power Commission to approve prices for natural gas under the "filed rate doctrine," while *Buckman* involved an unusual state law claim premised on fraud on FDA that this Court has been careful to distinguish from

traditional state tort law claims such as Plaintiffs assert here.

ARGUMENT

I. CONGRESS DID NOT INTEND TO PREEMPT STATE-LAW TORT CLAIMS AGAINST GENERIC DRUG COMPANIES.

"'[T]he purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Levine*, 129 S. Ct. at 1194 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Congress made clear its intent about failure-to-warn claims when it decided not to include an express preemption provision in either the FDCA or the Hatch-Waxman Amendments. As this Court said in *Levine*: "If Congress thought state law suits posed an obstacle to its objectives, it surely would have enacted an express preemption provision at some point during the FDCA's 70-year history. . . . Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 1200.

The same conclusion applies to Defendants' preemption arguments here. As the Eighth Circuit observed:

> The Hatch-Waxman Amendments are part of this 70 year history and they do not explicitly preempt suits against generic manufacturers. Congress could have crafted a preemption provision for generic drugs in its 1984 amendments, having done so for medical devices less

> than 10 years earlier. It chose not to do that.

J.A. 407.

The *Levine* decision also makes clear that any consideration of congressional intent is subject to a strong presumption against preemption. 129 S. Ct. at 1194-95 & n.3. The States have long regulated public health and safety through their tort systems. When Congress legislates "in a field which the States have traditionally occupied, . . . we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Id.* at 1194-95 (quoting *Lohr*, 518 U.S. at 585, and *Rice v. Sante Fe Elevator Corp.*, 331 U.S. 218, 230 (1947) (internal quotations omitted)).

The bar to a finding that Congress intended to take away Plaintiffs' long-established state cause of action is set even higher here, because federal law itself provides no remedy for persons injured by inadequately labeled drugs. As this Court has repeatedly noted, it is "'difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.'" *Lohr*, 518 U.S. at 487 (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984)); *see also Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 449 (2005) ("If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly.").

Moreover, in light of *Levine*, a ruling that Plaintiffs' claims are preempted would create an

arbitrary and irrational distinction between classes of patients: those whose prescriptions were filled with brand-name products would retain their right to sue, while those whose pharmacies substituted generic drugs would lose that right. There is certainly no evidence that Congress intended to draw this arbitrary distinction when it enacted the Hatch-Waxman Amendments.

To the contrary, as this Court observed in *Levine*, when Congress enacted the FDCA, "it determined that widely available state rights of action provided appropriate relief for injured consumers. It may also have recognized that state law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." 129 S. Ct. at 1199-1200. Defendants offer the Court no reason to believe that Congress reached a different determination when it amended the FDCA by enacting the Hatch-Waxman Amendments.

II. DEFENDANTS HAVE NOT ESTABLISHED THAT IT WAS IMPOSSIBLE TO COMPLY WITH BOTH FEDERAL AND STATE LAW.

"Impossibility pre-emption is a demanding defense." *Levine*, 129 S. Ct. at 1199. To prevail on it at this early procedural stage, Defendants would have to demonstrate, as a matter of law, that it would have been "impossible for [them] to comply with both state and federal law," no matter the factual circumstances. *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000); *Florida Lime & Avocado Growers, Inc., v. Paul*, 373 U.S. 132, 142-43 (1963) (state law is preempted "where compliance

with both federal and state regulations is a physical impossibility").

Defendants have not made this showing. As discussed in Part II.A., Defendants now concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide and they could have asked the agency to issue a DHCP letter warning of the risks of long-term use, but they did not do either. And as discussed in Part II.B., Defendants have not even attempted to show that FDA would have rejected such proposed warnings, which is their burden under the affirmative defense of impossibility preemption.

A. There Is No Dispute that Defendants Could Have Sought FDA Approval for New Warnings, But Did Not Do So.

1. Defendants concede that they could have asked FDA to approve a stronger warning or to send a DHCP letter.

In their brief to this Court, Defendants Pliva, Teva, and UDL for the first time "freely concede" that neither the Hatch-Waxman Amendments nor FDA regulations prohibited them from asking FDA to approve stronger warnings for both Reglan and generic metoclopramide about the risk of tardive dyskinesia. Pliva Br. 48. They likewise concede that, as both courts below held, J.A. 413, 553, they could have asked FDA to send a DHCP letter alerting prescribers to the dangers of long-term use of Reglan

or generic metoclopramide.[25] As discussed in Section II.B., *infra* pp. 36-46, those concessions are fatal to Defendants' impossibility preemption argument before this Court.

Moreover, in 1992, FDA advised that "if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17961 cmt. 40. Defendants were prohibited by federal law, as by state law, from selling their products with inadequate warnings. *Compare* 21 U.S.C. § 352(f)(2) (App. 1a) (defining drugs without adequate warnings as misbranded); 21 U.S.C. § 331 (prohibiting sale of misbranded drug; *and* 21 C.F.R. § 201.57 (further explaining that drug "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") *with McCormack v. Hankscraft Co.*, 154 N.W.2d 488, 496 (Minn. 1967) (manufacturer must provide a "a warning as to any dangers reasonably foreseeable in its [product's] intended use"); *Stahl v. Novartis Pharm. Corp.*, 283 F.3d 254, 264 (5th Cir. 2002) (under the Louisiana Products Liability Act, plaintiff must demonstrate "that the manufacturer

[25] For its part, Defendant Actavis never disputes that it could have asked FDA to strengthen the warnings on both products. Indeed, in its petition, No. 09-1501, Actavis did not even challenge the Fifth Circuit's rulings that it could have applied for a stronger warning through a PAS or asked FDA to issue a DHCP letter. The question presented in that petition was limited to whether states are preempted "from requiring additional safety information on a generic product label where the brand has not changed its label?" Actavis Pet. for Writ of Cert. i.

failed to use reasonable care to provide an adequate warning about . . . a potentially damage-causing characteristic" of its product).

If Defendants had asked FDA to approve stronger warnings, as they should have and now concede they could have done, FDA would have treated such a request promptly and seriously. MAPP 5200.6, at 3 ("ANDAs with serious safety concerns" are assigned the highest priority). But, despite mounting evidence of the serious risk of tardive dyskinesia associated with long-term metoclopramide use, *see supra*, p. 9, the Defendants never brought this information to the agency, nor did they ask FDA to "determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17961 cmt. 40.

