No. 17-290

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,
v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

BRIEF OF JEROME P. KASSIRER, M.D., MARCIA ANGELL, M.D., and GREGORY CURFMAN, M.D. AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

Whether the Third Circuit correctly denied summary judgment on Petitioner's preemption defense because clear evidence did not demonstrate that the FDA would have rejected a properly worded warning about atypical femoral fractures.

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INTEREST OF *AMICI CURIAE*[1]

Amici curiae are doctors, professors, and former editors of the most prestigious medical journals in the world. They have a keen interest in drug safety.

Jerome P. Kassirer, M.D., is Distinguished Professor and Senior Assistant to the Dean at Tufts University School of Medicine. Dr. Kassirer is the author of, *inter alia*, the books Acid-Base (1982), On The Take: How Medicine's Complicity With Big Business Can Endanger Your Health (2004), Learning Clinical Reasoning (2009), and Unanticipated Outcomes: a Medical Memoir (2017). Dr. Kassirer was formerly Editor-in-Chief of the *New England Journal of Medicine*.

Marcia Angell, M. D., is a corresponding member of the faculty of the Department of Global Health and Social Medicine at Harvard Medical School. Dr. Angell is the author of, *inter alia*, the books Science on Trial: The Clash of Medical Evidence and the Law in the Breast Implant Case (1996) and The Truth About the Drug Companies: How They Deceive Us and What to Do About It(2004). Dr. Angell was formerly Executive Editor and Editor-in-Chief of the *New England Journal of Medicine.*

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[1] Petitioners and Respondents have filed blanket consents to the submission of *amicus* briefs with this Court. No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae* or counsel made a monetary contribution to its preparation or submission.

Gregory Curfman, MD, is Deputy Editor of the Journal of the American Medical Association. Dr. Curfman was previously the editor in chief of Harvard Health Publications, the publishing division of Harvard Medical School, and, prior to assuming this role, had a 28-year career as an editor of the New England Journal of Medicine, most recently as the Journal's Executive Editor. At NEJM, he founded the Perspective section, which focuses on issues at the interface of medicine and society. HHe is a member of the Faculty of Medicine at Harvard Medical School (HMS) and holds an affiliated faculty appointment in the HMS Department of Health Care Policy.

The issue before this Court is one of immense importance from the perspective of public health and safety. *Amici* are familiar with the professional literature relevant to this Court's decision in this case and feel compelled to provide the Court with pertinent studies that bear on the question presented. The matter under review by this Court – whether the tort action is preempted – should be informed by a better understanding of the respective and complimentary roles played by the FDA and by tort litigation. In providing this information, amici ask this Court to affirm the decision of the Court below.

SUMMARY OF ARGUMENT

Pharmaceutical companies usually learn about dangers caused by their drugs long before the Food and Drug Administration (FDA) does, but those companies have not consistently disclosed this

information to the FDA. The records in state tort liability cases document too many instances where drug manufacturers withheld key information from the FDA or willfully chose not to investigate legitimate concern safer drug safety signals arose. Even when disclosed, the information may not be delivered in a timely fashion or its significance is improperly downplayed.

The process of developing appropriate drug safety labeling is inevitably a slow one. Manufacturers will often fight against stricter label warnings, even as they continue to market their problematic drugs to unsuspecting physicians and patients. Full information too often becomes public only when discovery in product liability cases unearths it. State tort law provides essential information-gathering tools through which the health care community obtains safety and effectiveness information about drugs.

Recent developments further highlight the importance of tort liability to the overall system of drug safety. The volume of new drugs seeking FDA approval continues to grow. More and more new drugs obtain approval through expedited development and review processes on the basis of abbreviated testing in clinical trials. These drugs require greater attention after approval to glean important information about associated adverse events and other harms. But the FDA has limited resources to monitor the prevalence or emergence of adverse events after an approved drug hits the market.

The FDA acknowledges that it cannot perform these necessary tasks alone. State tort liability plays a critically important part in that post-approval monitoring process, providing incentives for earlier disclosure by manufacturers and exposing information about risks key risks that might not have been clearly described to the FDA. To protect the drug safety system of which the FDA is only a part, this Court should not curtail patients' ability to bring tort actions about adverse drug events without rigorously clear evidence that the FDA would not have approved the precise warning that is the subject of the lawsuit.

ARGUMENT

Prescription drugs have enormous potential to address the various maladies that afflict the human condition, but also carry risks of adverse reaction and even fatality. The Centers for Disease Control and Prevention (CDC) estimates that "more than 1 million individuals are seen in hospital emergency departments for adverse drug events each year in the United States," with more than one-quarter of these patients requiring hospitalization for further treatment. CDC, *Medication Safety Program: Adverse Drug Event Monitoring*, https://www.cdc.gov/medicationsafety/program_focus_activities.html. One study by CDC researchers showed that four in every 1,000 individuals taking prescription drugs suffered an adverse drug event, which constitutes the most common form of iatrogenic harm in health care. Nadine Shehab, *et al.*, *US Emergency Department Visits for Outpatient*

Adverse Drug Events, 2013-2014, 316 J. Am. Med. Ass'n 2115, 2124, 2116 (Nov. 22/29, 2016).

