

In the
United States Court of Appeals
For the Seventh Circuit

No. 08-2265

BONNIE J. MASON, individually and
as co-administrator of the estate of
Tricia M. Mason, deceased, and
WILLIAM L. MASON, individually
and as co-administrator of the
estate of Tricia M. Mason, deceased,

Plaintiffs-Appellants,

v.

SMITHKLINE BEECHAM CORPORATION,
doing business as GlaxoSmithKline,
a Pennsylvania corporation,

Defendant-Appellee.

Appeal from the United States District Court
for the Central District of Illinois.
No. 05 C 1252—**Michael M. Mihm**, *Judge*.

ARGUED OCTOBER 5, 2009—DECIDED FEBRUARY 23, 2010

Before EVANS and SYKES, *Circuit Judges*, and SIMON, *District Judge*.*

EVANS, *Circuit Judge*. Twenty-three-year-old Tricia Mason committed suicide on March 2, 2003, two days after she started taking Paxil, a popular antidepressant. Her parents sued the manufacturer of the drug, the Smithkline Beecham Corporation, claiming it was negligent (among other things) for not warning that taking Paxil increases the risk of suicide, especially among young adults. The district court granted summary judgment for the company in 2008. The court concluded that the Masons' claims were preempted under federal law because the warnings they say should have been included about Paxil conflicted with the FDA-approved warning labeling for the drug.

One year after the district court granted the defendant's motion for summary judgment, the Supreme Court decided *Wyeth v. Levine*, 555 U.S. ____, 129 S. Ct. 1187 (2009), a case that represents a sea change in the way courts are to consider issues of federal preemption. Keeping the changed landscape in mind, we today consider the Masons' appeal in light of *Levine*.

Before going further, however, we note that the district court, on the opening page of its opinion granting summary judgment, said:

* The Honorable Philip P. Simon, United States District Court Judge for the Northern District of Indiana, sitting by designation.

The Court notes that the portions of the briefs addressing statements of undisputed and disputed fact that have been submitted by both Plaintiffs and Defendant are so replete with argumentative posturing that they are essentially useless both in determining the basic factual information underlying this case, as well as in resolving the pending motions. The inclusion of 13 and 11 pages of "Introduction" that is reminiscent of closing argument is also wholly inappropriate. Counsel should consider themselves on notice that future filings of this nature will be immediately stricken by the Court.

Any improvement in the tone and substance of the briefs on appeal is slight at best. They are still, as the district court observed, "replete with argumentative posturing." That's unfortunate. At this point in the proceeding, all that really needs to be said is that Tricia Mason committed suicide two days after taking Paxil. The briefs, however, go far beyond this statement. The plaintiffs paint a rather bright picture of Tricia. The defendant's picture is much darker.

The Masons tell us this about their daughter:

Throughout her life, Tricia Mason was an excellent student, she was close with her family and enjoyed dancing. She was the salutatorian of her high school graduating class, excelled in science and aspired to become a pediatrician. She was pursuing a Masters degree at Illinois State University.

On February 27, 2003, Tricia went to a medical clinic complaining of a sore throat. During her consultation

with the nurse practitioner, she informed the nurse that she was also having difficulty getting up in the morning, she was eating less and believed she might be suffering from seasonal affective disorder. The nurse practitioner diagnosed Tricia with depression and gave her some samples of Paxil. On March 2, 2003, two days after starting Paxil, Tricia committed suicide by ingesting cyanide.

Here's how the defendant paints the picture:

Tricia Mason had a family history marked by depression and suicide attempts. Ms. Mason herself struggled with depression long before her suicide in March 2003. In 1999-2000, Ms. Mason began experiencing depression during the winter months.

As time progressed, Ms. Mason's depression worsened. After a New Year's Eve party, Dones [Ms. Mason's boyfriend] again told Ms. Mason the relationship had no future. Upon hearing that, Ms. Mason told Dones she had prepared a mix of lethal chemicals and intended to kill herself. Dones made Ms. Mason promise she would not commit suicide.

Ms. Mason's depression continued throughout February 2003. Around Valentine's Day, Ms. Mason told Jason Pemberton, another boyfriend, she intended to kill herself.

....

On February 27, 2003, Ms. Mason visited her nurse practitioner complaining of cold symptoms. Ms. Mason

took the opportunity to discuss her depression and expressed interest in seeing a counselor. Contrary to the suicide threats she had recently expressed, Ms. Mason denied she had been having suicidal thoughts. The nurse provided Ms. Mason with samples and a prescription for Paxil.

