United States Court of Appeals
Fifth Circuit
F I L E D
August 22, 2006
Charles R. Fulbruge III
Clerk

In the United States Court of Appeals for the Fifth Circuit

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m 05-10509

SUE C. MCNEIL,

Plaintiff-Appellant,

VERSUS

WYETH,
FORMERLY KNOWN AS
AMERICAN HOME PRODUCTS CORPORATION,
DOING BUSINESS AS A.H. ROBINS COMPANY, INC.,

Defendant-Appellee.

Appeal from the United States District Court
for the Northern District of Texas

Before KING, SMITH, and BENAVIDES, Circuit Judges.

JERRY E. SMITH, Circuit Judge:

Sue McNeil appeals a summary judgment for defendant Wyeth, a pharmaceutical company. We reverse and remand.

I.

In August 2000, Dr. Eduardo Wilkinson prescribed Reglan, whose generic name is metoclopramide, manufactured by Wyeth, to treat McNeil's symptoms of gastroesophageal reflux disease ("GERD"). The prescription was for six months, though the Food and Drug Administration had approved the drug only for use of no more than twelve weeks. Thereafter, McNeil's prescription was continued by Dr. Roy Ragsdale for six months and then by Dr. William Mania for two months.

GERD is a disease whose expression ranges from infrequent heartburn to frequent heartburn accompanied by regurgitation. In severe cases it can lead to a narrowing of the esophagus by scarring.

Reglan is a "prokinetic" drug that helps control GERD by blocking dopamine receptors in the brain and throughout the body, thus enhancing movement or contractions of the esophagus, stomach, and intestines. Dopamine is a chemical produced naturally by the human body that sends signals from one nerve to the next. Simple movements of muscles, such as moving a finger, are controlled by what is known as the pyramidal system. More coordinated muscle movements, such as dancing or talking, require fine motor control from the extrapyramidal system.

By blocking dopamine receptors, Reglan can affect the extrapyramidal system by causing extrapyramidal symptoms ("EPS"), which "are a group of adverse drug reactions referred to generally as extrapyramidal symptoms because of the involvement of the extrapyramidal nervous system."[1] The clinical pharmacology section of Reglan's FDA-approved label explains that, like other "dopamine antagonists" such as phenothiazines, Reglan "may produce extrapyramidal reactions, although these are comparatively rare."

Tardive dyskinesia is a particularly severe form of EPS characterized by grotesque involuntary movements of the mouth, tongue, lips, and extremities, involuntary chewing movements, and a general sense of agitation. Reglan's label warned that Reglan may produce tardive dyskinesia.

In October 2001, about fourteen months after she started taking Reglan, McNeil was admitted to an emergency room complaining of shortness of breath, anxiety, and an involuntary "chewing motion" of her mouth. The nurse who first treated McNeil noted that she was also fidgeting, appeared nervous, and had an unsteady gait. The emergency room physician who later examined McNeil confirmed these observations and diagnosed EPS, likely occasioned by exposure to Reglan.

McNeil's primary care physician confirmed this diagnosis, discontinued Reglan, and prescribed a replacement drug. When McNeil's EPS symptoms failed to improve with time, she consulted a neurologist and two medical specialists in movement disorder; all three concluded that McNeil suffers from Reglan-induced tardive dyskinesia in addition to Reglan-induced EPS.

II.

McNeil sued Wyeth in state court. Her complaint alleged that Wyeth had failed adequately to warn physicians and consumers of the increased risk of tardive dyskinesia that accompanies long-term use of Reglan. McNeil argued that Wyeth's failure to warn rendered the inherently unsafe product unreasonably dangerous. Further, McNeil alleged that the Reglan label was misleading as to the risk of tardive dyskinesia and failed adequately to warn about the increase in risk associated with exposure to the drug for more than twelve weeks.

Wyeth removed to federal court pursuant to 28 U.S.C. § 1332(a)(1). Both parties consented to decision by a magistrate judge, whom we therefore refer to as the "district court."

Wyeth moved for summary judgment,

[1] *Windham v. Wyeth Lab., Inc.*, 786 F. Supp. 607, 612 (S.D. Miss. 1992).

which the court granted, concluding that the Reglan label was "adequate as a matter of law" because it "specifically mentions the circumstances complained of . . . ." More specifically, the court noted that the label

> specifies that the drug is intended for short-term use of 12 weeks or less, warns against the potential risk of tardive dyskinesia and other movement disorders, and discloses that the risk of developing tardive dyskinesia is highest among elderly women and increases with the duration of treatment and the total cumulative dose. The label also describes the possible symptoms associated with movement disorders caused by the drugSSthe very symptoms of which plaintiff complains.

