No. 17-3030

In the United States Court of Appeals for the Seventh Circuit

WENDY B. DOLIN, Individually and as Independent Executor of the Estate of STEWART DOLIN, Deceased,

Plaintiff-Appellee,

v.

GLAXOSMITHKLINE LLC, Formerly Known as SMITHKLINE BEECHAM CORPORATION,

Defendant-Appellant.

On Appeal from the United States District Court for the Northern District of Illinois
No. 12-cv-6403 (Hon. William T. Hart)

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INTRODUCTION

Stewart Dolin never took GSK's drug. Holding GSK responsible for deficiencies on the labeling of another manufacturer's drug would mark a radical departure from longstanding Illinois tort principles. Plaintiff cites no Illinois state-court decision imposing liability on a manufacturer that did not make or distribute the injury-causing product. Innovator liability would upset the settled expectations of manufacturers that invest massive resources on the understanding that they may be haled into court only for injuries caused by their own products. Illinois law rejects tort theories like innovator liability precisely to encourage manufacturers to develop drugs like Paxil, which saves and improves countless lives.

That is enough to preclude plaintiff's claim, but there is more. GSK and FDA have studied whether paroxetine poses an increased risk of suicide for decades, and GSK could not have changed its labeling to give the warning plaintiff demands. Plaintiff engages in misdirection, making baseless, irrelevant accusations of misconduct. But FDA knew of every instance of supposed misconduct plaintiff cites, and not only barred GSK from warning about the very risk plaintiff claims GSK concealed, but ordered GSK to stop doing so. There is no clearer case for preemption than this.

Finally, and unsurprisingly given FDA's decisions, plaintiff failed to prove that paroxetine causes suicide in adults over 24, or that Sachman was unaware of the purported risk. Holding GSK liable for Mylan's drug, FDA's labeling decisions, and Sachman's prescribing choice is Kafkaesque. The Court should reverse.

ARGUMENT

I. GSK Is Not Responsible for Injuries Allegedly Caused by Another Manufacturer's Drug

Holding GSK liable for injuries purportedly caused by a drug GSK did not make, distribute, or profit from contravenes Illinois and federal law. Plaintiff seeks an extreme expansion of tort law rejected by an "overwhelming national consensus." *Guarino v. Wyeth*, LLC, 719 F.3d 1245, 1252 (11th Cir. 2013).

A. Illinois Law Bars Innovator Liability

1. *Smith v. Eli Lilly & Co.*, 560 N.E.2d 324 (Ill. 1990), holds that a pharmaceutical company is not liable for failure to warn unless it manufactured the injury-causing drug. *Id.* at 340-44; Br.19-23. The Sixth Circuit has held that *Smith* and its progeny foreclose innovator liability under Illinois law. *In re Darvocet, Darvon, & Propoxyphene Prod. Liab. Litig.*, 756 F.3d 917, 944 (6th Cir. 2014); Br.23.

Plaintiff tries to limit *Smith* to the proposition that "a plaintiff must be able to identify the tortfeasor that caused the alleged injury." Opp.46-47. But *Smith* rejected a theory of liability indistinguishable from plaintiff's theory here. Br.20. The plaintiff in *Smith* sought to establish a "'sufficient connection' [to] each of the named defendants" by showing that the defendants "submitted an application for approval" that "formed the basis of subsequent FDA approval for the manufacturing of [the drug] by other companies." 560 N.E.2d at 340. Just as plaintiff here alleges that GSK obtained FDA approval later used by Mylan, the plaintiff in *Smith* alleged that the defendants there obtained approval later used by the actual manufacturer. *Smith* rejected that theory as "insufficient." *Id.*

Plaintiff argues that she seeks to hold GSK responsible "for crafting and controlling the paroxetine label." Opp.31, 47. But the manufacturing approval in *Smith* included labeling approval, and *Smith* considered and rejected a failure-to-warn claim. 560 N.E.2d at 326-27. *Smith*'s rationale applies here: even when one company obtains approval used by others, that cannot make the company "responsible for the injuries caused by … others' products." *Id.* at 341. Plaintiff contends that GSK relies on authority involving "products liability, as opposed to common law negligence." Opp.33. But *Smith* involved a negligence claim. Opp.46. And other Illinois negligence cases also hold that a manufacturer's duty to warn is limited "to those who will use its product or who might be injured by it." *Lewis v. Lead Indus. Ass'n, Inc.*, 793 N.E.2d 869, 875 (Ill. App. Ct. 2003). This principle is "a fundamental tenet of products-liability law," "[r]egardless of the theory which liability is premised upon, whether negligence … or other grounds." *Gillenwater v. Honeywell Int'l, Inc.*, 996 N.E.2d 1179, 1200 (Ill. App. Ct. 2013) (quotation marks omitted); *see* Chamber Br.8-11; WLF Br.15-19.

Plaintiff's attempts to distinguish labeling claims from product claims, Opp.31-33, also ignore that Paxil's labeling is a representation about GSK's product, attached to GSK's product, directed to patients who consume GSK's product and to physicians who prescribe GSK's product to those patients. Br.22; Chamber Br.9-11. Plaintiff and her amici cite various cases and Restatement provisions involving misrepresentations to the plaintiff (or the plaintiff's supplier) about the injury-causing product. Opp.32-33, 36-37; ITLA Br.10-11. But GSK never made any

statement to anyone about Mylan's product. Plaintiff also quotes from *Simpkins v. CSX Transp., Inc.*, 965 N.E.2d 1092, 1097 (Ill. 2012), that a manufacturer's duty can extend to "remote and unknown persons." Opp.36-37. But *Simpkins* concerned a claim for injuries caused by the defendant's *own* asbestos-containing materials. 965 N.E.2d at 1094.