Two days later, on March 2, Ms. Mason corresponded with Dones by instant messaging. Dones told Ms. Mason her behavior over the past few months made it “impossible” to continue their relationship. Ms. Mason told Dones, “Farewell, my love.” She then signed off her computer.

Hours later, Tricia Mason committed suicide by ingesting cyanide. She was 23 years old.

If this case ever gets to a jury, it will consider all the facts and circumstances surrounding Tricia’s life and suicide. We need not concern ourselves with how she should be viewed. In addition, a jury might well conclude that she committed suicide without any help from Paxil. These are not our concerns. Our issue is a legal one, and so we soldier on, mindful, however, that the parties have been extremely partisan in the way they have presented the case to us.

The central issue of this case is federal preemption, which occurs when a state law is invalidated because it conflicts with a federal law. The constitutional basis for federal preemption is found in the Supremacy Clause (Article VI, Clause 2 of the U.S. Constitution), which states, “[T]he Laws of the United States . . . shall be the

supreme Law of the Land[.]” Preemption comes in three forms. First, and the easiest to apply, is express preemption which occurs when Congress clearly declares its intention to preempt state law. Second, we have implied preemption which occurs when the “structure and purpose” of federal law shows Congress’s intent to preempt state law. Finally, we come to conflict preemption which occurs when there is an actual conflict between state and federal law such that it is impossible for a person to obey both. *See English v. Gen. Elec. Co.*, 496 U.S. 72, 79, 110 S. Ct. 2270, 110 L. Ed. 2d 65 (1990). Conflict preemption is the type of preemption at issue in this case.

Interestingly enough, the idea of conflict preemption in prescription drug cases is relatively new. Until the early 2000s, prescription drug companies infrequently invoked the preemption defense, and when they did, it rarely succeeded. *See, e.g., Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528, 537 (6th Cir.), *cert. denied*, 510 U.S. 914 (1993); *Hill v. Searle Labs.*, 884 F.2d 1064, 1068 (8th Cir. 1989). This changed in 2001 when district courts were inundated with preemption motions in prescription drug cases. In a number of these cases, the FDA filed *amicus* briefs in support of the pharmaceutical industry. In 2006, the FDA also released statements and revised its regulations in an attempt to bolster the drug manufacturers’ preemption defense. Not surprisingly, courts began to issue contradicting opinions, which led the Supreme Court to grant certiorari in *Levine* to decide the issue.

In *Levine*, the Supreme Court restored the preemption landscape to its pre-2001 form. The plaintiff in *Levine* was severely injured (she developed gangrene and her forearm had to be amputated) when a physician's assistant injected her artery with the antinausea drug Phenergan by using the "IV-push" method of injection. She sued Wyeth, the manufacturer of Phenergan, for failing to provide an adequate warning about the different risks involved with the various methods of administering the drug. A jury concluded that Wyeth had indeed failed to provide an adequate warning about the significant risks involved when Phenergan is administered by using the IV-push method.

On appeal, Wyeth argued that the plaintiff's state law failure-to-warn claims were preempted because it was impossible for the manufacturer to comply with both state law duties and federal labeling obligations. It also argued that the state law suits would undermine Congress's intent to trust labeling decisions to the expertise of the FDA. The Supreme Court rejected both contentions and held that there was no preemption in either instance. In fact, the Court noted that state law claims are an important complement to the FDA's Herculean task of regulating the safety and effectiveness of all prescription drugs. Although the Court found that preemption did not exist in *Levine*, it held that there could be preemption if the manufacturer met the stringent standard of proving that there was *clear evidence* the FDA would have rejected the proposed change in the drug's label. The Supreme Court, however, did not clarify what

constitutes “clear evidence.” Therefore, the only thing we know for sure is that the evidence presented in *Levine* did not meet this exacting standard.¹

The journey to deciphering the “clear evidence” standard begins with understanding how drug manufacturers receive approval to market new prescription drugs and to change a label once it has been approved. Before marketing a new drug, the manufacturer must submit a New Drug Application to the FDA, which demonstrates by “substantial evidence” that the medication is efficacious. 21 U.S.C. 355(d)(5). The FDA’s approval is then conditioned on the manufacturer’s use of the label it suggests. 21 C.F.R. § 314.105(b). Even after the medication is approved, the FDA continues to have authority over it and its label. 21 C.F.R. 314.80-.81. The manufacturer, however, has the ability to change the label without FDA approval through a “changes being effected” (CBE) labeling change. The CBE regulation allows a manufacturer to modify a label to “add or strengthen a contraindication, warning, precaution, or adverse reac-