Therefore, the court concluded that Wyeth was entitled to summary judgment on McNeil's marketing defect claims. In an additional paragraph, the court stated that "Wyeth is entitled to summary judgment on plaintiff's design defect claims." McNeil appeals only the failure-to-warn claims.

III.

Summary judgment is proper "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." FED. R. CIV. P. 56(c). Disputes about material facts are genuine "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). We review the district court's decision *de novo*. *Skotak v. Tenneco Resins, Inc.*, 953 F.2d 909, 912 (5th Cir. 1992). The evidence and inferences from the summary judgment record must be viewed in the light most favorable to the nonmovant. *Minter v. Great Am. Ins. Co.*, 423 F.3d 460, 465 (5th Cir. 2005).

IV.

Texas, like most jurisdictions, has adopted section 402A of the Restatement of Torts for product liability claims. *Nobility Homes, Inc. v. Shivers*, 557 S.W.2d 77, 79-80 (Tex. 1977). Under that section, "[i]f a product is unreasonably or inherently dangerous, a warning is required." *Gravis v. Parke-Davis & Co.*, 502 S.W.2d 863, 870 (Tex. Civ. App.SSCorpus Christi 1973, writ ref'd n.r.e.) (citing RESTATEMENT (SECOND) OF TORTS § 402A (1965)).

Texas law generally holds that the adequacy of a product's warning is a question of fact to be determined by the jury. *Williams v. Upjohn Co.*, 153 F.R.D. 110, 114 (S.D. Tex. 1994); *Alm v. Aluminum Co. of Am.*, 717 S.W.2d 588, 591-92 (Tex. 1986)). In prescription drug cases involving the learned intermediary doctrine, however, when "a warning specifically mentions the circumstances complained of, the warning is adequate as a matter of law." *Rolen v. Burroughs Wellcome Co.*, 856 S.W.2d 607, 609 (Tex. App.SSWaco 1993, writ denied).[2]

McNeil argues that the district court's reliance on *Rolen* to find adequacy as a matter of law is inapposite. We agree. Although Reglan's label mentions the conditions of which McNeil complains, McNeil's claim, unlike the

[2] In *Alm* the court also cited with approval decisions from Texas appellate courts that have adopted and applied the learned intermediary doctrine in cases involving a drug manufacturer's duty to warn about the potential hazards of prescription drugs.

claim of the plaintiff in *Rolen*, is not that the warning is inadequate because her condition was not mentioned. Rather, her argument is that the label is misleading as to the risk level for developing the condition.

We are aware of no Texas case allowing adequacy as a matter of law in such situations, and therefore we apply the default Texas rule that adequacy questions go to the jury. Our position is consistent with Texas law and the Restatement of Torts, which Texas courts follow, because, as the district court recognized, even in the context of a learned intermediary, "'if the warning to the intermediary is inadequate or misleading, the manufacturer remains liable for injuries sustained by the ultimate user.'"[3]

Warning the learned intermediary of a much lower risk than the actual risk could render the warning not just misleading, but ineffective. When the risk described on the label is so low as to induce a doctor to undertake the risk, had he not done so if he were warned of the real risk, we cannot say that no reasonable jury could conclude that a warning was inadequate. Thus, if the manufacturer decides to label a risk as "comparatively rare" and also to provide a numerical quantification of that risk, that number must be within a certain degree of accuracy.[4]

V.

The issue therefore is whether there is a genuine issue of material fact as to whether the label was misleading. This must be viewed in terms of significant differences between the disclosed risk and the actual risk of developing EPS and tardive dyskinesia, with use longer than twelve weeks.

A.

Wyeth argues that it does not have a duty to warn about risks of use longer than twelve weeks because the label clearly states that the drug is indicated for treatment for no more than that duration. Thus, not only would such a warning be superfluous, but it would also be improper, because Wyeth allegedly cannot tell a medical professional how to exercise professional judgment on whether a drug should be used longer than the period approved by the FDA. We disagree.

