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, Eastern Division, No. 1:12-cv-06403 (Hart, J.)

BRIEF OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF DEFENDANT-APPELLANT GLAXOSMITHKLINE LLC AND REVERSAL

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January 29, 2018

APPEARANCE & CIRCUIT RULE 26.1 DISCLOSURE STATEMENT

Appellate Court No: 17-3030

Short Caption: Dolin v. GlaxoSmithKline LLC

To enable the judges to determine whether recusal is necessary or appropriate, an attorney for a non-governmental party or amicus curiae, or a private attorney representing a government party, must furnish a disclosure statement providing the following information in compliance with Circuit Rule 26.1 and Fed. R. App. P. 26.1.

The Court prefers that the disclosure statement be filed immediately following docketing; but, the disclosure statement must be filed within 21 days of docketing or upon the filing of a motion, response, petition, or answer in this court, whichever occurs first. Attorneys are required to file an amended statement to reflect any material changes in the required information. The text of the statement must also be included in front of the table of contents of the party's main brief. **Counsel is required to complete the entire statement and to use N/A for any information that is not applicable if this form is used.**

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Pharmaceutical Research and Manufacturers of America

(2) The names of all law firms whose partners or associates have appeared for the party in the case (including proceedings in the district court or before an administrative agency) or are expected to appear for the party in this court:

Covington & Burling LLP

(3) If the party or amicus is a corporation:

i) Identify all its parent corporations, if any; and

None

ii) list any publicly held company that owns 10% or more of the party's or amicus' stock:

None

Attorney's Signature: s/ Michael X. Imbroscio Date: 1/29/2018

Attorney's Printed Name: Michael X. Imbroscio

Please indicate if you are *Counsel of Record* for the above listed parties pursuant to Circuit Rule 3(d). **Yes** X **No** ____

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Attorney's Signature: s/ Gregory L. Halperin Date: 1/29/2018

Attorney's Printed Name: Gregory L. Halperin

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Attorney's Signature: s/ Paul W. Schmidt Date: 1/29/2018

Attorney's Printed Name: Paul W. Schmidt

Please indicate if you are *Counsel of Record* for the above listed parties pursuant to Circuit Rule 3(d). **Yes** ____ **No** X

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STATEMENT OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association comprised of the leading biopharmaceutical research and technology companies.[1] PhRMA members are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members alone have invested more than half a trillion dollars in R&D since 2000, and in 2016, PhRMA members invested $65.5 billion in discovering and developing new medicines. PhRMA, *Biopharmaceuticals in Perspective: Spring 2017*, at 35 (2017), http://phrma-docs.phrma.org/files/dmfile/Biopharmaceuticals-in-Perspective-2017.pdf. PhRMA frequently files amicus briefs on issues that affect its members, and two issues presented in this case are especially crucial to them.

First, this case presents the question of whether the already substantial litigation risks that brand-name companies face are to be expanded to encompass the risks created by their generic competitors' products. Nearly every brand-name medicine eventually faces generic competition. Indeed, ninety percent of 2016 prescriptions were filled with generics. *Id.* at 49. Imposition of liability on innovator companies for the use of generic versions of their medicines would unfairly subject brand-name companies to unpredictable and potentially immense liability, stifling innovation and undermining public health.

Second, Ms. Dolin's verdict was premised on the failure of a pharmaceutical manufacturer to add a warning to a medicine's labeling that the Food and Drug Administration ("FDA") expressly rejected in response to a formal request for that change. Allowing for

[1] No party's counsel authored this brief in whole or in part. No party or party's counsel made a monetary contribution intended to fund the preparation or submission of this brief, and no person other than amicus curiae, its members, or its counsel made such a monetary contribution. Although GlaxoSmithKline LLC is a member of PhRMA, it has not contributed financially to the preparation of this brief.

liability in these circumstances not only runs counter to established Supreme Court precedent, but would also deprive pharmaceutical manufacturers of clear and fair liability standards that account for the rigorous federal regulatory scrutiny that all prescription medicines undergo.

SUMMARY OF ARGUMENT

The district court permitted Ms. Dolin to proceed on her state-law failure-to-warn claim against GlaxoSmithKline, even though her husband did not ingest its medicine, Paxil, and even though the Food and Drug Administration ("FDA") repeatedly rejected the warning she seeks. In so doing, the court undercut two bedrock principles of American jurisprudence: (1) defendants may be liable for injuries caused by their products, but not their competitors' products, and (2) defendants may not be liable under state law for the failure to do what federal law prohibits. The consequences of these rulings cannot be overstated.

First, subjecting companies who research and develop new medicines to liability for products they did not manufacture will both meaningfully disrupt the incentive structure that encourages companies to innovate and create a remarkable risk profile that will unfairly turn them into *de facto* insurers for their generic competitors' products. It will give innovator companies fewer incentives to research and develop new medicines and greater incentives to either prophylactically warn of every conceivable risk or withdraw their branded products from the market upon generic entry — all of which will harm public health.

Second, notwithstanding that FDA refused to add the warning sought by GlaxoSmithKline after conducting two decades of regulatory review and analysis of the suicide risk posed by antidepressants generally and Paxil specifically, the district court held that preemption still does not attach because the company did not seek a meeting to try to convince FDA to change its mind. Such a requirement would both afford insufficient deference to FDA's expert judgment and create perverse incentives for pharmaceutical manufacturers to overwhelm FDA with never-ending meetings and appeals whenever FDA duly rejects a labeling change.