¹ It’s perhaps worth noting that just a few months ago, the Eighth Circuit rejected, rather summarily, a preemption argument fairly close to the one Smithkline Beecham advances in this case. In *In re Prempro Products Liability Litigation*, 586 F.3d 547 (8th Cir. 2009), the plaintiff alleged that as a result of taking estrogen and progestin drugs, she developed breast cancer. She sued the drug manufacturers for failure to warn of the risk of breast cancer. In rejecting preemption in less than half a page, the Eighth Circuit said, “The Supreme Court’s recent decision in [*Levine*] has foreclosed this preemption argument.”

tion” or to “add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product” and to do so when it files its supplemental application, before the FDA has the opportunity to consider whether or not it will accept the change. 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). The ability to make CBE labeling changes underscores a central premise of federal drug regulation: A “manufacturer bears responsibility for the content of its label at all times.” *Levine*, 129 S. Ct. at 1197-98. While it is important for a manufacturer to warn of potential side effects, it is equally important that it not overwarn because overwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted and can dilute the effectiveness of valid warnings. Therefore, warnings may only be added when there is “reasonable evidence of an association of a serious hazard with the drug.” 21 C.F.R. § 201.57(e)(2003).² It is technically a violation of federal law to propose a CBE that is not based on reasonable evidence. 18 U.S.C. § 1001.

Since *Levine* is our intellectual anchor—if the evidence here is less compelling than it was in *Levine*, we will not find preemption—we must look at the long and fairly extensive administrative history of Phenergan and compare it to the administrative history of Paxil. The FDA approved Phenergan in 1955. Wyeth submitted supple-

² Section 201.57 was amended in 2006. The standard for “older drugs,” including Paxil, is now located at 21 C.F.R. § 201.80(e).

mental new drug applications in 1973 and 1976 which the FDA approved after proposing labeling changes. In 1981 Wyeth submitted a third supplemental application in response to a new FDA rule governing drug labels. The Court then notes that “[o]ver the next 17 years, Wyeth and the FDA intermittently corresponded about Phenergan’s label.” *Levine*, at 1192. The most notable of these correspondences occurred in 1987 when the FDA suggested alternative warnings regarding arterial exposure³ and in 1988 when Wyeth submitted a proposed label which incorporated the suggestions. The FDA did not contact Wyeth again until 1996 when it told Wyeth to retain the wording on its current label. In 1990, the FDA finally approved Wyeth’s 1981 application and mandated that the wording on the label must be identical to the package insert. On April 7, 2000, the plaintiff in *Levine* received the dose of Phenergan that caused her injury.

While the opinion in *Levine* covers the administrative history and record, the dissent delves even deeper. When the dissent and the majority disagree in the characterization of the record or administrative history, we of course follow the majority’s view.⁴ According to the

³ Phenergan causes gangrene when injected into an artery, which was the exact mishap responsible for the injury to the plaintiff in *Levine*.

⁴ The majority and dissent disagree about the categorization of the warning Wyeth proposed in 1988. *Compare, Levine* at 1218 n.1
(continued...)

dissent, “For at least the last 34 years, the FDA has focused specifically on whether IV-push administration of Phenergan is ‘safe’ and ‘effective’ And the record contains ample evidence that the FDA specifically considered and reconsidered the strength of Phenergan’s IV-push-related warnings in light of new scientific and medical data.” *Levine*, at 1222. The dissent then meticulously lists the various times the FDA considered a different warning label regarding the IV-push method. It begins in 1975 when several people from Wyeth and several members of the FDA met regarding Phenergan’s label and the FDA proposed that Phenergan should not be injected via Tubex, which is a syringe system used exclusively for IV push. Instead of banning the use of IV push altogether, both parties agreed that there was instead a need for better instruction regarding the problems of intra-arterial injection. A year later, an FDA committee recommended an additional IV-push-specific warning for Phenergan’s label but decided not to prohibit using the IV-push method. In its labeling

⁴ (...continued)

(Alito, J., dissenting) (“Indeed, respondent conceded below that Wyeth *did* propose an adequate warning of Phenergan’s risks. Specifically, respondent noted: ‘In 1988, Wyeth proposed language that would have prevented this accident by requiring a running IV and explaining why a running IV will address and reduce the risk [of intra-arterial injection].’”) (internal citations omitted), *with Levine* at 1199 n.6 (“The dissent’s suggestion that the FDA intended to prohibit Wyeth from strengthening its warning does not fairly reflect the record.”).

order, the FDA cited numerous sources describing the costs and benefits of IV push including published case reports from 1960 about cases of gangrene caused by the intra-arterial injection of Phenergan. Taking *Levine* as a whole, it is clear from the ample administrative record that the FDA strongly considered a similar warning to the one the plaintiff proposed and the Court still did not find preemption.