Wyeth was, or should have been, aware that Reglan was prescribed routinely for long-term use. Plaintiff's expert, Dr. Thompson, testified that by 1988 Wyeth had its "own market data that 84 percent of people" were using Reglan long-term. In 1992, an article by Dr. Ron Stewart and others drew attention to the common practice of long-term treatment with metoclopramide. The study involved 4,515 elderly patients at the Florida Geriatric Re-

[3] *Wyeth-Ayerst Lab. Co. v. Medrano*, 28 S.W.3d 87 (Tex. App.SSTexarkana 2000, no writ) (citing *Alm*, 717 S.W.2d at 591); *see also Bristol-Myers Co. v. Gonzales*, 561 S.W.2d 801 (Tex. 1978); *Crocker v. Winthrop Labs.*, 514 S.W.2d 429 (Tex. 1974).

[4] We do not mean to suggest that *de minimis* differences in risk would send the adequacy question to the jury, but when the differences in risk are signifi- (continued...)

[4](...continued)
cant, their potential misleading impact is a question for the jury. Other courts have also recognized that warnings that are "unreasonably diluted" may be misleading and thus inadequate. *See Salmon v. Parke, Davis & Co.*, 520 F.2d 1359 (4th Cir. 1975) (deciding that although a specific condition was mentioned in the label, "[c]omparing the company's warning with [that suggested in] the article, a jury could infer that Parke, Davis' version was unreasonably diluted").

search Program. Of the patients who reported using metoclopramide, 32% had used it for more than one year. This led the authors to conclude that long-term treatment with metoclopramide is "quite common" and that other prescription drugs were effective and safer for treating GERD:

> The routine use of metoclopramide for gastroesophageal reflux should be questioned in light of the availability of safer, more effective drugs such as histamine-receptor blocking agents cimetidine and ranitidine, and omeprazole. The long-term efficacy and symptomatic benefit of metoclopramide have not been documented.

Because the widespread long-term use of Reglan suggests that Wyeth's indication for use for no more than twelve weeks was widely disregarded, a jury could infer that Wyeth's warning was ineffective and thus inadequate. Therefore, McNeil's suggested additional warning about long-term use would not be superfluous.

Moreover, the FDA regulations require a manufacturer to inform a medical professional precisely how to exercise his professional judgment in certain circumstances. The "Contraindications" regulation requires that '[u]nder this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.' 21 C.F.R. § 201.57(d) (2000). Thus, the manufacturer must tell the physician when the drug should not be used if "the risk of use clearly outweighs any possible benefit."

One of McNeil's experts testified that the label should have indicated that use of Reglan for longer than twelve weeks was contraindicated (absent compelling circumstances). Wyeth's former medical monitor for Reglan also testified similarly by agreeing that "Reglan should not be prescribed for long-term therapy for GERD because the side effects are too dangerous and because its efficacy in longer term use has not been established."

In sum, because the widespread long-term use of Reglan suggests that Wyeth's indication for use for not more than twelve weeks was widely disregarded, a jury could infer that the warning was ineffective and therefore inadequate. It follows that Wyeth had a duty, under Texas law, adequately to warn the learned intermediary of known risks with long term use and not to be misleading as to that risk.

B.

Because Wyeth advertised that the risk of developing EPS is "comparatively rare," or that it is 0.2% for short term use, just noting that the risk is higher for long-term use may not put a physician on notice that certain studies have found that the risk could be a hundred times higher.[5] That is, because the advertised risk is negligibly low, the mere statement that the risk increases with use does not put a

[5] An 1989 study by Dr. Lucinda Miller and Dr. Joseph Jankovic looking at 1,031 patients concluded that the prevalence of metoclopramide-induced movement disorders is probably greater than Wyeth's estimate of 1 in 500. An article published by Dr. Linda Ganzini and others in 1993 described that 29% of the patients in a case-control study exposed to metoclopramide met the case definition of tardive dyskinesia. The average duration of exposure to the drug was 2.6 years. Another case-control study conducted by Dr. Daniel Sewell in 1994 found that 27% of the patients exposed to metoclopramide for longer than thirty days met the case definition of tardive dyskinesia.

physician on notice that the increase in risk is of a completely different order of magnitude and class of risk. Thus, a jury could find that the risk of developing EPS from long-term use was not just higher, but that it was "significantly" higher, and that the label was therefore misleading and inadequate.

Wyeth argues, however, that it was not required to update its label, because the studies indicating that the risk for long-term use could be a hundred times higher showed mere association with a disease, not necessarily causation. Thus, Wyeth argues, because there could be a variety of other factors responsible for the "association" found in these studies, that association does not necessarily require a warning to physicians. This argument, however, is contradicted by the FDA regulations that require that the labeling "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) (emphasis added).