ARGUMENT

I. Vastly Different Rules Apply to the Approval and Labeling of Brand-Name and Generic Medicines

For brand-name pharmaceutical companies, bringing a new medicine to market is an "onerous and lengthy" process. *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2471 (2013). Before studying a new medicine in humans, a company must conduct a series of laboratory and animal studies to test how the medicine works and assess its safety. 21 C.F.R. § 312.23(a)(8). If the results are promising, the company submits an Investigational New Drug application ("IND") to FDA, outlining the preclinical study results and offering a plan for clinical trials in humans. 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)-(b). Upon FDA approval of the IND, the company conducts three phases of clinical trials. 21 C.F.R. § 312.21. On average, the clinical trial phase takes six to seven years to complete. PhRMA, *Modernizing Drug Discovery, Development and Approval* 1 (2016), http://phrma-docs.phrma.org/sites/default/files/pdf/proactive-policy-drug-discovery.pdf. If clinical trial results show that the medicine's benefits outweigh its risks, the sponsoring company can seek FDA's approval to market the medicine by submitting a New Drug Application ("NDA"). 21 U.S.C. § 355(b).

Among other things, the NDA must contain proposed labeling for the new medicine. 21 U.S.C. § 355(b)(1). FDA also closely supervises medicine labeling during the approval process, and at all times thereafter, to ensure that "the public get[s] the accurate, science-based information they need[.]" Food & Drug Admin., *Statement of FDA Mission*, http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm298331.pdf. FDA regulations provide detailed labeling requirements, dictating mandatory categories, the precise content for those categories, and exact formatting standards. *See* 21 C.F.R. §§ 201.56, 201.57, 201.80.

FDA must approve labeling not only before a medicine can be marketed, but at all times thereafter. Before a manufacturer can amend its labeling, it generally must obtain FDA's approval through the submission of a "prior approval supplement" ("PAS") to its NDA. *See* 21 C.F.R. § 314.70(b)(2)(v). Manufacturers can, in some circumstances, add or strengthen a warning to reflect "newly acquired information." *See id.* § 314.70(c)(6)(iii)(A). Even then, however, a manufacturer cannot distribute the new labeling until it submits a "changes being effected" ("CBE") supplement to FDA. *See id.* § 314.70(c)(6). Unless FDA finds that the evidence "satisfies the standard for inclusion in the labeling," *id* § 314.70(c)(6)(iii)(A), it must retroactively reject the change and require the manufacturer to stop distributing products with the new labeling, *see id.* § 314.70(c)(7).

FDA's labeling responsibilities are not limited to reviewing changes that manufacturers propose. By law, FDA must ensure that labeling remains adequate at all times. Once it "becomes aware of new safety information" that it "believes should be included in the labeling," FDA must notify the manufacturer, which must either propose a change or explain why no change is warranted. *See* 21 U.S.C. § 355(o)(4)(A)-(C). New safety information often stems from FDA's continuous monitoring of adverse event reports and other research.[2]

Recognizing the central role that FDA plays in pharmaceutical labeling, the Supreme Court held in *Wyeth v. Levine*, 555 U.S. 555, 571–73 (2009), that a state-law failure-to-warn claim against a pharmaceutical manufacturer cannot proceed where there is "clear evidence" that FDA would not have approved the labeling that the plaintiff seeks. Specifically, the Court held that preemption is warranted where (1) a manufacturer "attempted to give the kind of warning"

[2] Manufacturers are required to report "serious and unexpected" adverse events to FDA within 15 days of receipt and to periodically report all other adverse events. 21 C.F.R. § 314.80. FDA also receives adverse event reports through a voluntary reporting system, MedWatch.

sought by a plaintiff but "was prohibited from doing so by the FDA," or (2) other evidence in the record demonstrates that "FDA would have prevented [the manufacturer] from adding a stronger warning" had it sought one. *Id.* at 572–73. Finding "no evidence in th[e] record that either the FDA or the manufacturer gave more than passing attention" to the warning at issue, the Court declined to find preemption in *Levine*. *Id.* at 572 (citation omitted).

The regulatory approval and labeling regime is fundamentally different for generic medicines. Under the Hatch-Waxman Amendments, a company may seek approval to market a generic medicine by filing an abbreviated new drug application ("ANDA") demonstrating that the generic version is biologically equivalent to an already-approved medicine. 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.92(a)(1). An ANDA applicant need not independently perform clinical studies to prove that the generic is safe and effective; instead, it can rely on "a prior agency finding of safety and effectiveness based on the evidence presented in [the] previously approved new drug application." 57 Fed. Reg. 17,950, 17,953 (Apr. 28, 1992). And because a generic medicine must contain "the same" active ingredient(s), delivered in "the same" dosage form, strength, and route of administration, in a formulation that is bioequivalent to an approved brand-name medicine, it must bear identical warnings. 21 U.S.C. § 355(j)(2)(A)(ii)-(v).

In *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 626 (2011), the Supreme Court held that the "federal statutes and regulations that apply to brand-name drug manufacturers are meaningfully different than those that apply to generic drug manufacturers," compelling "different pre-emption results." While preemption applies to brand-name manufacturers only where there is "clear evidence that the FDA would not have approved a change to [a medicine's] label," *Levine*, 555 U.S. at 571, failure-to-warn claims against generic manufacturers are generally preempted.