2. Defendants could also have utilized other procedures to warn of the risks of long-term metoclopramide use.

In addition to simply asking FDA to approve a stronger warning or to send a DHCP letter, the Defendants could have used a number of regulatory procedures to seek approval for revised labeling or to warn health care practitioners directly. These procedures include a prior approval supplement, a CBE supplement, a Citizen Petition, or issuance of a DHCP letter by the company itself. The Defendants did not employ any of these methods to warn of the risk of tardive dyskinesia associated with long-term use of metoclopramide.

The parties, the courts below, and the United States disagree about precisely which of these

procedures Defendants could have employed in this situation. In light of Defendants' concessions discussed in the previous section, any disagreement about the proper approach need not be resolved. Nevertheless, Plaintiffs here explain why each of these procedures was available.

1. Defendants could have sought FDA approval for stronger warnings by filing a PAS under 21 C.F.R. §§ 314.70(b) and 314.97 (making § 314.70 applicable to ANDA holders). Under the PAS process, a drug company submits an application for a change to an approved NDA or ANDA and must obtain FDA approval before implementing that change. Because FDA approval precedes implementation under the PAS process, this procedure would have allowed FDA to evaluate a strengthened warning for both Reglan and generic metoclopramide before any labeling change was introduced into use, thus satisfying any concern about "sameness." Both courts of appeals concluded that this procedure was available to Defendants. J.A. 412, 551-52.

Pliva (collectively Pliva, Teva, and UDL) argues that the PAS process could not be used to add or strengthen label warnings, because the PAS regulation, § 314.70(b), includes an exception for changes that can be made via the CBE provision, § 314.70(c), and the CBE provision refers to changes made "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." Pliva Br. 44-46. The United States does not assert that the PAS process was prohibited but does contend that it

was not "expressly available to petitioners" for the same reason. U.S. Amicus Br. 14-15.[26]

Both Pliva and the government are mistaken. Their reading depends on the false assumption that any change that can be made by CBE must be made by CBE, as opposed to PAS. The PAS regulation provides, in relevant part, that an "applicant shall submit a supplement, and obtain FDA approval of it, before making . . . [a]ny change in labeling, except one described in paragraphs (c)(2) or (d) of this section." 21 C.F.R. § 314.70(b) and (b)(3)(i). This does not *prohibit* manufacturers from seeking prior approval for a labeling change of the type described in (c)(2); it simply makes clear that the CBE provision is available as an alternative.

At the same time, the CBE provision is phrased permissively. It governs "[s]upplements for changes that *may* be made before FDA approval," including labeling changes to add or strengthen warnings. 21 C.F.R. § 314.70(c) (emphasis added). The regulation does not require the exclusive use of CBE; if it were intended to do so, it would refer to changes that "must" be made prior to FDA approval.

Taken together, the two provisions establish that any labeling change can be made through the PAS process, but that warning changes may also be implemented through the CBE process without waiting for FDA approval. The use of CBE rather than PAS for warning changes is permissive, not mandatory, and PAS remains available. *Cf.* J.A. 412-

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[26] For its part, Actavis does not contest the availability of the PAS process. This is consistent with the limited scope of its petition. *See supra*, n.25.

12 ("manufacturers are *required* to use the prior approval process for 'labeling changes' (with a few exceptions including permissive use of the CBE process for warning enhancements . . .)").[27]

2. The CBE process was also available to Defendants, as three courts of appeals, and numerous district courts, have held. J.A. 550-51; *Gaeta v. Perrigo Pharm. Co.*, No. 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011); *Foster v. Am. Home Prods. Corp.*, 29 F.3d 165, 170 (4th Cir. 1994).[28] As just discussed, the CBE provision refers explicitly to labeling changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction." 21 C.F.R. § 314.70(c)(2)(i); *see also* 21 C.F.R. § 314.97 (making § 314.70 applicable to ANDA holders).

Defendants, and the United States, argue that the court decisions approving generic drug manufacturers' use of the CBE process cannot be squared with the requirement that generic manufacturers include in all ANDAs, including supplements, a statement that the proposed labeling is the same as that for the RLD. 21 C.F.R. § 314.94(a)(8)(iiiv). This argument ignores that some

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[27] This reading of the regulations is also consistent with the history of the CBE process, which was created to allow drug companies to implement new warnings swiftly without prior approval, in the interest of drug safety and the public health. 30 Fed. Reg. 993-94.

[28] *See* district court decisions cited, *supra*, n.1. The Eighth Circuit concluded that it did not need to decide this issue, given the availability of other procedures to strengthen warnings on both Reglan and generic metoclopramide with FDA approval. J.A. 412.

differences in labeling are in fact permitted by § 314.94(a)(8)(iv), and the permitted differences include "labeling revisions made to comply with current FDA labeling guidelines or other guidance." As FDA explained when it proposed this regulation, that exception encompasses differences in proposed labeling because "the [RLD] labeling does not reflect current agency labeling standards," such as where "important new information about the safe use of a drug product" requires a labeling change, "but the reference listed drug's labeling has not yet been updated to reflect this change." 54 Fed. Reg. 28872, 28884 (July 10, 1989).

That is precisely the situation here: important new safety information required a change to the labeling for both brand-name Reglan and generic metoclopramide, but the Reglan label had not yet been updated to reflect the needed change. Thus, under § 314.94(a)(8)(iv), the generic manufacturers were permitted a difference in labeling to provide new safety information about the true risk of long-term metoclopramide use.

Under the CBE process, the manufacturer must submit its supplement application to FDA at the same time it makes the change to its label to strengthen warnings. 21 C.F.R. § 314.70(c). The CBE process is, therefore, another way for a generic drug manufacturer to bring evidence of the need for a new warning to FDA's attention and initiate consideration of whether the labels for both the RLD and generic drugs should be changed. 57 Fed. Reg. at 17961. If FDA approves the CBE change, it will also require the same new warning on the RLD label, thereby preserving the principle of consistent labeling across all bioequivalent products. Use of the

CBE process would, of course, lead to a temporary difference in labeling, just as it does when the RLD holder makes a CBE change. Section 314.94(a)(8)(iv), just like the CBE process itself, reflects FDA's determination that such temporary differences are justified in the interest of drug safety.[29]

3. The Defendants could also have sought FDA approval for a change to the warnings on both the Reglan and generic metoclopramide labels through the Citizen Petition process. 21 C.F.R. § 10.30. Under that process, any "person" may file a petition with FDA asking the agency to take any "form of administrative action." 21 C.F.R. §§ 10.30(a) and (b)(3). The filing of a Citizen Petition triggers formal FDA consideration of the request within a specified period of time. 21 C.F.R. § 10.30(e).