None of plaintiff's authorities hold, or even suggest, that manufacturers can be liable for inadequate warnings about their own products when a competitor's product caused the injury. Many suggest the opposite. Plaintiff quotes *Board of Education of City of Chicago v. A, C & S, Inc.*, 546 N.E.2d 580 (Ill. 1989), for example, and certain Restatement provisions discussed therein, Opp.32-33, but *A, C & S* held that plaintiffs asserting a negligent-misrepresentation claim alleging physical harm "must prove … that the statements made were to induce the plaintiffs to purchase the [injury-causing] products." *Id.* at 593. And plaintiff herself quotes the holding of *Wingstrom v. Evanston Hosp. Corp.*, 1992 WL 97934 (N.D. Ill. May 5, 1992), that a manufacturer must warn of the "dangers of *its* drugs." Opp.37 (emphasis added); *see* Restatement (Second) of Torts § 388 cmt. e (supplier of chattels owes a duty only to "those for whose use the chattel is supplied"); Chamber Br.8.

Smith also held that forcing manufacturers to act as "insurers of their industry" would violate Illinois public policy. 560 N.E.2d at 342-44; Br.21-22. Plaintiff responds that GSK would be its competitors' insurer only for failure-to-warn claims. Opp.42. That is cold comfort. "Failure to instruct or warn is the major

basis of liability for manufacturers of prescription drugs ….” Restatement (Third) of Torts: Prod. Liab. § 6, cmt. d. Plaintiff also notes that GSK derived revenue from an authorized generic for a different version of Paxil, Opp.42-43, but that does not mean GSK should insure generics it did *not* authorize, like Mylan’s here. And plaintiff does not dispute that under her theory, brand manufacturers’ exposure for all of their competitors’ sales would dwarf the market-share-proportionate exposure *Smith* found intolerable. Br.22. Plaintiff also suggests, counterintuitively, that added liability may spur innovation. Opp.43-44. *Smith* disagreed: “[A]dded potential for liability will likely contribute to diminishing participants in the market” and “will discourage desired pharmaceutical research and development.” 560 N.E.2d at 342 (quotation marks omitted); *see* Chamber Br.19-25; PhRMA Br.7-14.

2. Plaintiff contends that GSK seeks to “disavow [the] responsibilities placed squarely on it by federal law.” Opp.35, 37. That is preposterous. GSK accepts its federal responsibilities, and more than fulfilled them by proactively researching and unilaterally warning about adult suicidality until FDA intervened. Federal law thus *prohibited* GSK from giving plaintiff’s warning. *Infra* pp.11-21. And recognizing plaintiff’s theory would disrupt the federal scheme, not complement it. *Infra* pp.9-11.

Plaintiff and her amici repeatedly assert that federal law gives GSK “exclusive[]” control over the labeling for Paxil and generic paroxetine. Opp.3, 36, 44; *e.g.*, AARP Br.9. That is wrong twice over. If new safety information arises after FDA initially approves the labeling, FDA is required to order an update. 21 U.S.C.

§ 355(a)-(b), (o)(4). And FDA has determined that "[g]eneric drug manufacturers that become aware of safety problems must ask the agency to work toward strengthening the label that applies to both the generic and brand-name equivalent drug." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 616 (2011). To be sure, federal law preempts most state-law failure-to-warn claims against generic manufacturers. But responsibility for the adequacy of generic labeling still rests with generic manufacturers and FDA. WLF Br.12-13.

Plaintiff repeats the district court's assertion of "misconduct" by GSK. Opp.3. But plaintiff's fraud-on-FDA allegations are (1) irrelevant, Br.25-26; (2) preempted, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001); and (3) baseless. Plaintiff faults GSK for not giving FDA data from "locally funded" trials, Opp.11, but FDA "didn't ask" for that data, which GSK "d[id]n't have" and "couldn't … aggregate[]." Tr.3362:15-19, 3367:1. And this Court has rejected plaintiff's "run-in" and coding issues. *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 393-94 & n.6 (7th Cir. 2010); Opp.7-10; Br.26.

Plaintiff invokes the principle that for every wrong there must be a remedy. Opp.34-35, 53. This argument is circular—plaintiff assumes the violation of a legal duty, which is the question on appeal. GSK "breached no duty and, therefore, there was no 'wrong.'" *Behrens v. Harrah's Ill. Corp.*, 852 N.E.2d 553, 557 (Ill. App. Ct. 2006). The absence of a remedy for generic consumers, moreover, stems not from any gap in Illinois law, but from the Supreme Court's decision in *Mensing*. To the extent there is a gap in *federal* law, that is for Congress or FDA to fill, not state

courts, and certainly not this Court in the first instance. Br.27-28; Chamber Br.17-18; WLF Br.22-25.

3. Plaintiff acknowledges the "overwhelming national consensus" against innovator liability, *Guarino*, 719 F.3d at 1252, but suggests that this consensus amounts to one decision, *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994). Opp.47-48. It does not. Br.23-24 & n.2. Plaintiff faults *Foster* for not anticipating *Mensing* 17 years in advance, Opp.48-49, but numerous courts have rejected innovator liability post-*Mensing*, Br.23.

The handful of cases recognizing innovator liability are not persuasive. Plaintiff asserts that *T.H. v. Novartis Pharmaceuticals Corp.*, 407 P.3d 18 (Cal. 2017), addressed "the same factors and considerations employed under Illinois law," Opp.34, but she does not respond to GSK's explanation of how California and Illinois law diverge, Br.26-27. Plaintiff neglects to mention that *Wyeth, Inc. v. Weeks*, 159 So. 3d. 649 (Ala. 2014), was swiftly superseded by statute, Ala. Code § 6-5-530(a), and does not dispute that *Weeks* ignored the burdens and consequences of innovator liability, Br.27 n.3. Similarly, *Kellogg v. Wyeth*, 762 F. Supp. 2d 694 (D. Vt. 2010), recognized innovator liability only after finding it "unnecessary" to consider anything beyond foreseeability. *Id.* at 706. And *Garner v. Johnson & Johnson*, 2017 WL 6945335 (C.D. Ill. Sept. 6, 2017); Opp.34, 38, 50, adds nothing of substance to the district court's flawed analysis of Illinois law below.