II. Innovator Pharmaceutical Companies Should Not Face Liability For the Use of Generic Medicines

Because *Mensing* bars her claim against the manufacturer of the medicine that her husband ingested, Ms. Dolin instead sought to impose a duty on GlaxoSmithKline, manufacturer of branded paroxetine, Paxil. In Illinois, "the existence of a duty turns in large part on public policy considerations." *Jones v. Chi. HMO Ltd. of Ill.*, 730 N.E.2d 1119, 1134 (Ill. 2000). Because shifting liability to innovator companies for injuries allegedly sustained by individuals who ingest generic manufacturers' products will chill innovation, impair the usefulness of pharmaceutical warnings, and unfairly expose innovators to limitless liability, Ms. Dolin's claim should be rejected as a matter of law.

A. Holding Innovators Liable for Generic Competitors' Products Will Harm Innovation

Innovator companies undertake the process of developing new medicines at tremendous expense. On average, developing and obtaining FDA approval of a new medicine takes ten to fifteen years and costs $2.6 billion. PhRMA, *Biopharmaceuticals in Perspective: Spring 2017*, at 29 (2017), http://phrma-docs.phrma.org/files/dmfile/Biopharmaceuticals-in-Perspective-2017.pdf (hereinafter, PhRMA, *Biopharmaceuticals in Perspective*); *see also* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20 (2016). Pharmaceutical companies spend even more money developing compounds that are never approved: just one out of every 5,000 to 10,000 compounds under development, and fewer than one out of every eight medicines entering clinical trials, obtains FDA approval. PhRMA, *Medicines in Development: Mental Illnesses* 26 (2012), http://phrma-docs.phrma.org/sites/default/files/pdf/phrmamedsindevmentalillness2012.pdf; PhRMA, *2016 Profile: Biopharmaceutical Research Industry*, at ii (2016), http://phrma.org/sites/default/files/pdf/biopharmaceutical-industry-profile.pdf (hereinafter PhRMA, *2016 Profile*); PhRMA,

Biopharmaceutical Research & Development: The Process Behind New Medicines 10 (2015), http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf; *see also* PhRMA & Battelle, *Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies* 12 (2015), http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf (reporting that in 2013, pharmaceutical companies sponsored an estimated 6,199 clinical trials involving 1.1 million participants). PhRMA's member companies invest approximately one quarter of their total annual domestic sales on research and development — an estimated $65.6 billion in 2016. PhRMA, *Biopharmaceuticals in Perspective*, *supra*, at 35; PhRMA, *2016 Profile*, *supra*, at 2.

These costs and risks do not end when the medicine makes it through the rigorous approval process. Once a new medicine is brought to market, the innovator company is required to monitor, review, and report to FDA all adverse events received from any source, "including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers." 21 C.F.R. § 314.80(b). *See also* Food & Drug Admin., *Reports Received and Reports Entered into FAERS by Year* (2015), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm (stating that FDA received over 1.2 million adverse event reports from pharmaceutical companies in 2014). Innovator companies must also submit to FDA annual reports summarizing all information received about their medicines, including adverse drug events and clinical trial results. 21 C.F.R. §§ 314.80-314.81.

Apart from adverse event reporting, FDA frequently requires innovator companies to undertake additional clinical studies after approval. *See* 21 U.S.C. § 355(o)(3). According to

one estimate, more than three quarters of all new medicine approvals are accompanied by a commitment by the sponsor to conduct one or more post-marketing, or "Phase IV," studies. Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 Food & Drug L.J. 295, 300 (2006). PhRMA's member companies spend more than $8.8 billion annually conducting these Phase IV studies. PhRMA, *Annual Membership Survey* 6 tbl.4 (2016), http://phrma-docs.phrma.org/sites/default/files/pdf/annual-membership-survey-results.pdf.

Given the enormous costs associated with researching and developing a new medicine, the added potential cost of litigation bears heavily on a company's decision to invest in innovation. *See Smith v. Eli Lilly & Co.*, 560 N.E.2d 324, 342 (Ill. 1990) (rejecting market-share liability for pharmaceuticals because "th[e] added potential for liability will likely contribute to diminishing participants in the market as well as research and availability of drugs"); W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418, 1419 (1994) ("[T]he net effect of the surge in liability costs ha[s] been to discourage innovation in the pharmaceutical industry."); Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L. Rev. 1139, 1153 (1987) ("If in the aggregate the net gains are wiped out by the liability costs, then the product will no longer be made.").[3]

[3] The scope of litigation against pharmaceutical companies is already immense and rapidly expanding. In 2016 alone, 21,517 product liability lawsuits were filed against pharmaceutical companies in federal courts alone, up from 6,791 lawsuits just five years earlier and just 2,700 lawsuits in 2001. *See* Admin. Office of the U.S. Courts, *Table C-2A: U.S. District Courts--Civil Cases Commenced, by Nature of Suit, During the 12-Month Periods Ending September 30, 2012 Through 2016*, http://www.uscourts.gov/sites/default/files/data_tables/jb_c2a_0930.2016.pdf; Lisa Girion, *State Vioxx Trial Is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1. Today, out of seventy pending product liability multidistrict litigation proceedings, twenty-eight involve pharmaceuticals. *See* U.S. Judicial Panel on Multidistrict Litig., MDL Statistics Report - Distribution of Pending MDL Dockets by District (Jan. 16, 2018), http://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_District-January-16-2018.pdf. By comparison, between 1960 and 1999, there were only six MDL product liability actions involving