The Citizen Petition process has often been used to request agency action concerning the safety of particular drugs and drug companies often file

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[29] Defendants and FDA also cite another regulation that permits, but does not require, FDA to withdraw approval of an ANDA where the labeling for the generic drug "is no longer consistent" with that for the RLD. 21 C.F.R. § 314.150(b)(10). As the *Demahy* court explained, this provision was adopted in order to empower FDA to compel a generic company to make a labeling change already made by the RLD, not to prevent a generic manufacturer from acting promptly to comply with its obligations under § 201.57 to add warnings of serious new risks. J.A. 539 (quoting 57 Fed. Reg. at 17970 cmt. 78). Moreover, as this Court said in *Levine*, "the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept—neither Wyeth nor the United States has identified a case in which the FDA has done so." 129 S. Ct. at 1197.

Citizen Petitions with FDA. *See supra*, pp. 16-17. Defendants could have filed a Citizen Petition here.

4. Finally, Defendants could themselves have issued a DHCP letter. The courts below were incorrect that such unilateral action was unavailable, as the government acknowledges. U.S. Amicus Br. 17.[30] Nothing in FDA regulations prohibits generic drug companies from sending DHCP letters without prior FDA approval. *Id.*

Defendants still argue that they were prohibited from sending a DHCP letter, because such a letter is considered "labeling" under the FDCA and therefore subject to the "sameness" requirement. Pliva Br. 46-47; Actavis Br. 24-25. But this argument ignores the critical regulatory distinction between approved labeling and promotional labeling. *See supra*, p. 17. Approved labeling, such as a drug's package insert, is, as the name suggests, the labeling language approved as part of the NDA or ANDA, and is therefore subject to the "sameness" requirement in § 314.94.[31] By contrast, what FDA terms "promotional labeling," including product advertising and DHCP letters, is not subject to that requirement.

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[30] Both courts of appeals concluded that Defendants could only ask FDA to issue a DHCP letter, not issue one on their own. J.A. 413-14, 553. As FDA has now made clear, this conclusion was erroneous. The courts of appeals based their conclusion on a provision in the 2007 FDAAA to implement a specific new risk evaluation and mitigation strategy (REMS). *Id.* (citing 21 U.S.C. § 355-1(i)(2)). That provision does not apply to DHCP letters that are not part of a REMS and, in any event, has no relevance to the question whether Defendants could have sent a DHCP letter long before it was enacted.

[31] Except, as discussed above, for differences permitted under 21 C.F.R. § 314.94(a)(8)(iv).

Id., at (a)(8)(iv) (sameness requirement applies to "container label, package insert, and Medication Guide").

Promotional labeling is subject to requirements that it not be misbranded, 21 C.F.R. § 314.150(b)(3), and that it include a true statement of product risks, 21 C.F.R. § 201.100(d)(1). The United States speculates that such a DHCP letter might misleadingly imply that generic metoclopramide was not therapeutically equivalent to its RLD and therefore constitute misbranding. U.S. Amicus Br. 17-18. Especially at the motion to dismiss stage, the Court must assume that the Defendants could have drafted a letter that would not have implied any such therapeutic difference.

In any event, as the United States acknowledges, FDA regulations state the Defendants were not prohibited from issuing a DHCP letter without prior FDA approval. As with a CBE change, any agency review of such a letter would have occurred only after it had been issued.[32]

* * * *

In sum, there were numerous procedures available to Defendants to warn Plaintiffs and their prescribers of the risks associated with long-term metoclopramide use, including two that Defendants themselves concede—and the United States agrees—they could have employed.

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[32] As this Court noted in *Levine,* because the FDCA "contemplates that federal juries will resolve most misbranding claims, FDA's belief that a drug is misbranded is not conclusive." 129 S. Ct. at 1197 (citing 21 U.S.C. §§ 331, 332, and 334(a)-(b)).

B. Defendants Have Not Even Attempted to Show that FDA Would Have Rejected a Stronger Warning, Which Remains Their Burden Under the Affirmative Defense of Impossibility Preemption.

Defendants, having conceded that they could have sought FDA approval for stronger warnings, must prove that FDA would have denied authorization for the new warnings to establish that it was impossible for them to comply with both state and federal law. *Levine*, 129 S. Ct. at 1198 ("absent clear evidence that FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements"); *see also Gade v. Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 110 (1992) (Kennedy, J., concurring) (quoting *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)) (a "hypothetical or potential conflict is insufficient to warrant . . . pre-emption"). Federal preemption is an affirmative defense upon which the defendants bear the burden of proof. *Brown v. Earthboard Sports USA, Inc.*, 481 F.3d 901, 912 (6th Cir. 2007) (internal citation omitted); *see Levine*, 129 S. Ct. at 1198 (placing burden on defendant to provide clear evidence of impossibility).

Such a showing would undoubtedly be difficult, if not impossible, for Defendants to make. Prior to the time that metoclopramide was first prescribed to Ms. Mensing and Ms. Demahy, there was already considerable evidence that the risk of tardive dyskinesia associated with long-term use was far greater than the labeling approved by FDA in 1985 suggested. *See supra,* p. 9. Moreover, FDA's

2009 decision to order that a Boxed Warning regarding the risk of tardive dyskinesia be added to the Reglan and metoclopramide labels is strong evidence that the agency would have approved a stronger warning earlier, had any manufacturer asked FDA for authorization to add one. And the agency's decision to issue a Medwatch Safety Alert and accompanying news release at the time that it ordered the Boxed Warning, is strong evidence that FDA would have issued a similar DHCP letter, if any manufacturer had asked the agency to do so. *See supra*, pp. 10-11.

In the courts below, Defendants did not even attempt to show that, as a matter of fact, FDA would have rejected a stronger warning if Defendants had proposed one. Instead, in both *Mensing* and *Demahy*, Defendants filed motions to dismiss, asserting impossibility preemption as a "purely legal issue of statutory interpretation." J.A. 403, 522. Essentially, Defendants argued that they were absolutely prohibited from even proposing a stronger warning, because of the requirement that their labels remain consistent with the Reglan label; they never before acknowledged the possibility that they could have asked FDA to consider stronger warnings. Both courts of appeals properly rejected Defendants' extreme position, as has the United States. U.S. Amicus Br. 15-16.

Defendants have now abandoned the argument that the Hatch-Waxman Amendments prohibited them from even asking FDA to consider stronger warnings, "freely conceding" before this Court that they could have gone to FDA with information supporting a stronger warning and asked the agency to take action. The obvious

implication of this concession is that it converts the impossibility preemption inquiry into a question of fact—what would FDA have done in response to such a request?—that is inappropriate for resolution on a motion to dismiss.