Pecher v. Owens-Illinois, Inc., 859 F.3d 396 (7th Cir. 2017), did not "endorse[]" innovator liability. Opp.34. There, employees injured by asbestos in the

doors they manufactured sued the holder of a patent on the doors' design, analogizing their claim to innovator liability. 859 F.3d at 398-99, 401. This Court described the "causal chain in [the innovator liability] context" as "attenuated," and dismissed the employees' claim as "frivolous." *Id.* at 401. If anything, *Pecher* offers a glimpse of the even-more-outlandish theories courts will confront if innovator liability gains acceptance.

4. Lacking any Illinois authority supporting innovator liability, plaintiff urges the Court to "weigh[]" various factors and public-policy interests to "predict Illinois law." Opp.37, 53. But this Court has "no basis for even considering the pros and cons of innovative [state-law] theories." Br.28 (quoting *Dayton v. Peck, Stow & Wilcox Co.*, 739 F.2d 690, 694 (1st Cir. 1984)).

Regardless, those factors preclude innovator liability. Generic consumers' injuries "are not the foreseeable result" of brand manufacturers' *own* statements about their *own* products to their *own* consumers and those consumers' physicians. *Darvocet*, 756 F.3d at 944. Brand manufacturers have no control over generic entry. Br.29. And the federal government—not brand manufacturers—mandates the content of generic labeling. Br.5; Opp.5. It "stretches foreseeability too far" to hold brand manufacturers responsible for statements generic manufacturers include in generic labeling directed to generic consumers. *Darvocet*, 756 F.3d at 944. If foreseeable copying is enough, then innovator liability has no limiting principle, and any industry leader anticipating reverse engineering by its competitors—not just

for drugs, but for car seats, power tools, and many other products—will become its competitors' insurer. Chamber Br.26-27.

The burdens and consequences of innovator liability, moreover, would be significant. Even assuming courts could cabin plaintiff's theory to pharmaceuticals, innovator liability would burden the development of new life-saving medicines by punishing innovative companies. Br.30. Plaintiff responds that innovator liability is necessary to give brand manufacturers a duty and incentive to warn of known risks. Opp.44-45. Plaintiff's own brief shows why that is wrong. Federal law already requires brand manufacturers to update their labeling. Opp.4-5, 35, 37. Brand manufacturers that fail to do so face state-law failure-to-warn claims by their own customers. Opp.37. And under existing law, without innovator liability, GSK added a new adult suicidality warning in 2006, Opp.11-12, until FDA made GSK remove it.

Plaintiff argues that brand manufacturers can avoid any burdens "by simply warning." Opp.41. But innovator liability would encourage "overwarning," deluging FDA with labeling updates about speculative risks that would discourage the use of beneficial drugs. *Mason*, 596 F.3d at 392; PhRMA Br.15-17. And brand manufacturers pour resources into research and development on the settled understanding that they are responsible only for injuries caused by their own products. By tying brand manufacturers' exposure not to their own sales but to factors beyond their control, innovator liability would not only increase the financial risks of innovation, but make them more uncertain—and perhaps uninsurable.

Br.30; Chamber Br.21-25. Moreover, innovator liability could induce brand manufacturers to relinquish their NDAs on existing products and withdraw from the market entirely, depriving consumers of brand manufacturers' safety monitoring capabilities. PhRMA Br.17-19; Opp.6; Public Citizen Br.6-9, 15-16. The end result would be more speculative warnings, more demands on FDA, weakened safety monitoring, decreased investment in research, and less innovation.

Like *Smith* and its progeny, general Illinois negligence principles foreclose innovator liability. There is no need for certification to the Illinois Supreme Court, Opp.53, because there is"[n]o genuine uncertainty" about Illinois law. *In re Zimmer, NexGen Knee Implant Prod. Liab. Litig.*, 2018 WL 1193431, at *6 (7th Cir. Mar. 8, 2018).

B. Federal Law Preempts Innovator Liability

Plaintiff's theory independently fails because it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hillman v. Maretta*, 569 U.S. 483, 490 (2013) (quotation marks omitted); Br.30-36.

1. Plaintiff does not dispute that Hatch-Waxman embodies a balance between competing objectives. Br.32. She does not defend the district court's erroneous assertion that Hatch-Waxman's exclusivities "compensate[]" brand manufacturers for innovator liability. A11; Br.35. And she does not contest that those exclusivities aim to encourage innovation, or that innovator liability would dampen that incentive. Br.31-35. Because innovator liability would "second-guess" Congress's balance between innovation and competition, *Bonito Boats, Inc. v. Thunder Craft*

Boats, Inc., 489 U.S. 141, 152 (1989), and indeed would impose costs "large enough … to offset substantially the very benefits Congress intended to confer," *Xerox Corp. v. Cty. of Harris*, 459 U.S. 145, 153 (1982), plaintiff's theory is preempted.

Plaintiff responds that "the 'balance' brokered by [Hatch-Waxman]" involves only "the length of a brand name manufacturer's monopoly," not tort liability. Opp.51. But extended exclusivities were the means—the financial incentive—Congress chose to encourage innovation. Br.31-32. States may not interfere with that goal by imposing a massive financial *dis*incentive, no matter the form. *Xerox*, which plaintiff ignores, rejected the notion that states can avoid preemption based on *how* they interfere with federal law—there, by imposing a "property tax" instead of a sales or import tax. *Id.* at 148-49, 153. And although Hatch-Waxman does not cap prices, the statute preempted a D.C. price-capping law, because a price cap would "re-balance the statutory framework of rewards and incentives insofar as it relates to inventive new drugs." *Biotech. Indus. Org. v. District of Columbia*, 496 F.3d 1362, 1374 (Fed. Cir. 2007). Innovator liability would do the same. Br.33-35.