The anti-nausea drug Bendectin, the only FDA-approved prescription medicine for the treatment of severe morning sickness in pregnant women, illustrates how. After Bendectin was alleged to cause of birth defects in thousands of lawsuits, its manufacturer withdrew the medicine from the market in 1983, only later to be vindicated by scientific studies showing that Bendectin posed no risks to either mothers or fetuses. *See* Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 Stan. L. Rev. 1, 7 (1993). *See also* Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262, S262–63 (2002); *see also* David E. Bernstein, *The Breast Implant Fiasco*, 87 Cal. L. Rev. 457, 460 (1999); Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. Rev. 371, 392 (2002). In 2013, after nearly thirty years off the market, Bendectin returned under a new name. *See* News Release, Food & Drug Admin., *FDA Approves Diclegis for Pregnant Women Experiencing Nausea and Vomiting* (Apr. 8, 2013). In the interim, however, hospital admissions for excessive vomiting during pregnancy had doubled, costing the U.S. economy $1.7 billion annually in time lost from work, caregiver time, and hospital expenses. *See* Nina Nuangchamnong & Jennifer Niebyl, *Doxylamine Succinate–Pyridoxine Hydrochloride (Diclegis) for the Management of Nausea and Vomiting in Pregnancy: An Overview*, 6 Int'l J. Women's Health 401, 401–02 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3990370/pdf/ijwh-6-401.pdf.

Similarly, by 1990, eight of the nine major U.S. pharmaceutical companies that had been involved in researching and developing new contraceptives had abandoned their efforts. Nat'l

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FDA-approved medicines. *See* Deborah R. Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883, 897–903 tbl.1 (2007).

Research Council & Inst. of Med., Comm. on Contraceptive Dev., *Developing New Contraceptives: Obstacles and Opportunities* 59 (Luigi Mastroianni, Jr., et al. eds., 1990), https://www.nap.edu/read/1450. According to the National Research Council and the Institute of Medicine, "recent products liability litigation and the impact of that litigation on the cost and availability of liability insurance have contributed significantly to the climate of disincentives for the development of contraceptive products." *Id.* at 141. In 1989, the inventor of the birth control pill, Carl Djerassi, recommended changes to the product liability regime, commenting that "the United States is the only country other than Iran in which the birth-control clock has been set backward during the past decade." Carl Djerassi, *The Future of Birth Control*, Wash. Post (Sept. 10, 1989), https://www.washingtonpost.com/archive/opinions/1989/09/10/the-future-of-birth-control/7e25f2cc-ae35-4a79-8daf-031db02f81be/?utm_term=dd4d8bbcf626. The executive director of the Society for the Advancement of Women's Health Research similarly testified before Congress that "the current liability climate is preventing women from receiving the full benefits that science and medicine can provide." S. Rep. No. 104-69, at 7 (1995).

The country's experience with vaccines is also illustrative. Lawsuits in the late 1970s alleging that the whooping-cough component of the DPT vaccine caused permanent brain damage led nearly all of its manufacturers to cease production, resulting in nationwide shortages. *See* Linda A. Willett, *Litigation as an Alternative to Regulation: Problems Created by Follow-on Lawsuits with Multiple Outcomes*, 18 Geo. J. Legal Ethics 1477, 1488 n.60 (2005). Although the allegation that the DPT vaccine causes neurological harm was subsequently "discredited," Stephen D. Sugarman, *Cases in Vaccine Court – Legal Battles Over Vaccines and Autism*, 357 N. Eng. J. Med. 1275, 1276 (2007), by 1986, there was only one American manufacturer of the polio vaccine, one manufacturer of the measles, mumps, and rubella vaccine, and two

manufacturers of the DPT vaccine, H.R. Rep. No. 99-908, at 7 (1986), *reprinted in* 1986 U.S.C.C.A.N. 6344. Congress, realizing the "inadequacy — from both the perspective of vaccine-injured persons as well as vaccine manufacturers — of the current approach to compensating those who have been damaged by a vaccine," *id.*, passed the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3743, which removed many personal-injury cases involving vaccines from the state-law tort system. Congress hoped that once "manufacturers ha[d] a better sense of their potential litigation obligations, a more stable childhood vaccine market w[ould] evolve." H.R. Rep. No. 99-908, at 7. And, in fact, the Act appears to have "succeeded in stabilizing prices and stemming further exit from the market" for listed vaccines. Noah, *supra*, at 393.

In short, the past 40 years have repeatedly demonstrated that dramatic increases in potential liability — particularly unpredictable, long-enduring liability — can drive biopharmaceutical companies to abandon the research and production of medicines. The unpredictable liability that would follow from innovator liability is worse by an order of magnitude: all the examples discussed above took place in a legal landscape where companies were potentially liable for injuries to plaintiffs who used medicines that they themselves manufactured. If allowed to stand, the district court's holding will subject innovator companies to decades of potential liability for products manufactured by their competitors, years after revenue trails off. And because so much of the harm from litigation arises from the costs and burdens of being forced to defend mass lawsuits, harm would accrue even when an innovator company ultimately establishes — by post-discovery motions practice, at trial, or on appeal — that it acted reasonably.