Apparently recognizing this dilemma, Defendants have attempted to invert the preemption inquiry and shift the burden to Plaintiffs to prove that FDA would have approved a request for stronger warnings. They do this by mischaracterizing Plaintiffs' claims. Plucking a phrase out of context from the Eighth Circuit's decision, Defendants contend that Plaintiffs' claims are not traditional state-law inadequate warning claims at all, but rather claims that state law required generic manufacturers of metoclopramide to "take steps" to seek FDA approval for stronger warnings. Pliva Br. 49-50; Actavis Br. 16-17. And, they argue that to prove this hypothetical "take steps" claim, Plaintiffs bear the burden of showing that FDA would have approved a stronger warning in order to establish that their failure to "take steps" was the "cause" of Plaintiffs' injuries. Pliva Br. 53; Actavis Br. 17.[33] This proposition is wrong. Plaintiffs assert traditional, black-letter products liability claims under Minnesota and Louisiana law for injuries caused by a product sold with inadequate warnings[34]

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[33] Defendants' "take steps" argument depends on the assumption that they could not have provided adequate warnings of metoclopramide's risks without prior FDA approval. For this reason, if the Court agrees with Plaintiffs that Defendants could have made a CBE change or sent a DHCP letter, *supra*, pp. 31-33, 35-36, then Defendants' entire argument on this point would become moot.

[34] It is clear, in context, that the Eighth Circuit did not think it was adjudicating a "taking steps" claim. The first time

and such claims do not require Plaintiffs to prove that FDA would have approved a stronger warning. The only causation Plaintiffs must demonstrate is that the absence of an adequate warning caused their injuries.[35]

Moreover, although Defendants claim to find support for their theory in this Court's decision in *Levine*, nothing in *Levine* prevents Plaintiffs from bringing traditional inadequate warning claims in this situation or shifts the burden of proof to Plaintiffs. Instead, *Levine* explicitly recognized that the burden of proving impossibility remains on Defendants. 129 S. Ct. at 1198.

1. Proof regarding whether FDA would have approved a stronger warning is not an element of Plaintiff's cause of

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the court of appeals used that phrase, it was referring to federal regulatory requirements, not the elements of Ms. Mensing's cause of action. J.A. 410 ("The regulatory framework makes clear that a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug.") When the court returned to that phrase at the end of its impossibility preemption discussion, it was not a description of Plaintiff's claim, but rather part of a shorthand description of its reasons for rejecting the generic drug companies' preemption defense.

[35] Plaintiffs do not argue that whether FDA would have approved a stronger warning had one been requested is irrelevant. It is relevant to the preemption inquiry, but it is an issue on which the Defendants bear the burden of proof. *Levine*, 129 S. Ct. at 1198 ("absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements. Wyeth has offered no such evidence.").

action under Minnesota or Louisiana law, but rather of Defendants' affirmative defense.

The principal causes of action asserted by both Ms. Mensing and Ms. Demahy in these cases are traditional products liability claims for inadequate warnings. J.A. 106-13 (strict liability); 115-21 (negligence); 143-45 (implied warranty); J.A. 442-45 (La. Prods. Liab. Act).[36] To establish causation for this type of claim, a plaintiff must show that the absence of adequate warnings caused her injuries. That is the *only* causation element of an inadequate-warning claim. *See, e.g., Restatement (Third) of Torts: Products Liability* § 6 (1998);[37] David G.

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[36] Ms. Mensing also asserts claims for misrepresentation by omission, negligent misrepresentation, fraud by concealment, constructive fraud, infliction of emotional distress, and violation of the Minnesota Consumer Protection Act. J.A. 122-49. Ms. Demahy also asserts a claim under the Louisiana Unfair Trade Practices and Consumer Protection Law. J.A. 445-47.

[37] Section 6 of the *Third Restatement* provides, in relevant part:

> (a) A manufacturer of a prescription drug . . . who sells . . . a defective drug . . . is subject to liability for harm to persons caused by the defect.
>
> (b) For purposes of liability under Subsection (a), a prescription drug . . . is defective if . . . the drug . . .
>
> (3) is not reasonably safe due to inadequate warnings as defined in Subsection (d)
>
> (d) A prescription drug . . . is not reasonably safe due to inadequate . . . warnings if

Owen, *Products Liability Law* § 9.1 (2d ed. 2008) ("If a user or consumer is injured as a result of a warning defect, because such danger or safety information was not provided, the manufacturer is subject to liability for the harm."); *id.* at § 11.4 ("the plaintiff must prove that the absence of that safety information caused the plaintiff's injury"); *see also* Pliva Br. 51 (in a "typical failure-to-warn case" plaintiff "needs to show only that (a) the drug is responsible for his or her injuries and (b) the existing warning's alleged inadequacy proximately caused the drug use that precipitated those injuries").

Minnesota and Louisiana follow these black-letter principles regarding proof of causation in an inadequate warning claim. The critical link for purposes of causation is that the drug's inadequate warnings cause the plaintiff's injury. Michael K. Steenson, *Minnesota Practice Series: Products Liability Law* § 4.11 (2006);[38] Louisiana Products

---

> reasonable . . . warnings regarding foreseeable risks of hare are not provided to:
>
> (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the . . . warnings . . . .

[38] Consistent with this principle, the standard Minnesota special verdict form in an inadequate warning case asks the jury to answer only two questions: 1) "Was the product in a defective condition unreasonably dangerous to (the user) because (defendant manufacturer) failed to provide adequate (warnings) for the safe use of the product?" and 2) "Was the defective condition a direct cause of the (injuries) sustained by the plaintiff?" *Minnesota Jury Instructions Guides–Civil*, Special Verdict Form 75.90.

Liability Act (LPLA), La. Stat. Ann. §§ 2800.54.A., B.(3), & D. Proof that FDA would have rejected a stronger warning is an essential element of a manufacturer's preemption defense; proof that FDA would have approved the warning is not an element of the plaintiff's affirmative case.

Thus, in either state, to make out a prima facie case, Ms. Mensing or Ms. Demahy must prove that the absence of adequate warnings about the risks of long-term metoclopramide use was the cause of her injuries. But it is left to Defendants to try to prove that FDA would not have permitted stronger warnings at that time, as an element of their impossibility preemption affirmative defense.