Plaintiff observes that brand manufacturers' state duties under innovator liability would parallel their existing federal duties. Opp.51. But Hatch-Waxman's legislative bargain involved innovation and generic entry, not the duty to update labeling, which predated Hatch-Waxman, 44 Fed. Reg. 37,434, 37,447 (1979). And *Mensing* never held that Hatch-Waxman makes brand manufacturers responsible for *generic* labeling. Opp.51. To the contrary, in passages plaintiff ignores, *Mensing* assumed that generic consumers have no tort remedy whatsoever. Br.35. Moreover,

obstacle preemption does not concern federal duties; it concerns whether state law impedes federal law's purposes and intended effects. Br.31-34. Innovator liability impedes both.

2. Preemption is all the more warranted because innovator liability hijacks one aspect of Hatch-Waxman to defeat the statute's carefully balanced scheme. Br.34-35. In *Buckman*, the Supreme Court held that federal law preempted a state-law "fraud-on-the-FDA" claim in part because the claim did not "rely[] on traditional state tort law which had predated the federal enactments in question," but instead "exist[ed] solely by virtue of [federal] … requirements." 531 U.S. at 353. Here too, federal law supplies "a critical element in [plaintiff's] case." *Id.*; Opp.39; Public Citizen Br.15-17; AARP Br.11-12. And like a "fraud-on-the-FDA" claim, innovator liability would commandeer one piece of an integrated federal scheme—here, generic manufacturers' duty of sameness—to create a new tort that perversely undermines the federal scheme's very purpose. 531 U.S. at 349-51. The fact that Hatch-Waxman "has *nothing* to do with tort liability," Opp.51, just reinforces that using it to underlie a novel, far-reaching state tort is incompatible with Congress's design.

3. This issue is not "waived." Opp.50. GSK argued below that innovator liability "[c]ontradict[s] the federal regulatory scheme governing prescription medications." R.79 at 2; *see id.* at 5; R.89 at 7-8. The district court rejected that argument. A5, A11, A14 n.8, A23. The court's conclusion was wrong, and this Court should not affirm without reviewing it.

In any event, federal law is inextricably intertwined with the interpretation of Illinois law. Plaintiff advocates filling a perceived gap in federal law by using one portion of an integrated federal scheme as the foundation for a novel state tort. This Court cannot intelligently evaluate plaintiff's theory without considering the balance struck by the federal scheme and whether innovator liability would disrupt it.

II. Plaintiff's Claim Is Preempted Because Federal Law Prohibited GSK from Providing Plaintiff's Requested Warning

Plaintiff's claim is separately preempted under *Wyeth v. Levine*, 555 U.S. 555 (2009), because it was impossible for GSK to "independently do under federal law what state law [purportedly] requires of it." *Mensing*, 564 U.S. at 620.

A. Preemption Is a Legal Question Reviewed De Novo

The "issue" of *Wyeth* preemption "is a legal one," *Mason*, 596 F.3d at 390, to be decided "by courts," *Guilbeau v. Pfizer Inc.*, 880 F.3d 304, 318 (7th Cir. 2018) (quotation marks omitted). This Court "review[s] a district court's federal preemption decision de novo." *Costello v. BeavEx, Inc.*, 810 F.3d 1045, 1050 (7th Cir. 2016).

1. Plaintiff never argues that *Wyeth* preemption is a question of fact. Presumably that is because she argued below that "preemption is a legal defense …, not something for the jury," R.584 at 41, and that GSK was "judicially estopped from being able to assert that it is a factual issue," Tr.4249:18-19. Instead, plaintiff argues that *if* this Court were to agree with *In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 852 F.3d 268 (3d Cir. 2017), that the "clear evidence" prong of

Wyeth preemption is a factual question, then GSK waived *Wyeth* preemption entirely. Opp.22-23. This argument fails on every level.

To start, as explained, this Court has held that *Wyeth* preemption is a legal question for the court. Even *Fosamax* recognized as much. 852 F.3d at 287 (discussing *Mason*). Fundamentally, moreover, *Wyeth* preemption concerns the compatibility of state and federal duties, and questions of duty are questions of law. *Swearingen v. Momentive Specialty Chems., Inc.*, 662 F.3d 969, 972 (7th Cir. 2011); *United States ex rel. Garbe v. Kmart Corp.*, 824 F.3d 632, 645 (7th Cir. 2016). And not even *Fosamax* suggested that the "newly acquired information" prong of *Wyeth* preemption is a jury question. 852 F.3d at 293. Regardless, if *either* prong of *Wyeth* preemption presents a factual question, no reasonable jury could have ruled against GSK. *Infra* p.14-21.

And GSK did not waive anything. Op.23. The district court proposed a jury instruction on the "clear evidence" prong of *Wyeth* preemption, and GSK objected. Tr.4250:11-22. The court barred GSK from attempting to alter the instruction, and instead omitted it. Tr.4246:16-4247:3, 4250:22. GSK raised *Wyeth* preemption in motions on summary judgment and during and after trial. Br.17. Nothing more was required. *Unitherm Food Sys., Inc. v. Swift-Eckrich, Inc.*, 546 U.S. 394, 400-01 (2006).