A tort regime that discourages innovator companies from making future investments in the research and development of new medicines directly undermines Hatch-Waxman's "careful balance" of the interest in lower-cost medicines against the need to "encourag[e] research and innovation." 57 Fed. Reg. at 17,951; *see also* H.R. Rep. No. 98-857, at 15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647 ("The purpose of Title II of the bill is to create a new incentive for increased expenditures for research and development . . . .").[4] It also has profound consequences for public health.[5] The biopharmaceutical industry provides the majority of funding to discover, develop, and manufacture transformative medicines. PhRMA, *Biopharmaceuticals in Perspective*, *supra*, at 30. Its investments have produced dozens of major scientific

[4] For this reason, as explained in GlaxoSmithKline's opening brief, innovator liability should be preempted. *See Biotechnology Indus. Org. v. District of Columbia*, 496 F.3d 1362, 1374 (Fed. Cir. 2007) (holding that Hatch-Waxman preempted a law capping prices for patented medicines, because "[t]he underlying determination about the proper balance between innovators' profit and consumer access to medication . . . is exclusively one for Congress to make").

[5] *Accord In re Darvocet, Darvon, & Propoxyphene Prod. Liab. Litig.*, 756 F.3d 917, 944 (6th Cir. 2014) ("[T]here are grave health policy consequences associated with recognizing brand manufacturer liability in these situations including higher priced brand name drugs and fewer innovative drugs"); *Huck v. Wyeth, Inc.*, 850 N.W.2d 353, 377 (Iowa 2014) (plurality opinion) ("[E]xtending liability to brand manufacturers for harm caused by generic competitors would discourage investments necessary to develop new, beneficial drugs by increasing the downside risks."); *Rossi v. Hoffmann-LaRoche*, No. ATL-L690-05, 2007 WL 7632318 (N.J. Super Ct. Law Div. Jan. 3, 2007) (innovator liability "could only act to stigmatize the ability of companies to develop new and innovative drugs"); *Sloan v. Wyeth*, No. MRS-L-1183-04, 2004 WL 5767103 (N.J. Super Ct. Law Div. Oct. 13, 2004) ("Brand name manufacturers would be less likely to develop new products if [innovator] liability were imposed . . . ."); Anna B. Laakmann, *The Hatch-Waxman Act's Side Effects: Precautions for Biosimilars*, 47 Loyola L.A. L. Rev. 917, 926 (2014) (innovator liability "could further dampen the incentives to create new drugs and thus reduce overall patient welfare"); Lars Noah, *Adding Insult to Injury: Paying for Harms Caused by a Competitor's Copycat Product*, 45 Tort Trial & Ins. Prac. L.J. 673, 688–89 n.69 (2010) (innovator liability "threatens to chill therapeutic product innovation"); Victor E. Schwartz et al., *Warning: Shifting Liability to Manufacturers of Brand-Name Medicines When the Harm Was Allegedly Caused by Generic Drugs Has Severe Side Effects*, 81 Fordham L. Rev. 1835, 1871 (2013) (innovator liability makes it "riskier for brand-name manufacturers to dedicate resources to researching and developing potentially life-saving or life-improving medicines"); Samantha Koopman, *Hidden Risks of Taking Generic Drugs over Brand Name: The Impact of Drug Labeling Regulations on Injured Consumers and the Pharmaceutical Industry*, 34 J. Nat'l Ass'n Admin. L. Judiciary 112, 140 (2014) ("Overall, innovator liability likely results in less new drug development.").

breakthroughs. For example, over the past two decades, innovative diagnostic techniques and treatments have reduced the death rate from cancer by twenty-five percent. *See id.* at 11. Innovations have reduced the death rate from heart disease by thirty-five percent since 2000. *See id.* at 14. And innovative treatments for HIV/AIDS have contributed to a nearly eighty-seven percent decline in death rates since the mid-1990s, preventing over 862,000 premature deaths. *See id.* at 9. Without ongoing investments from pharmaceutical companies in research and development, none of these advances would have been possible.[6]

B. Holding Innovator Companies Liable for Injuries Allegedly Sustained from Their Generic Competitors' Products Could Impair the Usefulness of Pharmaceutical Labeling and Harm Public Health

Innovator liability places brand-name companies in an untenable position: although they capture just a tiny fraction of sales upon generic entry, they would become the sole guarantors for the entire market. *See* Henry G. Grabowski et al., *Updated Trends in US Brand-Name and Generic Drug Competition*, 19 J. Med. Econ. 836 (2016) (reporting that for brand medicines facing generic entry in 2013-2014, generics captured an average of 93 percent of the market by volume within the first year). Faced with the prospect of dwindling market share and unending lawsuits, innovators may opt to warn of every conceivable risk or withdraw their branded products from the market upon generic entry. The former could erode the meaningfulness of scientifically-justified warnings and deter beneficial uses of medications. And because innovator companies have more significant regulatory responsibilities, greater access to clinical and post-

[6] Advances in medicine not only save lives, but also benefit the economy. According to one estimate, the development of a new medicine that could delay the onset of Alzheimer's disease by just five years would save the U.S. economy over $376 billion. *See* PhRMA, *Prescription Medicines: International Costs in Context* 18 (2017), http://www.phrma.org/report/prescription-medicines-international-costs-in-context.

marketing data, and more experience in monitoring the safety of their medicines, the latter would substantially impair public health.[7]

1. *Innovator Liability Could Encourage Companies to Warn of Speculative and Hypothetical Risks*

Because liability in pharmaceutical cases usually hinges on whether a company adequately warned of potential risks, companies looking ahead to the generic phase of a medicine's lifespan may "pile on warnings for every conceivable adverse reaction, no matter how remote the odds," in order to protect themselves "from the 20/20 hindsight of juries." Frank Scaglione, Comment, *Resolving Drug Manufacturer Liability for Generic Drug Warning Label Defects*, 47 St. Mary's L.J. 219, 238 (2015). Overwarning harms consumers in two ways.