Even if Defendants were correct that federal law required them to obtain FDA approval before changing their warnings, they offer no explanation why this would change the elements of Plaintiffs' causes of action under state law. Plaintiffs' claims remain traditional inadequate-warning claims, not the hypothetical "take steps" claims imagined by Defendants.[39]

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[39] Pliva repeatedly cites the brief filed by the United States in *Warner-Lambert Co. v. Kent*, 552 U.S. 440 (2008), as support for its "take steps" argument. Pliva Br. 5, 29, 56. But unlike Minnesota and Louisiana law, the Michigan statute at issue in *Kent* did require a plaintiff to prove how FDA would have acted in a hypothetical situation. Mich. Comp. Laws § 2946(5)(b) (requiring proof that FDA would not have approved a drug if the manufacturer had submitted all required information to overcome a statutory FDA-approval affirmative defense). The facts here are entirely different, which is why the United States opposes preemption in this case.

2. *Wyeth v. Levine* does not support Defendants' effort to shift the burden of proof to the Plaintiffs.

Wyeth v. Levine squarely placed the burden of proof on the defendant drug manufacturer to offer "clear evidence" that FDA "would not have approved" a warning change in order to establish its impossibility preemption affirmative defense. 129 S. Ct. at 1198. Defendants nevertheless argue that this Court's decision in *Levine* somehow shifts the burden to Plaintiffs in this case to prove that FDA would have approved a request for stronger warnings, in order to defeat their preemption defense. Defendants claim to find this requirement in this Court's discussion of the CBE process in *Levine*, Pliva Br. 52; Actavis Br. 25-26, but their argument rests on a "fundamental misunderstanding" of that ruling. 129 S. Ct. at 1197.

The central issue in *Levine* was whether a drug manufacturer or FDA "bears primary responsibility for drug labeling." 129 S. Ct. at 1197. This Court answered decisively that the responsibility rests with the manufacturer: "[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Id.* at 1197-98 (citing 21 C.F.R. § 201.80(e)).[40]

[40] 21 C.F.R. § 201.80(e) is the same regulation as 21 C.F.R. § 201.57(e), as redesignated in 2006. *See supra*, n.17.

That core holding in *Levine* applies with full force to the manufacturers of generic drugs and weighs heavily against preemption in this case.

The Defendants ignore that holding and argue that *Levine* turned on the availability of a single procedure, CBE. But *Levine* focused on CBE, not because that particular procedure is necessary to avoid preemption, but rather because the trial judge had instructed the jury, without objection from Wyeth, that FDA regulations permitted a drug manufacturer to change its product label through that process. *Id.* at 1192-92. There was no reason for the Court to consider any other procedure because Wyeth conceded that CBE was an appropriate way to add or strengthen a label warning.[41]

Moreover, in light of the broad language this Court used in *Levine* in rejecting federal preemption under the FDCA, it makes no sense to read that decision as turning on the fact that CBE proposals may be implemented prior to formal FDA approval. As this Court recognized, even under the CBE process "the FDA retains authority to reject labeling changes . . . in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications." 129 S. Ct. at 1198.

In other words, there is no meaningful difference between the CBE process and the other procedures discussed above. Under any procedure, a manufacturer's proposed warning change is subject

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[41] Wyeth did argue that there was insufficient new evidence of Phenergan's risks to justify a CBE change and that FDA would have denied approval, but the Court rejected those arguments. *Id.* at 1196-97.

to FDA approval; therefore, as this Court recognized, the preemption inquiry turns on whether FDA would have denied approval of the change at the relevant time, and the burden of proof on that point belongs to Defendants. The Court gave no indication that it matters whether that FDA review follows, rather than precedes, implementation. To the contrary, the Court said that the defendant's focus on the terms of the CBE regulation reflected a "more fundamental misunderstanding" of the central issue in that case, which was the manufacturer's primary responsibility for the content of its label. *Id.* at 1197-98.

* * * *

Defendants concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide or to issue a DHCP letter warning of the risks of long-term metoclopramide use. And Defendants have not even attempted to establish that FDA would have denied such requests. It was therefore not impossible, as a matter of law, for Defendants to comply with their duties under both state and federal law, and their argument for impossibility preemption must be rejected.

III. STATE-LAW LIABILITY FOR FAILURE TO WARN WOULD NOT OBSTRUCT THE PURPOSES AND OBJECTIVES OF FEDERAL REGULATION OF GENERIC DRUGS

In the courts below, Defendants argued not only that it was impossible for them to comply with both federal and state law, but also that state tort liability would obstruct Congress's purposes and objectives in enacting the Hatch-Waxman

Amendments. In their briefs to this Court, Defendants appear to have largely abandoned this argument. Nevertheless, because their *amici* press this frustration-of-purpose argument, Plaintiffs address it here.[42]

A. State Tort Remedies Complement Congressional Purposes and the Federal Regulatory Scheme.

In *Levine*, this Court considered and rejected the argument that state tort remedies obstruct the purposes of federal law. "Congress enacted the FDCA to bolster consumer protection against harmful products." 129 S. Ct. at 1199. Congress did not create a federal remedy for consumers injured by unsafe drugs, because it recognized that "widely available state rights of action provided appropriate relief for injured consumers" and "further[ed] consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id.* at 1199-1200. "If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's history." *Id.* at 1200.

As this Court also recognized, "the FDA has limited resources to monitor the 11,000 drugs on the market." *Id.* at 1202. State tort law "complements FDA regulation" by "uncover[ing] unknown drug hazards and provid[ing] incentives for drug manufacturers to disclose safety risks promptly. [It] also serve[s] a distinct compensatory function that

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[42] *See* Apotex, Inc. Amicus Br. in Supp. of Pet'r 26-30; *see generally* GPhA Amicus Br. in Supp. of Pet'r 19-32.

may motivate injured persons to come forward with information." *Id.*

Both courts of appeals recognized that these policy considerations apply with full force to state-law inadequate warning claims against generic drug companies. J.A. 417-18, 562. They took note that Congress had not included an express preemption provision in the Hatch-Waxman Amendments, even though it had included such a provision in the Medical Device Amendments only eight years before. J.A. 407, 533. They rejected the Defendants' argument that the sole purpose of the Hatch-Waxman Amendments was to make lower-cost generic drugs more widely available; because the Hatch-Waxman Amendments were enacted as amendments to the FDCA, they had to be considered in conjunction with that statute's fundamental emphasis on drug safety. J.A. 416-17, 561.