2. Plaintiff's argument that this Court should review only for clear error is equally meritless. The Supreme Court in *Wyeth* gave no deference to the ultimate preemption decision below. 555 U.S. at 568-73. And this Court "review[s] a district

court's federal preemption decision de novo." *Costello*, 810 F.3d at 1050. That makes sense. A court's ultimate preemption decision is a "legal conclusion[]" subject to "de novo review." *Grede v. FCStone, LLC*, 867 F.3d 767, 788 (7th Cir. 2017). Even to the extent *Wyeth* preemption presents a mixed question of fact and law, the issue generally involves documentary evidence that appellate and trial courts are equally well "positioned" to evaluate. *Salve Regina College v. Russell*, 499 U.S. 225, 233 (1991). *Wyeth* preemption also involves the Supremacy Clause, and this Court reviews mixed questions "concerning constitutional issues" de novo. *Isby v. Brown*, 856 F.3d 508, 521 (7th Cir. 2017).

If clear error review applied at all, it would apply only to the district court's findings of "historical fact," not its conclusions about the "legal effect" of those facts. *United States v. Newman*, 144 F.3d 531, 535 n.4 (7th Cir. 1998). Here, the relevant historical facts are documented in undisputed written correspondence. Br.7-11. And deferential review applies only to findings the district court "actually made." *Lovely v. United States*, 570 F.3d 778, 782 (6th Cir. 2009). The court below made only two relevant factual findings: FDA told GSK that it could request a meeting, and GSK did not do so. A28. Neither is disputed.

B. GSK Had No Basis for a Unilateral Labeling Change

Regardless of the standard of review, plaintiff's claim is preempted because after FDA in 2007 mandated class-wide SSRI labeling that omitted any Paxil-specific warning, GSK lacked the "newly acquired information" necessary to make a

unilateral labeling change under the CBE regulation. Br.36-38. Plaintiff buries her response, Opp.29-30, but this issue alone requires reversal.

1. Plaintiff asserts, without citation, that the *only* way for GSK to establish *Wyeth* preemption is to "show, with clear evidence, that the FDA would have rejected an adult suicidality warning in 2007." Opp.29. Not so; there are two ways. The "newly acquired information" and "clear evidence FDA would have rejected" inquiries are separate, independent forms of *Wyeth* preemption. Br.36-37. Showing either suffices. If "unilateral changes to [the drug]'s label were not possible, state-law claims alleging a failure to take that action are preempted." *Guilbeau*, 880 F.3d at 318. *Wyeth*'s "would have rejected" analysis comes into play only if the manufacturer could have changed its labeling unilaterally; if not, what FDA would have done after such a change is irrelevant.

Unilateral labeling changes are possible only through the CBE regulation. Br.36-37; Opp.5-6. Failure-to-warn claims accordingly are preempted whenever the "CBE process [i]s not open," *Mensing*, 564 U.S. at 614-15, including when the manufacturer lacks the "newly acquired information" the CBE regulation requires. Br.36-37.

Puzzlingly, plaintiff asserts that "GSK's actions *after* 2007 are not really at issue." Opp.29. But the critical facts here occurred in June 2010, when Sachman prescribed Dolin paroxetine. Earlier, in 2006, GSK provided an adult suicidality warning, but FDA made GSK remove it when FDA instituted the class-wide SSRI warning in August 2007. Br.8-11. Unless GSK could have made a unilateral

labeling change after August 2007 and before June 2010, plaintiff's claim is preempted. But if plaintiff wants to limit the inquiry to whether GSK had new information in 2007, that only makes the inquiry easier.

2. Either way, GSK could not have made a unilateral labeling change in 2007 or 2010, because GSK acquired no new information about adult suicidality after 2006. The only relevant analyses of placebo-controlled data were submitted to FDA or generated by FDA itself in 2006. Br.37-38. Because those analyses were "previously submitted to the Agency," 21 C.F.R. § 314.3(b), they did not authorize GSK to make a unilateral labeling change after 2006.

Plaintiff responds by pointing to a "reanalysis of [GSK] suicide data in 2008." Opp.29. Neither plaintiff nor the district court relied on this "reanalysis" below, and for good reason: It is not a new analysis, but a medical journal article that "presents the results" of GSK's *earlier* analysis submitted to FDA in 2006. R.590-10 at 2. Plaintiff's own expert acknowledged that the article was "submitted for publication in 2008 and published in 2011," but "was based on [GSK's] 2006 analysis." Tr.1624:10-12; *see* Tr.3274:7-17. Plaintiff references testimony about figures from the article, Opp.29; the 2006 analysis contains *identical* figures. *See* Tr.1229:23-1232:23, 1625:12-1627:20, 3229:25-3231:17 (discussing figures from table in article); *compare* R.590-10 at 7 (table from article) *with* R.589-21 at 92 (table from 2006 GSK analysis). Plaintiff observes that "newly acquired information" encompasses new analyses of old data. Opp.29. But it does not encompass *old* analyses of old data.

Plaintiff also provides a glancing citation—without any accompanying explanation—to testimony opining that GSK could have made a unilateral labeling change based on challenge/de-challenge/re-challenge reports and "information on what the mechanisms of action might be, particularly with regard to akathisia." Tr.1571:7-18; Opp.29 (citing Tr.1571:7). But plaintiff does not dispute that FDA wanted "information from placebo controlled trials only." R.589-14 at 50; Br.7, 37. Regardless, plaintiff identifies *no* scientific evidence, old or new, linking paroxetine-induced akathisia to suicide. Br.50. FDA has known of akathisia as a *potential* biological mechanism since at least 1992. R.308-13 at 92. And the challenge/de-challenge/re-challenge reports plaintiff cites were published in 1991 and involved *other* SSRIs, not paroxetine. Opp.57; R.590-2; Tr.317:8-16; Tr.316:10-17, 325:8-328:20; *see* Tr.2321:18-25.[1]

In short, the only "newly acquired information" plaintiff identifies indisputably was not "new." That ends this case. Absent "newly acquired information" authorizing a unilateral labeling change, it was impossible for GSK to "independently satisfy th[e] state duties" plaintiff seeks to enforce. *Mensing*, 564 U.S. at 624.