First, consumers and physicians may disregard lengthy labeling that is filled with speculative warnings, thereby overlooking important, scientifically-founded safety information. *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); H.R. Rep. No. 86-1861, at 2837 (1960), *reprinted in* 1960 U.S.C.C.A.N. 2833 (speculative warnings "invit[e] indifference to cautionary statements"); 73 Fed. Reg. 49603, 49605–06 (Aug. 22, 2008) (unfounded statements in FDA labeling may cause "more important warnings" to be "overshadow[ed]"). Warnings on pharmaceutical labeling are already extensive. The average package insert today lists 70 potential adverse events, and one out of every ten labels contains over 150 warnings. Jon Duke et al., *A Quantitative Analysis of Adverse Events*

[7] The California Supreme Court recently dismissed concerns about the public health consequences of sweeping innovator liability standards by noting the paucity of data proving that those consequences will accrue. *T.H. v. Novartis Pharms. Corp.*, 407 P.3d 18, 33 (Cal. 2017). That argument is nothing more than a truism: because virtually every court has rejected innovator liability, real-world data on the consequences of a non-existent regime cannot be generated.

and "Overwarning" in Drug Labeling, 171 Archives Internal Med. 944, 945 (2011), http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/487051.

Second, warnings that are not grounded in science discourage the beneficial use of medicines. *See Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391–92 (7th Cir. 2010) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted . . . ."). *See also* 73 Fed. Reg. at 49605–06 ("[O]verwarning . . . may deter appropriate use of medical products . . . ."). All medicines have risks, and all prescribing decisions are based on a balancing of those risks against the medicine's potential benefits. Overstating risk thus keeps physicians from making optimal prescribing decisions.

FDA has long been aware of the dangers that overwarning presents. The agency has long held the view that "it would be inappropriate to require statements in drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation." 44 Fed. Reg. 37,434, 37,435 (June 26, 1979); *see also* 150 Cong. Rec. 17,045 (2004) (letter from former FDA Chief Counsels) ("If every state judge and jury could fashion their own labeling requirements for drugs and medical devices, . . . FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded."). Because innovator liability could produce the very result that FDA considers in its expert scientific judgment to be "inappropriate," the concept should be rejected.

Nor is innovator liability necessary to adequately incentivize innovators to maintain adequate warnings once their market share dwindles. At all times, pharmaceutical labeling must warn of all "clinically significant hazard[s]" for which there is "reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6)(i). If a company learns of new evidence that meets this standard at any time after approval of its NDA, it must submit a supplement to modify the

labeling. *Id.* § 314.70(b)(2)(v), (c)(6). A medicine that bears labeling that fails to warn of risks for which there is reasonable evidence of a causal association is "misbranded." *See* 21 U.S.C. § 352(a)(1). Pharmaceutical companies have ample incentives to comply with these labeling obligations, because the consequences for misbranding include an injunction against the medicine's distribution, *id.* § 332, criminal penalties, *id.* § 333,[8] and serious reputational harm that can negatively affect a company's entire portfolio of medicines. More fundamentally, innovators who market their branded products face the same risk of civil product liability suits by patients who continue to use their branded medicine.

2. *Innovator Liability Could Negatively Affect Safety Monitoring*

Faced with the prospect of massive liability that bears no relationship to its products, sales, or revenue, an innovator company may alternatively be pressured to cease selling the branded drug, withdraw from the market, and relinquish its NDA. *See* 21 C.F.R. § 314.150(c) (requiring FDA to withdraw approval of NDA "if the applicant requests its withdrawal because the drug subject to the application . . . is no longer being marketed"). By relinquishing their NDAs and leaving the market, companies could stem the risk of unending liability because they

[8] Penalties for misbranding have reached into the billions. *See* Press Release, U.S. Dep't of Justice, *Justice Department Announces Largest Health Care Fraud Settlement in Its History* (Sept. 2, 2009), https://www.justice.gov/opa/pr/justice-department-announces-largest-health-care-fraud-settlement-its-history ($2.3 billion); Press Release, U.S. Dep't of Justice, *Johnson & Johnson to Pay More Than $2.2 Billion to Resolve Criminal and Civil Investigations* (Nov. 4, 2013), https://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations; Press Release, U.S. Dep't of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigations of Off-label Promotion of Depakote* (May 7, 2012), https://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote; Press Release, U.S. Dep't of Justice, *Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa* (Jan. 15, 2009), https://www.justice.gov/opa/pr/eli-lilly-and-company-agrees-pay-1415-billion-resolve-allegations-label-promotion-zyprexa; Press Release, U.S. Dep't of Justice, *U.S. Pharmaceutical Company Merck Sharp & Dohme to Pay Nearly One Billion Dollars Over Promotion of Vioxx®* (Nov. 22, 2011), https://www.justice.gov/opa/pr/us-pharmaceutical-company-merck-sharp-dohme-pay-nearly-one-billion-dollars-over-promotion.