The courts below also properly rejected Defendants' more specific argument that state tort liability would undermine the goal of low-cost generic drugs by requiring generic drug companies to conduct expensive clinical trials to develop the scientific evidence necessary to support a labeling change; both courts recognized that "reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), can be found in adverse event reports and in published literature on metoclopramide, as Plaintiffs alleged. J.A. 416-17, 558-59. And, as documented above, considerable evidence was available to Defendants well before the time that metoclopramide was first prescribed to Ms. Mensing and Ms. Demahy. *See supra*, p. 9.

For all these reasons, the United States is correct when it says that state-law duties to warn do not obstruct the purposes and objectives of federal law. U.S. Amicus Br. 20-22 ("That argument is wrong.").

B. Preemption of Claims Against Generic Manufacturers Would Interfere with Congressional Objectives.

Not only does state tort liability complement the federal regulatory scheme, but a decision in favor of preemption would significantly *interfere* with federal objectives. Most importantly, it would pose a threat to public health, by eliminating any incentive for generic drug companies to ensure that drug labeling accurately reflected the risks posed by those products. *Cf.* J.A. 557 (preemption would necessarily require the conclusion "that Congress intended the name brand drug manufacturer to bear the sole burden of coping with incipient risks, even when it has ceased manufacturing the drug and left the market to generics").

"Adverse drug reactions (ADRs) are believed to be a leading cause of death in the United States." Lasser, *et al., supra*, at 2215. Contrary to Defendants' assertions, many new drug risks do not emerge (or have not been addressed in labeling) until long after generic versions enter the market. *Id.* Indeed, almost a quarter century elapsed between the time the first generic metoclopramide entered the market and the time when a black-box warning about the risk of tardive dyskinesia was added to the label. Preemption would only increase the risk of such adverse drug events.

In so doing, preemption would also conflict with Congress's purpose of reducing health care costs. Each adverse drug event creates additional health care costs. In some cases, such as the Plaintiffs', these costs are substantial. If generic drug companies are not responsible for the costs that their negligence imposes on the health care system, those increased costs must be borne by the patients themselves, their insurers, and both state and federal governments through the Medicare and Medicaid programs.

A finding of preemption here would also undermine another central purpose of the Hatch-Waxman Amendments: to promote public confidence in the therapeutic equivalence of generic drugs and their RLDs. Once doctors, pharmacists, and patients understand that manufacturers of branded drugs are legally responsible for the adequacy of their warnings, but that manufacturers of generic drugs are not, they will each need to think twice about whether to substitute a generic drug for the RLD. Indeed, a ruling in favor of preemption might even lead state legislatures to rethink their support for generic drugs through their state substitution laws. And each time someone decides not to substitute a generic drug because of concerns about their therapeutic equivalence, that too will increase costs to the health care system. FDA, FY2011 Budget, *Protecting Patient Safety*, at 410 (2011) (cost savings from generic substitution depend on "the public's confidence in the safety, quality, and comparability of generic drugs to their brand equivalents").[43]

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[43] *Available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM205622.pdf.

A ruling in favor of preemption would also leave persons injured by inadequately labeled prescription drugs without remedy for their injuries. That would frustrate Congress's purpose of preserving state law remedies that protect injured consumers and complement the federal regulatory scheme.[44]

During hearings on the Hatch-Waxman Amendments, concerns were raised about whether generic drugs would really be as safe as branded

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[44] Defendant Actavis argues that any lack of legal remedy is not the result of Defendants' preemption arguments, but rather was caused by the Plaintiffs' "strategic decision" not to sue their physicians for malpractice for prescribing metoclopramide for more than the approved twelve weeks. Actavis Br. 26 n.14. However, off-label prescribing is an accepted form of medical practice, as FDA has long acknowledged:

> Congress did not intend FDA to interfere with the practice of medicine. . . . A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed on the FDA-approved labeling. . . . Under certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice.

Unapproved Uses of Prescription Drugs, Before the S. Comm. on Labor and Human Resources, 104th Cong. (Feb. 22, 1996) (testimony of William B. Schultz, Deputy Commissioner for Policy, FDA).

Estimates are that close to half of all drug prescriptions are written for indications that have not been approved by FDA. Kaspar J. Stoffelmayr, *Products Liability and "Off-Label" Uses of Prescription Drugs*, 63 U. Chi. L. Rev. 275, 278 (1996). Actavis does not explain how the Plaintiffs' physicians could be held liable for prescribing metoclopramide long-term when it failed to warn them of the serious risks associated with this practice.

drugs. Representatives of the generic drug industry repeatedly assured Congress that they would be, that generic drug companies were responsible manufacturers with large research departments, capable of reviewing adverse reactions and keeping up with the scientific literature, and that they would do whatever was necessary "to provide for the safety and well-being of those that are using the drug."[45] Congress relied on these representations of corporate responsibility when it enacted the Hatch-Waxman Amendments. This Court should not allow Defendants to disclaim those responsibilities now.

IV. THE PLAINTIFFS' CLAIMS ARE NOT PREEMPTED UNDER *ARKANSAS LOUISANA GAS CO. V. HALL* OR *BUCKMAN V. PLAINTIFFS' LEGAL COMMITTEE*

Apparently recognizing that Defendants cannot meet their burden of proving that Plaintiffs' traditional state-law inadequate warning claims are preempted on the basis of either impossibility or frustration of purpose, Pliva offers two final arguments. Both are premised on Defendants' false

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[45] *Drug Legislation: Hearings Before the Subcomm. on Health and the Environment of the H. Comm. on Energy and Commerce*, 98th Cong. 48 (July 25, 1983) (testimony of Kenneth N. Larsen, Chairman, Generic Pharmaceutical Industry Association and President, Zenith Laboratories, Inc.); *see also id.* at 45-47 (generic manufacturers "are sensitive to the importance of looking at adverse reactions" and "are expected to know . . . what the literature says"); *Id.* at 50 (testimony of William Haddad, Executive Officer and President, Generic Pharmaceutical Industry Association) (every generic drug company "has a large research staff" and "researches adverse reaction").

assertion, discussed earlier, that Plaintiffs' claims are not traditional state-law inadequate warning claims at all, but rather claims that state law required generic manufacturers of metoclopramide to "take steps" to seek FDA approval for stronger warnings. Pliva argues that such a "take steps" claim is preempted under *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981), because speculation about how FDA would have responded to a request for stronger warnings would "necessarily usurp the agency's authority," and is also preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), because it would "directly interfere with a federal regulatory regime." Pliva Br. 49. Actavis does not join in these arguments in its brief.

The short answer to these arguments, as discussed above, is that Plaintiffs' claims are not some sort of unprecedented new "taking steps" claim, but rather traditional, black-letter products liability claims under Minnesota and Louisiana law for injuries caused by a product sold with inadequate warnings.