[1] GSK's opening brief mistakenly stated that one report involved paroxetine. Br.46. It did not. Tr.317:8-12; W. Creaney *et al.*, *Antidepressant Induced Suicidal Ideation*, 6 Human Psychopharmacology 329 (1991). The point is academic here, since regardless, the report is from 1991.

C. FDA Would Not Have Approved Plaintiff's Warning

Plaintiff's claim is independently preempted because there is "clear evidence" FDA "would not have approved" plaintiff's warning. *Wyeth*, 555 U.S. at 571. In 2007, FDA ordered GSK to *delete* an adult suicidality warning and rejected four GSK requests to retain it. This "smoking gun" denial establishes preemption under any standard of review. *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1103 n.11 (10th Cir. 2017); Br.38-42.

1. Plaintiff protests that the warnings GSK proposed to FDA "were insufficient." Opp.17. But according to plaintiff, what Illinois law requires, and what she told the jury the labeling lacked, is "a short plain statement that paroxetine ingestion is associated with suicidality in adults of all ages." Opp.24. GSK's 2006 labeling and 2007 proposals stated: "In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo …." R.589-27 at 2; R.589-4 at 12; R.589-32 at 17. FDA rejected exactly what plaintiff demands. Regardless, in plaintiff's view, GSK's proposals were insufficient because the next two sentences supposedly "suggest[ed] the risk of suicidality is limited to people under thirty." Opp.24. But FDA determined that no warning was warranted *past age 24*. Br.9-11. Even indulging plaintiff's notion that GSK's reference to "all ages" was inadequate, a "clearer" warning for adults of all ages would have been, if anything, *less* acceptable to FDA than a warning up to age 30.

Plaintiff also asserts that FDA "never considered" and "never *rejected*" GSK's proposals for a Paxil-specific warning. Opp.26. The record contradicts that assertion. To recap: FDA directed GSK to replace Paxil's warning for "adults with MDD (all ages)," R.589-27 at 2, with a class-wide warning stating that there was no increased risk "beyond age 24," R.589-23 at 2. FDA then again directed GSK to "replace the previous warning section with the new language [FDA] provided." R.589-25 at 1. FDA then revised the class-wide warning, retaining the statement that antidepressants pose no increased risk past age 24, but omitting GSK's proposed Paxil-specific warning. R.589-29 at 1. Finally, FDA stated that it "d[id] not believe that [GSK's] product specific analysis should be included in the class labeling revisions." R.589-30 at 1. FDA considered and rejected GSK's proposals.

Plaintiff's contrary argument distorts the record. Plaintiff's description of the interactions between FDA and GSK is notably devoid of quotations. Opp.25. The internal GSK periodical plaintiff references, Opp.26, concerns not the whole FDA-GSK interaction, but FDA's June 21, 2007 class-wide labeling revision, which did "not address[]"—*i.e.*, omitted—GSK's Paxil-specific warning, Tr.3382:16. And plaintiff mischaracterizes the testimony of GSK's witness, Opp.26, who stated unequivocally that FDA "did not accept" GSK's "Paxil-specific language," Tr.3375:23. Regardless, the actual communications between FDA and GSK are in the record, and they speak for themselves.

2. Plaintiff next contends that FDA only rejected "GSK's very narrow request, *i.e.*, to include the paroxetine-specific language in the middle of the class labeling."

Opp.27. That argument fails for four reasons. First, federal law required GSK to place the Paxil-specific warning within the class-wide labeling. The class-wide labeling covered the entire Warnings and Precautions section regarding suicidality, R.589-23 at 2-5; R.589-29 at 3-6; Tr.3375:19-22, and FDA regulations require that section to "describe clinically significant adverse reactions," 21 C.F.R. § 201.57(c)(6)(i); *see* Tr.3302:5-17. Separating the class-wide warning from the Paxil-specific warning, moreover, would have been misleading. 21 U.S.C. §§ 321(n), 331(a). Testimony from plaintiff's expert, Opp.27, cannot override federal law.

Second, neither GSK's requests nor FDA's rejections were framed narrowly. GSK proposed a place for the Paxil-specific warning, as any proposal must, but GSK told FDA it wanted "to maintain paroxetine specific language … in the label," R.589-32 at 1, because the Paxil-specific warning "would complement the class labeling" and "could help physicians," R.589-27 at 1; *accord* R.589-31 at 1. FDA's rejections made clear that the problem was not placement, but the fact that GSK's Paxil-specific warning was specific to Paxil. FDA insisted upon warnings "targeted at the class of drugs," R.589-30 at 2, because in FDA's view, "it [wa]s critical that the labeling [be] consistent for all [SSRIs]," R.589-29 at 2. GSK acquiesced because it "understood FDA's reasons for keeping the language generic to the class." R.589-31 at 1. If that were not FDA's rationale, the agency could have corrected GSK's understanding. It did not.

Third, it beggars belief that an expert public-health agency would reject repeated requests to warn about a serious risk the agency had extensively studied

solely because the warning would appear within class-wide labeling. Br.43. Plaintiff responds that "FDA was not on trial" and "sometimes make[s] mistakes." Opp.27-28. True, but irrelevant. The question is not whether FDA was right or wrong to reject GSK's proposals, but *what* FDA rejected—the kind of Paxil-specific warning plaintiff demands, or the placement of such a warning within the labeling. As explained, FDA rejected any Paxil-specific warning.

Fourth, placement within class-wide labeling is not a valid ground for rejecting an update. Br.44. And if FDA learns new information warranting an update, it must "notify" the manufacturer and "initiate discussions to reach agreement" on appropriate changes. 21 U.S.C. § 355(o)(4). FDA took no such action here. Plaintiff contests none of this. Br.44. Plaintiff thus does not dispute that her position effectively accuses FDA of not just regulatory malpractice, but knowing violations of federal law.