would no longer have the ability to effect a labeling change. *See Mensing*, 564 U.S. at 620 (holding that failure-to-warn claims are preempted when manufacturers cannot "independently do under federal law what state law requires"); *see also Lyman v. Pfizer, Inc.*, No. 2:09-CV-262, 2012 WL 2970627, at *16 (D. Vt. July 20, 2012) (recognizing that upon sale of medicine at issue, former manufacturer "lost any ability to change the . . . label"); *In re Darvocet, Darvon and Propoxyphene Prods. Liab. Litig.*, No. 2:11-md-2226, 2012 WL 767595, *7 (E.D. Ky. Mar. 7, 2012).[9]

The monitoring and evaluation of a medicine's risks in the post-market environment is crucial to public health. *See* Food & Drug Admin., *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* 3 (2005), https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071696 ("[P]ostmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization."). Despite the intensive scientific testing and analysis required before FDA authorizes a medicine for sale, these pre-market studies are by their nature limited to a finite pool of patients. As a result, some risks are not discovered until after the medicine is on the market and used in sufficiently large numbers. But if innovators were driven from the market to avoid the kind of perpetual liability that innovator liability would entail, safety surveillance, and consequently the public health, would suffer.

[9] The only way for a company to change a medicine's labeling is by submitting a PAS or CBE supplement to its NDA. 21 C.F.R. § 314.70(b)(2)(v), (c)(6). Since only the NDA holder may "submit a supplement to an application," a former manufacturer has no control over a product's labeling after it has left the market. *Id.* § 314.71(a).

First, innovators have unparalleled experience and expertise on their medicine due to their extensive efforts studying and bringing the medicine to market. This expertise includes a deep understanding of both the mechanism of the medicine and the data from the many clinical trials that allow the company to better understand post-marketing reports and to identify trends or new subtle safety signals that might not otherwise be apparent. Indeed, innovators have on average some 12.5 additional years' experience monitoring a medicine's safety in the marketplace. *See* PhRMA, *Prescription Medicines: International Costs in Context*, *supra* note 6, at 39.

Second, while innovator companies have created elaborate systems to fulfill their post-marketing surveillance obligations — including hundreds of employees worldwide whose sole purpose is to monitor safety — generic manufacturers have far more limited post-marketing obligations, and thus devote comparatively few resources to monitoring trends and conducting other post-marketing safety surveillance activities.

If it becomes the norm that innovators routinely exit the market after generic entry, a regulatory vacuum will exist that will meaningfully diminish the level of safety monitoring of generic medicines, and this void would meaningfully impact public health. *Accord* Schwartz 2013, *supra* note 5, at 1870–71 ("Should the brand-name manufacturer prematurely withdraw from the market over liability, consumers will have lost the company most familiar with a medicine and the one that likely has the greatest infrastructure and resources to facilitate postmarket research and analysis into any late developing safety issues with a drug.").

C. Innovator Liability is Fundamentally Unfair

Under the Hatch-Waxman Act's streamlined procedures for generic entry, researching and developing a generic version of an FDA-approved medicine costs under $2 million — less than one-tenth of one percent of the cost of developing the innovative medicine itself. U.S.

Dep't of Health and Human Servs., *Expanding the Use of Generic Drugs* 4–5 (2010), https://aspe.hhs.gov/system/files/pdf/76151/ib.pdf; PhRMA, *Biopharmaceuticals in Perspective*, *supra*, at 29. Generic manufacturers pass these cost savings onto consumers. Having paid nearly all the costs associated with researching and developing a new medicine, only to lose a substantial proportion of their market share to generic manufacturers upon generic entry, innovator companies would nevertheless have to pay for the harm allegedly caused by their generic competitors' products. Yet "manufacturers are not insurers of their industry." *Smith*, 560 N.E.2d at 344.

This case starkly illustrates the unfairness of holding innovators liable for products that their competitors control, produce, and profit from. FDA first approved a generic version of Paxil in June 2003. Within sixteen months, Paxil sales had dropped by 85%. Ernst R. Berndt et al., *Authorized Generic Drugs, Price Competition, and Consumers' Welfare*, 26 Health Affairs 790, 796 (2007), https://www.healthaffairs.org/doi/full/10.1377/hlthaff.26.3.790. Ms. Dolin's husband was last prescribed generic paroxetine in June 2010, and she did not sue until July 2012, by which time GlaxoSmithKline's revenue from brand-name Paxil was negligible. GlaxoSmithKline is thus being subjected to potential liability for a competitor's product, even when that product was manufactured well after its market share (and corresponding revenue) dropped precipitously.

III. The District Court's Interpretation of the Clear Evidence Standard Would Vitiate the Central Holding of *Wyeth v. Levine* and Hamstring FDA's Regulatory Role

A. FDA's Implementation of Class-Wide Labeling on Suicidality Risk Indicates Careful Attention that Merits Particular Deference

It is hard to imagine clearer evidence that FDA would not have approved the warning a plaintiff seeks than where, as here, FDA repeatedly rejected the exact warning sought. On April 27, 2006, GlaxoSmithKline updated its Paxil labeling via a CBE supplement to provide Paxil-

specific data about its potential suicide risk in adults. R.589-22 at 1. One year later, FDA informed GlaxoSmithKline that it would "need to make revisions to [the Paxil] labeling, as outlined below, so as to ensure standardized labeling pertaining to adult suicidality with all of the drugs to treat major depressive disorder." R.589-23 at 1. GlaxoSmithKline not only wrote to FDA on three separate occasions to request permission to keep the Paxil-specific data, R.589-25 at 1; R.589-26 at 1; R.589-30 at 1, but also implemented a second labeling change via a CBE supplement that complemented the standardized language with Paxil-specific data that FDA had already rejected, R.589-32 at 2. Unsurprisingly, GlaxoSmithKline's efforts were met with the same response: "[W]e do not believe that your product specific analysis should be included in class labeling revisions since the labeling is targeted at the class of drugs." R.589-30 at 1.[10]