Of course, it does not immediately follow, from the fact that Wyeth is required under federal law to warn physicians of a significant "association" between tardive dyskinezia and long-term use of Reglan, that Texas law requires the same thing. Texas law, however, does not absolve a manufacturer, as a matter of law, of a duty to warn on grounds that no existing studies or clinical trials prove actual causation.

In *Jordan v. Geigy Pharms.*, 848 S.W.2d 176 (Tex. App.—Fort Worth 1992, no writ), the court observed that although the drug manufacturer warned that cases of "*significant* renal failure in patients receiving Voltaren have been reported from postmarketing experience, but were not observed in over 4,000 patients in controlled clinical trials," it had not warned of the possibility of "*acute* renal failure." *Jordan*, 848 S.W.2d at 182. In other words, even if the clinical studies did not show significant renal failure and thus, also did not show acute renal failure, there was a genuine issue of material fact on adequacy raised solely by association evidence (anecdotal case reports, not clinical trials).

McNeil's expert, Dr. Thompson, also noted that manufacturers frequently change their labels and warn physicians of side effects based on simple case reports, not on actual studies showing causation. For example, a pharmaceutical company for which she was working at the time (Eli Lily) inserted a warning that a certain use of the drug Papaverine is contraindicated based only on a few case reports of its apparently causing heart attacks, and no epidemiological or other studies showing causation. She explained that the contraindication attracted a lot of hate mail from physicians who had practiced the off-label use, but that it had to be done, and it took little time to do. This is not to say that a manufacturer is always required to change a label based on case reports; we mention Thompson's testimony only to counter Wyeth's contention that manufacturers never change labels based on case reports (as distinguished from clinical trials) and that they never tell physicians how to exercise their judgment.

Thus, it is not uncommon for drug companies to do precisely what Wyeth claims it cannot do: tell physicians that a certain use is contraindicated even if no clinical or epidemiological studies exist that confirm causation or degree of risk. Certainly, it is easier for a manufacturer to make an off-label use contraindicated when that use provides only a minimal amount of sales from that drug as opposed to when the off-label use provides the majority of

its sales, as allegedly it is with Wyeth and Reglan. But it is precisely this factSSthat off-label use allegedly provided a majority of Wyeth's salesSSthat would create Wyeth's duty to physicians not to be misleading about the risk of long-term use.

Admittedly, the physician, in the exercise of professional judgment, can disregard the warnings or contraindications provided by the manufacturer. But then he does so at his own risk, and most physicians are likely reluctant to do so absent more concrete evidence about the benefits of long-term use, evidence that is absent in this case. Even Dr. Wilkinson, who initially indicated that he would not have changed his long-term prescription of Reglan even if he had read the studies now cited by McNeil, acknowledged that he would not have prescribed Reglan for more than twelve weeks had Wyeth provided a contraindication on Reglan's label.

Therefore, we cannot say as a matter of law that the peer-reviewed studies cited by McNeil do not describe a significant risk about which Wyeth should have warned Texas physicians. Of course, Wyeth is free to argue, to a jury, its view of the proper weight to be given to these studies; it can also challenge (if still timely) the admissibility of these peer-reviewed studies under *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993).

McNeil has also raised a genuine issue of material fact as to whether pharmacological evidence should have alerted Wyeth about the significantly increased risk from long-term use. Under Texas law, causation is generally an issue of fact. *Lenger v. Physician's Gen. Hosp., Inc.*, 455 S.W.2d 703, 706 (Tex. 1970). An expert opinion is legally sufficient evidence to establish a causal relationship between the condition and the event. *See Rodriguez v. Reeves*, 730 S.W.2d 19 (Tex. App.—Corpus Christi 1987, writ ref'd n.r.e.).

McNeil's expert, Dr. Thompson, testified that the well-known, scientifically established pharmacology of dopamine antagonists that block a D2 dopamine receptor such as metoclopramide or schizophrenia medications (Haldol and Thorazine) is to diminish the effects of dopamine in the brain. The inability of dopamine to produce its effects causes EPS (including Parkinsonian side effects such as rigidity, tremor, and dystonia, and the more severe side-effect known as tardive dyskinesia), because the extrapyramidal system needs dopamine to function. Thompson also testified that these side-effects for metoclopramide are "highly predictable," given the function it performs (blocking dopamine receptors) and the known effects of other dopamine blockers:

> [M]ost of [metoclopramide's] side effects are related to its action, which is, in fact, blocking the dopamine effects in the brain and elsewhere. And so what it does is to produce the whole array of side effects that we associate with dopamine blockers. And in this sense, it's really no different that any so-called neuroleptics, the drugs that produce the calming effect in schizophrenia. So it's just like Thorazine or Haldol or any of the other antipsychotics. It's highly predictable that this would be its effect . . . .