A. *ArkLa Gas* Is Inapplicable Because "Congress Did Not Intend FDA Oversight to be the Exclusive Means of Ensuring Drug Safety and Effectiveness."

Starting from the false premise that Plaintiffs' claims are "taking steps" claims, Pliva argues that these claims are barred by *ArkLa Gas*, a case involving the federal "filed rate doctrine" under the Natural Gas Act. In *ArkLa Gas*, this Court held that a state-law breach of contract action for damages based on a contractual purchase price for natural gas

that differed from the rate that had been filed with and approved by the Federal Power Commission (FPC) was preempted by the filed rate doctrine. 453 U.S. at 584-85.

Pliva describes *ArkLa Gas* as standing for the sweeping proposition that any claim that depends on "speculation about what a federal agency would have done in hypothetical proceedings" is preempted because "the trial of such state-law claims unavoidably usurps the federal agency's exclusive authority." Pliva Br. 53. But that is a dramatic overstatement of the holding in *ArkLa Gas*, which was a narrow holding about the authority of the FPC. Indeed, this Court has never even cited *ArkLa Gas* outside the context of the filed rate doctrine.

Under the Natural Gas Act, Congress had granted the FPC exclusive authority to decide whether rates for natural gas were "just and reasonable," and the definition of a "just and reasonable" rate was one that had been filed with and approved by the Commission. 453 U.S. at 577 ("The authority to decide whether the rates are reasonable is vested by § 4 of the Act solely in the Commission, and the right to a reasonable rate is the right to the rate which the Commission files or fixes.") (internal citations and quotations omitted). Because Congress had "established an exclusive form of regulation," state courts were precluded from awarding contract damages that departed from the approved filed rate. *Id.* at 580.

Here, by contrast, "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Levine*, 129 S. Ct. at 1200. Congress and FDA both recognize that state

regulation of prescription drugs through the tort system complements and furthers the federal interest in drug safety. *See supra*, p. 47-48. For this reason, *ArkLa Gas* is wholly inapplicable to this case.

B. *Buckman* Does Not Apply to Plaintiffs' Inadequate Warning Claims, Which Long Pre-date the Hatch-Waxman Amendments and Which Congress Contemplated Would be Part of the Regulatory Scheme.

Finally, Pliva argues that Plaintiffs' claims are preempted by this Court's holding in *Buckman*. But this argument too depends on Pliva's mischaracterization of Plaintiffs' claims as some sort of novel "take steps" claim, because *Buckman* has no application to traditional state causes of action such as Plaintiffs here assert.

In *Buckman*, this Court held that a state-law "fraud-on-the-FDA" claim was preempted, because such a claim would interfere with the "delicate balance of statutory objectives" that FDA must try to achieve in deciding whether and how to police fraud against the agency. 531 U.S. at 348. Central to the Court's holding was its recognition that "[p]olicing fraud against federal agencies is hardly 'a field which the States have traditionally occupied,'" *id.* at 347 (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)), and therefore the presumption against preemption did not apply. *Id.* at 348. The Court was also concerned that state court policing of fraud on the agency would cause applicants to "deluge" FDA with information, which would interfere with fulfillment of its regulatory duties, *id.*

at 351, the specific concern that Pliva reiterates here. Pliva Br. 59-61.

Buckman is not relevant here because, unlike the fraud-on-the-agency claim at issue there, this case involves traditional state law causes of action; in light of "the historic primacy of state regulation of matters of health and safety," *Lohr*, 518 U.S. at 485, the presumption against preemption is fully applicable. *Levine*, 129 S. Ct. at 1195-96. The *Buckman* court expressly distinguished that case from cases involving a "traditional state tort law principles of [a manufacturer's] duty of care," 531 U.S. at 352 (distinguishing both *Silkwood* and *Lohr* on this basis), and, in *Levine*, this Court distinguished the claim at issue in *Buckman* from failure-to-warn claims against drug manufacturers on the same basis. 129 S. Ct. at 1195 n.3.

This Court found that the claim at issue in *Buckman* might skew the "delicate balance of statutory objectives" FDA seeks to achieve in deciding when and how best to punish and deter fraud. 531 U.S. at 348. By contrast, Plaintiffs' claims here complement federal drug regulation by providing "incentives for drug manufacturers to disclose safety risks promptly." *Levine*, 129 S. Ct. at 1202. Moreover, unlike a "fraud-on-the-FDA" claim, traditional failure-to-warn claims long "predated the federal enactments in question," and thus, it must be assumed, were a part of the regulatory scheme contemplated by Congress when it enacted the Hatch-Waxman Amendments. *Buckman*, 531 U.S. at 353; *see also South Dakota v. Yankton Sioux Tribe*, 522 U.S. 329, 351 (1998) ("Congress is aware of existing law when it passes legislation.") (internal citation and quotation marks omitted).

There is also no reason why a ruling in favor of Plaintiffs should lead to a deluge of submissions to FDA. The duty to revise warning labels arises only when "there is reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), not every time "a single adverse event report" is received. Pliva Br. 60. Plus, generic drug companies already have a duty to submit all adverse event reports to the agency and to provide FDA with an annual summary of significant new information that might affect the safety, effectiveness, or labeling of their product. 21 C.F.R. §§ 314.98(a) and (c). If they are already fulfilling those duties, there should be little left to submit.

The same "deluge" argument was made in *Levine*,[46] and this Court implicitly rejected that argument when it found no conflict preemption in that case. Nor did the *Levine* decision itself trigger a flood of labeling supplement submissions to the agency; FDA reports that supplement applications have actually fallen since that decision.[47]

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[46] PhRMA & BIO Amicus Br. in Supp. of Pet'r, at 36-38, *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (No. 06-1249).

[47] *See* FDA, Dep't of Health & Human Servs., *FY 2010 Performance Report to the President and Congress for the Prescription Drug User Fee Act*, at 26 (2010) (table showing that for fiscal year 2010, the first full fiscal year after *Levine* was decided, both the number of supplements not requiring prior agency approval (*i.e.,* CBE supplements) and the total number of manufacturing supplements filed with the agency dropped to its lowest level in five years), *available at* http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm243357.htm. Nor is there any evidence that *Levine* prompted a flood of failure-to-warn litigation. *See* Office of Judges Programs, Admin. Office of the U.S. Courts, *Fed. Judicial Caseload*

In short, neither *ArkLa Gas* nor *Buckman* supports Pliva's argument that Plaintiffs' traditional state-law inadequate warning claims are preempted.