Now that we know what falls short of “clear evidence,” we turn our attention to the administrative record of Paxil and see if it is any more compelling. Paxil belongs to a class of prescription antidepressants known as selective serotonin re-uptake inhibitors (SSRIs). SSRIs operate by controlling the manner in which serotonin is processed by brain cells. They force serotonin to stay longer between brain cells, which allegedly improves the mood of patients. Prozac, the first SSRI, is quite well-known. Anyone who has ever watched *The Sopranos*⁵ knows that it’s the drug Dr. Jennifer Melfi prescribed for Tony Soprano after telling him “no one needs to suffer from depression with the wonders of modern pharmacology.”

Smithline Beecham (we’ll refer to the company from now on as “GSK,” the initials of an entity that it does

⁵ *The Sopranos*, of course, was a critically acclaimed drama that aired between 1999 and 2007 (86 episodes) on HBO. It is the most financially successful cable series in the history of television and is acknowledged as one of the greatest television series of all time.

business under) recounts the regulatory history of Paxil to show that there is clear evidence that the FDA would not have approved the labeling change the plaintiffs say was necessary. GSK filed a “New Drug Application” (NDA) with the FDA in 1989 seeking approval to market Paxil for the treatment of depression in adults. The FDA approved Paxil—without a warning about suicide.

The plaintiffs allege⁶ that the FDA was misled because GSK included suicides and suicide attempts that occurred during the wash-out phase⁷ of the clinical trials for Paxil and counted them as if they occurred during the actual trial when a subject was on a placebo. Since

⁶ The plaintiffs also allege that GSK contaminated the administrative history of Paxil by using the term “emotional lability” to disguise suicidal behavior that was reported during the clinical trials. GSK does not deny that it coded data as “emotional lability” but maintains that when the FDA analyzed this data in February of 2003—a month before Tricia’s death—it included all of the proper suicide data regardless of coding and still did not find any relationship between suicidal behavior and Paxil. Therefore, this allegation does not call into question the data the FDA used to evaluate Paxil.

⁷ One of the difficulties with conducting studies for Paxil is that the participants are frequently taking other medications when they begin the study. In order to start the study with a clean slate, there is a “wash-out” phase that usually lasts for one or two weeks where everyone in the study is given a placebo to make sure their old drugs are out of their systems and are not responsible for any changes in mood or behavior.

the wash-out phase occurs before the study begins, events that occur during that phase should not be counted. By attributing the negative outcomes that occurred during this period to the placebo, Paxil looks better by comparison.

This allegation is partially true. In its 1989 NDA, GSK presents the suicide data in a table that counts wash-out suicidal behavior as if it occurred during the study while subjects were taking placebos. However, each erroneous datum had a star by it which noted that part of the suicidal behavior occurred during the wash-out phase. It appears that Dr. Brecher, the FDA scientist who reviewed GSK's application, understood that the wash-out events were included when he analyzed the data and found no relationship between Paxil and suicidal behavior. Furthermore, in May 2002 and February 2003, GSK re-analyzed the data by excluding wash-outs and noncontrolled⁸ studies and submitted that data to the FDA. GSK's analysis found that there was still

⁸ A noncontrolled study is a study where there is no control group. In other words, a noncontrolled study is a study in which all of the participants take a prescription drug and none of them take a placebo. Having a control group is important when analyzing suicidal behavior data because suicidal behavior is a symptom of depression and related diseases. Therefore, a certain number of depressed people who are not taking medication will exhibit suicidal behavior. Having a control group establishes a baseline with which the manufacturer can compare the suicidal behavior rate of participants taking the prescription drug.

no relationship between suicide and Paxil. Overall, the plaintiffs' allegations do not taint the administrative history of Paxil.