3. Plaintiff repeats the district court's rationale that FDA "invited GSK to discuss inserting into the label the language it claims the FDA would have rejected." Opp.28. But FDA's boilerplate invitation came on the heels of ordering GSK to delete an adult suicidality warning and rejecting *four* GSK proposals to keep it. Requesting a meeting to make the same request a fifth time while expecting a different result would have been the proverbial definition of insanity. And what if GSK took the meeting, and FDA rejected the warning again but told GSK, "our door is always open"? If common courtesy could defeat preemption, *Wyeth* preemption would be "all but meaningless." *Mensing*, 564 U.S. at 621.

Recognizing the futility of a meeting would not shift the burden of proof. Opp.30. GSK more than carried its burden by showing that FDA repeatedly rejected GSK's warning requests and ordered Paxil's labeling to state that studies do *not* show an increased suicidality risk past age 24. It is incumbent upon plaintiff to offer some reason—not mere "conjecture[]," *Mensing*, 564 U.S. at 621—that a meeting would have changed FDA's mind. Yet conjecture is all plaintiff provides.

Tucker v. SmithKline Beecham Corp., 596 F. Supp. 2d 1225 (S.D. Ind. 2008), did not reject "this *exact same* preemption challenge." Opp.27. The suicide there occurred in 2002, years before the critical FDA-GSK exchanges in 2007. 596 F. Supp. 2d at 1227, 1236. And *Tucker*, which pre-dated *Wyeth*, did not even analyze whether FDA would have approved a labeling change. Instead, *Tucker* held that "FDA's power to disapprove" a labeling change can *never* preempt state law. *Id.* at 1229. That is no longer good law—*Wyeth* holds that failure-to-warn claims are preempted if there is "clear evidence" FDA "would not have approved" the warning state law requires. 555 U.S. at 571. *Tucker* is thus irrelevant, factually and legally.

Forst v. SmithKline Beecham Corp., 639 F. Supp. 2d 948 (E.D. Wis. 2009); Opp.28, is equally irrelevant. The suicide attempt in *Forst* occurred in 2004—again, years before 2007. 639 F. Supp. 2d at 954. And while *Forst* asserted that FDA in 2007 "did not preclude Paxil-specific language changes" outside the class-wide warning, *id.*, it provided no reasoning to support that conclusion.

4. FDA's mandated class-wide suicidality warning for all SSRIs independently provides the "clear evidence" *Wyeth* requires. The class-wide warning

is unequivocal: "Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24." R.589-3 at 11. Plaintiff does not dispute that her claim is preempted if her warning conflicts with this class-wide warning. Br.41-42. Nor does plaintiff explain her assertion below that her warning and the class-wide warning are "in *direct* conflict." R.325 at 17; Br.42.

Instead, plaintiff asserts that there is no conflict because the class-wide warning "applies to antidepressants generally, not paroxetine specifically." Opp.31. That is nonsensical—plaintiff herself acknowledges that FDA "issued a class-wide warning for *all* antidepressant drugs," including Paxil. Opp.12 (emphasis added). Plaintiff asserts that the class-wide warning "is not accurate for paroxetine," Opp.12, but FDA decided otherwise when it ordered GSK to include the class-wide warning on *Paxil's* labeling. Br.10-11; PhRMA Br.21. Plaintiff's disagreement with FDA's judgment is no basis to avoid preemption.

III. Plaintiff Presented Insufficient Evidence of Causation and Duty

A. Plaintiff Presented Insufficient Evidence that Paroxetine Causes Suicide in Adults over Age 24

Fundamental methodological flaws render plaintiff's experts' testimony insufficient to support a verdict on causation. That is unsurprising—FDA prohibited GSK from giving plaintiff's warning precisely because the scientific evidence does not even show association, let alone causation. Br.50.

Plaintiff principally relies on two subgroup analyses conducted by GSK and FDA. Opp.55. But she does not dispute that subgroup analyses are "almost

guarantee[d] [to] yield 'significant' findings, even when there is no real effect." Br.48 (quoting Reference Manual on Scientific Evidence 256 (3d ed. 2011) (*Reference Manual*)). FDA discounted the significance of subgroup analyses in its comprehensive antidepressant study precisely because they are unreliable, R.589-14 at 23; Tr.2778:14-2779:23, as plaintiff's own expert acknowledged, Br.48. Nor does plaintiff dispute that the purported increase in GSK's analysis stemmed from unusually low suicidality in the placebo group, not increased suicidality among paroxetine users. Br.49.

Plaintiff also recites a laundry list of other types of evidence, but responds with silence to the authority showing that such evidence is scientifically and legally insufficient. She cites "uncontrolled paroxetine data" from the 1980s, Opp.56, but uncontrolled data are "not even sufficient to show association." Br.47 (quoting *Reference Manual* at 218). That her experts "discussed" "clinical observation, health[y] volunteer studies, and challenge, de-challenge, and re-challenge studies," Opp.55-56, is irrelevant. Such uncontrolled, anecdotal case reports are categorically insufficient to prove causation. Br.46-47. As for plaintiff's "peer-reviewed" articles "confirming [an] association," Opp.55-56, association is not causation. Br.45-46. One article expressed "uncertainty" even as to association, R.590-1 at 9, and the others used "unreliable" subgroup analyses, Tr.2885:25-2886:19.

That GSK's expert *conducted* one challenge/de-challenge/re-challenge study, Opp.57, does not mean that such studies establish causation. *Reference Manual* at 724. To show causation, case studies must be confirmed by "repeated, consistent,

statistically significant human epidemiological findings, and studies which address suspected confounders and biases." Br.45-46 (quoting *In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 176 F. Supp. 3d 483, 498 n.89 (E.D. Pa. 2016)). Moreover, the challenge/de-challenge/re-challenge studies plaintiff cites did not even concern paroxetine. *Supra* p.16.