FDA's focus on class-wide labeling only strengthens the case for preemption. Although brand-name manufacturers conduct extensive post-marketing surveillance, the data they collect is inherently siloed to their own medicine. FDA, by contrast, collects data from the entire industry and is therefore able to take a broader view of the science. Class labeling thus reflects FDA's review and analysis of the full data to "describe a risk or effect that is typically associated with members of the class, based on what is known about the pharmacology or chemistry of the drugs" as a whole. Food & Drug Admin., *Guidance for Industry: Labeling for Human Prescription Drug & Biological Products — Implementing the PLR Content and Format Requirements* 21 (2013), https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm075082.pdf.

[10] Nor was 2007 the first time FDA had considered the potential link between SSRIs and suicide. Over the prior two decades, FDA had, among other things, independently analyzed data provided by GlaxoSmithKline and other SSRI manufacturers, rejected three Citizen Petitions seeking action on the alleged suicide risk of antidepressants, and convened independent Advisory Committees to assist in its review of antidepressant safety on at least six different occasions.

FDA's class-wide vantage point on the science concerning a group of related medications is one a jury does not and cannot have. State law failure-to-warn actions necessarily involve a particular plaintiff's ingestion of a particular medicine, making it nearly impossible to account for the need for consistency of warnings across drugs in the same class, a goal FDA pursued here, and one it regularly pursues when multiple medicines share the same potential risk. State law actions, such as this one, thus stand in opposition to FDA's stated goal of ensuring that all modern antidepressants contain a consistent message that conveyed FDA's best understanding and scientific judgment regarding the relationship between suicidality and antidepressants. This conflict between a clearly-expressed federal desire for class-wide labeling and a state-law claim calling for piecemeal labeling reinforces the conclusion that there is ample "clear evidence" to meet the strictures of *Levine* that FDA would not permit the kind of warning upon which Ms. Dolin rested her claims.

B. The Decision Below Incentivizes Manufacturers to Overwhelm FDA's Review Capabilities

Despite FDA's repeated rejection of the warning Ms. Dolin seeks, the district court declined to find preemption because GlaxoSmithKline could have "asked for a formal meeting." *Dolin v. SmithKline Beecham Corp.*, No. 12 C 6403, 2016 WL 537949, at *1 (N.D. Ill. Feb. 11, 2016). The district court's holding has no logical conclusion. Plaintiff lawyers can always dream up some hypothetical further action that the manufacturer could have taken that might have changed FDA's mind, particularly given that FDA rarely takes the time to memorialize the full scientific rationale for its labeling decisions. Under the decision below, federal preemption now hinges on a judge's *post hoc* conjecture regarding how FDA might have hypothetically responded to those additional efforts by the company to convince FDA it was wrong.

Setting aside that judges lack such prophetic powers, the district court's holding threatens to overwhelm FDA's resources. The implication of the district court's directive for the pharmaceutical industry is clear: No matter how many times FDA rejects a request to change labeling, companies must request additional meetings, submit another CBE, or take other actions designed solely to create a litigation record. If followed, this directive would divert FDA's resources away from the study of new potential safety issues in favor of defending decisions it has already made. *Levine* does not require such a nonsensical result. *Accord Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1279 (W.D. Okla. 2011) ("[T]his court does not interpret *Levine* as imposing upon the drug manufacturer a duty to continually 'press' an enhanced warning which has been rejected by the FDA."). Indeed, it makes no sense to craft a rule that encourages companies to submit additional labeling changes that the FDA by law cannot grant. *See* 21 C.F.R. § 317.70(c)(6)(iii) (allowing manufacturers to make labeling changes through the CBE process only "to reflect newly acquired information"); *id.* at § 314.3 ("Newly acquired information is data, analyses, or other information *not previously submitted to the Agency* . . . ." (emphasis added)); *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41–43 (1st Cir. 2015) (finding CBE process unavailable to manufacturer, and therefore granting preemption, where plaintiffs relied solely on data available to FDA at time of label approval).

In *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), the Supreme Court held that state-law "fraud-on-the-FDA" claims are preempted. The Court reasoned that such claims incentivize manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" out of "fear that their disclosures . . . will later be judged insufficient in state court," thereby creating "additional burdens on the FDA[]." *Id.* at 351. Requiring companies to

request a formal meeting after every FDA rejection of a proposed labeling change would produce the same result *Buckman* found impermissible.

CONCLUSION

For the foregoing reasons, the Court should reverse the district court, reject innovator liability, and hold that Ms. Dolin's claims are preempted.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitations of Cir. R. 29 because it contains 6,891 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f). This brief complies with the typeface and type style requirements of Cir. R. 32(b) because it has been prepared in a proportionally spaced typeface using Microsoft Word 2016 in Times New Roman 12-point font.

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CERTIFICATE OF FILING AND SERVICE

I hereby certify that on January 29, 2018, I caused the foregoing Brief to be electronically filed with the Clerk of the United States Court of Appeals for the Seventh Circuit and served upon counsel for all parties using the appellate CM/ECF system.

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