That the FDA initially approved Paxil after considering the proper data does not provide much, if any, evidence that the FDA would have rejected the warning the plaintiffs say should have been in place before Tricia took her life. In *Levine*, the Court held that FDA approval by itself does not warrant preemption. *Levine*, 129 S. Ct. at 1191. Furthermore, since GSK, not the FDA, retains responsibility for Paxil's label, the FDA's initial approval, more than a decade before, isn't a great comfort to GSK's case.

Next, GSK highlights that the FDA had been thoroughly reviewing the data available about SSRIs and suicide and concluded there was not an increased risk of self-harm from SSRIs. In particular, it points out that on three separate occasions the FDA rejected a citizen petition for a labeling change for Prozac that would have included a warning about suicide. The FDA's rejection of the Prozac warnings, however, is not as clear-cut as GSK would have us believe. During a meeting of the FDA's psychopharmacological drug committee, Dr. Paul Leber—the Director of the Division of Neuropharmacological Drug Products—gave a presentation about the potential link between suicide and antidepressants and stated, “[N]obody in the agency dismisses the possibility that antidepressants in general and fluoxetine in particular may have—and I emphasize ‘may’—the capacity to cause untoward injurious behaviors, acts, and/or

intensify them.” Additionally, in the very letter that rejected a citizen petition to change the label on Prozac, the FDA noted that more research needs to occur to explore the relationship between antidepressants and suicidality. Overall, we do not find the FDA’s rejection of the citizen petitions or its call to do more research very compelling for either side. Even the latest of these findings was made several years before Tricia’s suicide. This temporal gap is especially important in the analysis of prescription drugs because it constantly evolves as new data emerges. Furthermore, even though Prozac and Paxil are both SSRIs, they are different drugs made by different manufacturers. Therefore, we give little weight to the administrative history of Prozac when we are concerned with whether there is clear evidence that the FDA would have rejected a labeling change in Paxil.

GSK also tries to show that the FDA’s inaction, as in its failure to mandate a warning about the risk of suicide, around the time of Tricia’s death is clear evidence that the FDA would not have approved the change in the label the plaintiffs seek. GSK highlights that after Paxil’s approval, it submitted a detailed annual report that included postmarketing adverse events and clinical investigations of Paxil to the FDA. Additionally, it points out that the FDA approved nine new indications⁹ for Paxil, each time reviewing all of the safety data about Paxil, including the suicide data. In particular, GSK

⁹ In medical terminology, an indication is a disease or condition a drug can treat.

emphasizes that it submitted the available data on Paxil and suicide ten months and one month prior (May 2002 and February 2003) to Tricia's suicide, and three months after (June 2003) Tricia's suicide the FDA published a press release that concluded there was no increased risk of suicide in adults. GSK maintains that the FDA appropriately failed to issue a warning about Paxil and suicidality because there was no evidence to merit it from the information available. While what GSK points out is true, it only tells one side of the story. For example, GSK ignores the main purpose of the June 2003 press release, which was to recommend that doctors stop using Paxil to treat pediatric major depressive disorder (MDD) because the FDA was currently reviewing reports of increased risks of suicide and suicidal behavior with the drug. Then, in October of 2003, the FDA informed health care providers of a possible increased risk of suicidality in pediatric, but not adult, patients. Therefore, it seems unlikely that the FDA would have refused to allow GSK to warn about a possible risk of suicide for young adults when it had already warned the public that Paxil was potentially unsafe for 17-year-olds with MDD.

Finally, in 2006, using a CBE labeling change, GSK warned that Paxil was associated with an increased risk of suicide in adults. Then, in May of 2007, the FDA ordered all antidepressant manufacturers to include an additional warning about the increased likelihood of suicidality in young adults under the age of 24. GSK maintains that the methods used to analyze the data were not available at the time of Tricia's death. Further-

more, it claims that it did not have access to the pool of data that the FDA used to determine that these risks exist. Since these events occurred well after Tricia's suicide, they are not persuasive in determining whether there was clear evidence that the FDA would have rejected the proposed warning at the time of Tricia's death. To the extent these subsequent events have any sway, however, they clearly cut towards making it less likely that the FDA would have rejected the plaintiffs' proposed warning in 2003. Therefore, in light of the extensive showing required by *Levine*, we conclude that GSK did not meet its burden of demonstrating by clear evidence that the FDA would have rejected a label change warning about the risk of suicide by young adults before Tricia's life came to an end at 23. Consequently, the plaintiffs' claims are not preempted.

For these reasons, the judgment of the district court is REVERSED and the case REMANDED for further proceedings.