Plaintiff further asserts that Dr. Healy identified "mechanisms" by which paroxetine might induce suicidal behavior—"akathisia, emotional blunting, and decompensation"—which he "observes in practice." Opp.56. But plaintiff does not dispute that "'none' of these 'possible mechanisms' have been 'scientifically confirmed.'" Br.50 (quoting Tr.1641:23-1642:15). "[R]aw speculation" about potential mechanisms based on anecdotal observations is not valid proof of causation. Br.50 (quoting *Sakaria v. Trans World Airlines*, 8 F.3d 164, 172-73 (4th Cir. 1993)).

B. Dr. Sachman's Actual Knowledge of Paroxetine's Purported Risk Precludes Liability

Dr. Sachman's testimony that he knew of paroxetine's purported risks precluded the jury from finding that GSK breached its duty to warn or that different labeling would have prevented Dolin's suicide. Br.51-56.

Plaintiff does not dispute that drug manufacturers have "no duty to warn of a risk that is already known by" prescribing physicians. Br.51. Nor does plaintiff dispute that such awareness breaks the "causal link between a patient's injury and the alleged failure to warn." Br.54. And plaintiff never actually asserts that Sachman was unaware of a purported risk of suicide in patients over age 24. Instead, plaintiff points to Sachman's testimony that, in his view, Paxil's 2010

labeling did not warn of that purported risk. Opp.58. That is irrelevant. "The only relevant issue is whether the prescribing physician was aware of the risks." Br.53 (quoting *Wooten v. Johnson & Johnson Prods., Inc.*, 635 F. Supp. 799, 803 (N.D. Ill. 1986)). Once the physician knows the risks—whether from the labeling or another source—he is a learned intermediary with the exclusive responsibility to balance those risks, provide appropriate warnings, and recommend appropriate treatment. The learned intermediary doctrine bars plaintiff from foisting the consequences of Sachman's informed, independent medical judgment onto GSK. Br.51.

Sachman knew of paroxetine's purported risks. Plaintiff does not dispute that Sachman reviewed the 2006 labeling, that the 2006 labeling included the information Sachman said he needed, or that Sachman was unaware until after Dolin's death that FDA had ordered the 2010 labeling to omit that information. Br.15, 52. And Sachman testified that he knew "to look out for akathisia … as *one of the possible or potential side effects of taking Paxil*, or paroxetine, and that [akathisia] *could be reflective of suicidal thoughts or behavior*." Tr.1751:13-17 (emphases added); Br.52. He also testified that "before [he] wrote [Dolin's] last prescription …, [he] recognized that the increased risk of suicidal thoughts or behavior was not limited to patients who were 24 or younger." Tr.1805:9-12; Br.52. Sachman even testified that he actually warned Dolin about "suicidal ideation" and "akathisia"—in 2005, when he first prescribed Dolin paroxetine, *and* in 2010, when he prescribed it again. Tr.1753:5-10; Br.52-53. The decision in *Forst v. SmithKline Beecham Corp.*, 602 F. Supp. 2d 960 (E.D. Wis. 2009); Opp.59-60, is thus inapposite.

The court there saw "no evidence that [the prescribing physician] knew that Paxil increased the risk of suicidality." 602 F. Supp. 2d at 968. That is not the case here.

Plaintiff misrepresents that Sachman's testimony concerned only "the risks associated with depression and anxiety" generally and "not the drug itself." Opp.59. Sachman testified that he knew of the "potential side effects *of taking Paxil*," which he understood to be associated with "suicidal thoughts or behavior." Tr.1751:13-17 (emphasis added). Plaintiff also asserts that, had the 2010 labeling adequately warned, Sachman never would have prescribed Dolin paroxetine. Opp.60. But, as explained, Sachman testified that when he prescribed Dolin paroxetine, he understood the risk at issue and warned Dolin about it. Sachman also testified that he "would not take a patient off a drug he was doing well on because of a label." Br.56 (quoting Tr.1770:12-19).

Plaintiff argues that Sachman's testimony is, "at worst," "inconsisten[t]" because he "testif[ied] at one point that he knew of the suicide risk and at another point that he did not." Opp.60. But Sachman never testified that he *did not know* of paroxetine's purported risks. In the snippets plaintiff cites, he testified that, in his view, those risks were not clear in the 2010 labeling, Tr.1681:19-1682:10; Tr.1683:25-1684:4, and that he would not have prescribed Dolin paroxetine had the labeling been clear, Tr.1847:3-9. Again, that is irrelevant. And no reasonable jury could understand Sachman's general statements about the labeling or his conclusory assertion of reliance to mean that he did not understand the risk—especially when Sachman testified that he *did* understand the risk, actually warned

Dolin, and would not have changed his prescribing decision regardless. As a matter of law, GSK had no further duty to warn, and its labeling did not cause Dolin's suicide.

CONCLUSION

The judgment below should be reversed.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

The foregoing brief complies with the type-volume limitation of Circuit Rule 32(c). The brief contains 6,999 words, excluding those parts of the brief exempted by Federal Rule of Appellate Procedure 32(f). This brief complies with the typeface and type-style requirements of Federal Rule of Appellate Procedure 32(a)(5)-(6) and Circuit Rule 32(b) because this brief has been prepared in a proportionately spaced typeface using Microsoft Word 2010 in New Century Schoolbook 12-point font.

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CERTIFICATE OF FILING AND SERVICE

Pursuant to Federal Rule of Appellate Procedure 25, I hereby certify that on March 14, 2018, I electronically filed the foregoing Brief of Appellant via ECF, and service was accomplished on counsel of record by that means.

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