Thompson testified that the propensity of neuroleptics such as Thorazine and Haldol to cause tardive dyskinesia was discovered about twenty years after the beginning of the use of Thorazine, that is, in the late 1970's. She further testified that the rate of developing tardive dyskinesia with long term use of D2 receptor blockers was 25%. Therefore, she found to be misleading the label's claim that like other

"dopamine antagonists" such as phenothiazines (which include Thorazine), Reglan "may produce extrapyramidal reactions, although these are comparatively rare. As Thompson testified,

> Most of the papers I've seen would give about the same prevalence rate of tardive dyskinesia in Metoclopramide long term and Thorazine long-term. So [the label] wouldn't be correct in terms of being comparatively rare . . . . 25 percent isn't rare compared to anything.

Therefore, we cannot say as a matter of law that Reglan's label was adequate even if it failed to warn that the risk of developing tardive dyskinesia was not "comparatively rare," but increased significantly with long-term use.

VI.

Under Texas law, a plaintiff who complains "that a prescription drug warning is inadequate must also show that the alleged inadequacy caused her doctor to prescribe the drug for her." *Porterfield v. Ethicon, Inc.*, 183 F.3d 464, 468 (5th Cir. 1999); *accord Stewart v. Jannssen Pharm.*, 780 S.W.2d 910, 912 (Tex. App.—El Paso 1989, writ denied). In other words, a plaintiff must show not only that a warning was inadequate, but that it was a "producing cause" of his injuries.

Wyeth is correct that although the district court has not addressed this issue, the matter was before the court, so we could affirm for this reason if we were to find for Wyeth on this question. We do not so decide, however, because there is a genuine issue of material fact as to whether the label's inadequacy caused McNeil's doctor to prescribe the drug.

Wilkinson gave conflicting testimony. On the one hand, he stated that he still would have prescribed the drug had he known that the risk was "significant," but would have alerted the plaintiff to that risk. On the other hand, he testified that he would not have prescribed the drug had its label stated that use for longer than twelve weeks is contraindicated because the risks are significant and the benefits have not been proven. Therefore, McNeil has raised a genuine issue of fact as to whether Wilkinson would have prescribed the drug had the label's warning been adequate.

Moreover, because Wilkinson testified that he was never informed of the significant risk of tardive dyskinesia associated with long-term Reglan use and that such information certainly would have changed the "risk/benefit" analysis" and the conversation he would have had with McNeil about the risks, the inadequate labeling could be a producing cause of the injury even if Wilkinson had never testified that he would not have prescribed Reglan had a contraindication been inserted. Sworn testimony from McNeil establishes that she was never told of the significantly increased risk of tardive dyskinesia with use of Reglan for greater than twelve weeks and that, if she had known of such a risk, she would not have taken Reglan for longer than that.

The doctrine of the "learned intermediary" presupposes that the physician will act as an intermediary. This function includes discussing the cost-benefit ratio with the patient if necessary. Where the physician would have adequately informed a plaintiff of the risks of a disease, had the label been sufficient, but fails to do so on that account, and where the plaintiff would have rejected the drug if informed, the inadequate labeling could be a "producing" cause of the injury, because it effectively sabo-

tages the function of the intermediary.[6]

We note that our discussion of "permissible inferences is intended neither to define nor to decide the issues in this case." *Salmon*, 520 F.2d at 1364. It serves merely to illustrate our reasons for concluding that summary judgment is inappropriate. Reasonable minds can differ on whether not mentioning that the increase in risk for long-term use was significant would be misleading. But this is precisely why that question should go to the jury. The summary judgment is REVERSED, and this matter is REMANDED for further proceedings.

[6] "[T]he mere presence of an intermediary does not excuse the manufacturer from warning those whom it should reasonably expect to be endangered by the use of its product." *Alm*, 717 S.W.2d at 591. Instead, the issue "in every case is whether the original manufacturer has a reasonable assurance that its warning will reach those endangered by the use of its product." *Id.* Although usually the manufacturer can rely on the "learned intermediary," *id.*, this reliance seems less reasonable where the learned intermediary fails to pass necessary information to the patient because the manufacturer has understated the degree of risk.