CONCLUSION

The judgments of the Fifth and Eighth Circuit Courts of Appeals should be affirmed.

February 23, 2011 Respectfully submitted,

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Statistics, at 46 (March 2010) (Table C-2, showing that excluding airline-, marine-, motor vehicle- and asbestos-specific cases, fewer "Personal Injury/Product Liability" cases were commenced in federal court during the 12 months prior to March 31, 2010 than during the previous year), *available at* http://www.uscourts.gov/Statistics/FederalJudicialCaseloadStatistics/FederalJudicialCaseloadStatistics2010.aspx.

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APPENDIX

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APPENDIX A:

21 U.S.C. § 352(f)(2) (2001) – (excerpt)

UNITED STATES CODE

TITLE 21. FOOD AND DRUGS

CHAPTER 9. FEDERAL FOOD, DRUG, AND

COSMETIC ACT

SUBCHAPTER V. DRUGS AND DEVICES

PART A. DRUGS AND DEVICES

§ 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users.

* * *

APPENDIX B:

21 C.F.R. § 10.30 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER A. GENERAL

PART 10. ADMINISTRATIVE PRACTICES AND PROCEDURES

SUBPART B. GENERAL ADMINISTRATIVE PROCEDURES

§ 10.30 Citizen petition.

(a) This section applies to any petition submitted by a person (including a person who is not a citizen of the United States) except to the extent that other sections of this chapter apply different requirements to a particular matter.

(b) A petition (including any attachments) must be submitted in accordance with § 10.20 and in the following form:

* * *

Citizen Petition

The undersigned submits this petition under ——— (relevant statutory sections, if known) of the ——— (Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10) to request the Commissioner of Food and Drugs to ——— (issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action).

A. Action requested

((1) If the petition requests the Commissioner to issue, amend, or revoke a regulation, the exact wording of the existing regulation (if any) and the proposed regulation or amendment requested.)

((2) If the petition requests the Commissioner to issue, amend, or revoke an order, a copy of the exact wording of the citation to the existing order (if any) and the exact wording requested for the proposed order.)

((3) If the petition requests the Commissioner to take or refrain from taking any other form of administrative action, the specific action or relief requested.)

B. Statement of grounds

(A full statement, in a well organized format, of the factual and legal grounds on which the petitioner relies, including all relevant information and views on which the petitioner relies, as well as

representative information known to the petitioner which is unfavorable to the petitioner's position.)

* * *

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

* * *

(c) A petition which appears to meet the requirements of paragraph (b) of this section and § 10.20 will be filed by the Dockets Management Branch, stamped with the date of filing, and assigned a docket number.

* * *

(d) An interested person may submit written comments to the Dockets Management Branch on a filed petition, which comments become part of the docket file.

* * *

(e)(1) The Commissioner shall, in accordance with paragraph (e)(2), rule upon each petition filed under paragraph (c) of this section, taking into consideration (i) available agency resources for the category of subject matter, (ii) the priority assigned to the petition considering both the category of subject matter involved and the overall work of the agency, and (iii) time requirements established by statute.

* * *

APPENDIX C:

21 C.F.R. § 200.5 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER C. DRUGS: GENERAL

PART 200. GENERAL

SUBPART A. GENERAL PROVISIONS

§ 200.5 Mailing of important information about drugs.

Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care. In the public interest, such mail should be distinctive in appearance so that it will be promptly recognized and read. The Food and Drug Administration will make such mailings in accordance with the specifications set forth in this section. Manufacturers and distributors of drugs are asked to make such mailings as prescribed by this section and not to use the distinctive envelopes for ordinary mail.

* * *

APPENDIX D:

21 C.F.R. § 201.57(e) (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER C. DRUGS: GENERAL

PART 201. LABELING

SUBPART B. LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

* * *

(e) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The 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. A specific warning relating to a use not provided for under the

"Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box.

* * *

APPENDIX E:

21 C.F.R. § 314.70 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART B. APPLICATIONS

§ 314.70 Supplements and other changes to an approved application.

(a) Changes to an approved application. The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant shall notify FDA about it in a supplemental application under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

* * *

(b) Supplements requiring FDA approval before the change is made. An applicant shall submit a supplement, and obtain FDA approval of it, before making the changes listed below in the conditions in an approved application, unless the change is made to comply with an official compendium.

* * *

(3) Labeling.

(i) Any change in labeling, except one described in paragraphs (c)(2) or (d) of this section.

* * *

(c) Supplements for changes that may be made before FDA approval. An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application, unless the change is made to comply with an official compendium.

* * *

(2) Changes labeling to accomplish any of the following:

(i) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(ii) To add or strengthen a statement about drug abuse, dependence, or overdosage; or

(iii) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(iv) To delete false, misleading, or unsupported

indications for use or claims for effectiveness.

* * *

APPENDIX F:

21 C.F.R. § 314.80(b) and (c) (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART B. APPLICATIONS

§ 314.80 Postmarketing reporting of adverse drug experiences.

* * *

(b) Review of adverse drug experiences. Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

* * *

(c) Reporting requirements. The applicant shall report to FDA adverse drug experience information, as described in this section.

* * *

(1)(i) Postmarketing 15-day "Alert reports". The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

* * *

(2) Periodic adverse drug experience reports.

(i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals.

* * *

APPENDIX G:

21 C.F.R. § 314.81 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART B. APPLICATIONS

§ 314.81 Other postmarketing reports.

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

* * *

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

* * *

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report

to the FDA division responsible for reviewing the application . . . . The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.

* * *

APPENDIX H:

21 C.F.R. § 314.94(a)(8)(iii) and (iv) (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART C. ABBREVIATED APPLICATIONS

§ 314.94 Content and format of an abbreviated application.

* * *

(a) Abbreviated new drug applications. Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

* * *

(8) Labeling—

* * *

(iii) Statement on proposed labeling. A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) Comparison of approved and proposed labeling. A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

APPENDIX I:

21 C.F.R. § 314.97 (2001)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART C. ABBREVIATED APPLICATIONS

§ 314.97 Supplements and other changes to an approved abbreviated application.

The applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

APPENDIX J:

21 C.F.R. § 314.98 (2001)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART C. ABBREVIATED APPLICATIONS

§ 314.98 Postmarketing reports.

(a) Except as provided in paragraph (b) of this section, each applicant having an approved abbreviated new drug application under § 314.94 that is effective shall comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences.

(b) Each applicant shall submit one copy of each report required under § 314.80 to the Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(c) Each applicant shall make the reports required under § 314.81 and section 505(k) of the act for each

of its approved abbreviated applications.