The Federal Food, Drug, and Cosmetic Act (FDCA), 52 Stat. 1040, *as amended*, 21 U.S.C. § 301 *et seq*., provides a mechanism for addressing drug safety and seeks "primarily to protect consumers from dangerous products." *United States v. Sullivan*, 332 U.S. 689, 696 (1948). With respect to drugs, the statute addresses patient safety by requiring new drugs to proceed through a regulatory approval process conducted by the Food and Drug Administration (FDA), while operating alongside traditional state tort liability, which, by providing compensation for avoidable injuries, incentivizes drug manufacturers to monitor adverse events and convey accurate warnings. *Wyeth v. Levine*, 555 U.S. 555, 575 (2009).

A key component of the FDA's regulatory scheme is proper labeling of drugs to assure that medical authorities and patients have the information necessary to make informed decisions about the risks associated with taking a prescription drug. *See* FDA, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934 (2006). Proper labeling that incorporates adequate warnings seeks to minimize the instances in which physicians prescribe and patients suffer avoidable harms from prescription drugs. Tort liability attaches, for example, when the drug manufacturer fails to warn adequately in its drug's labeling or otherwise about a particular adverse reaction and the plaintiff suffers harm caused by that adverse reaction as a result.

According to the FDA's rules, a drug's labeling "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57. The brand-name manufacturer bears responsibility to update the labeling as needed, which the FDA subsequently reviews.

The tort system plays a critically important role in that system of patient safety. By itself, the FDA lacks the resources and information needed to monitor patient outcomes arising from the drugs it has approved. The agency relies heavily on manufacturers to convey to it reported adverse events, as well as the results of post-approval clinical trials and other studies that the manufacturer has conducted. The manufacturers do not consistently discharge those obligations, sometimes withholding information about adverse events and drug safety concerns expressed by their own researchers. Too often, when they do notify the FDA, the information conveyed is incomplete or reflects the manufacturer's desire to minimize problems to maintain the drug's position in the marketplace.

Time and time again, tort litigation has revealed risks of medical products that the FDA had not known about or that the manufacturers had actively sought to obscure. Tort litigation therefore serves a vital purpose in informing patients, their caregivers, and the FDA about the risks and benefits of medical products. Insofar as this case either reopens the preemption question settled in Wyeth or

contemplates changes to its application that would reduce the viability of tort litigation, it poses grave risks to public health, and impinges on the work of researchers and doctors seeking to improve drug safety.

I. THE FDA LACKS SUFFICIENT INFORMATION AND RESOURCES TO MONITOR PHARMACEUTICAL RISK AND NEEDS THE ASSISTANCE PROVIDED BY TORT LAW.

A. The Number of New Drug Applications (NDAs) Remains High.

In *Wyeth*, this Court recognized that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness" because it was "aware[] of the prevalence of state tort litigation" and chose not to enact an express preemption provision. 555 U.S. at 575. It further understood that the "FDA has limited resources" and that "manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id.* at 578-79.

The task the FDA faces in approving new drugs and monitoring the emergence of new risk continues to grow. An August 2016 industry report, using data from the FDA, found that the agency had approved 478 new prescription medicines since 2000. Genia Long, *The Biopharmaceutical Pipeline: Innovative Therapies in Clinical Development,* at 1-2, available at http://phrma-docs.phrma.org/files/dmfile/Biopharmaceutical-Pipeline-Full-Report.pdf. The new

approvals during that period represented an average of 28 per year. Still, averaging the approval rate masks the increased rate experienced in recent years and the high likelihood that the recent rise in NDAs is the new norm.

The FDA reports that in 2015, 45 new prescription drugs were approved.[2] Although there was a drop in 2016 to 22 new approvals,[3] the number more than doubled in 2017 to 46.[4] As of November 16, 2018, the number of new drug approvals for 2018 have already surpassed every year since 2000 with 49 new drugs approved.[5]

This recent increase in new drug applications and approvals shows no signs of abating. The industry report that track new drug approvals indicates that, as of August 2016, manufacturers had lined up more than 6,300 new drugs that will soon be submitted to the FDA for review, while thousands more are in clinical development. *Biopharmaceutical*

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[2] FDA, Novel Drug Approvals for 2015, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm.

[3] FDA, Novel Drug Approvals for 2016, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

[4] FDA, Novel Drug Approvals for 2017, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

[5] FDA, Novel Drug Approvals for 2018, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

Pipeline, at 5. Most investigational drugs that reach the NDA stage receive approval. Leonard V. Sacks *et al*., *Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012,* 311 J. Am. Med. Ass'n 378, 383 (2014), available at https://jamanetwork.com/journals/jama/fullarticle/1817795 (finding 73.5% of the 302 applications during the study period were approved). The pace of new drug approvals makes reliance upon all means of determining adverse events during the postmarketing phase, including tort litigation, a priority. Tort cases can identify undisclosed risks, illuminate flaws in study design, and identify areas of concern that require further study. These gaps cannot otherwise be filled.

B. Today, Drugs Obtain Approval More Quickly, Relying on Thinner Initial Evidence.

When this Court decided Wyeth, the FDA received more information about medicines in the premarket phase than it receives, on average, today. For that reason, the postmarketing information-gathering role of tort liability is more important than it has ever been. The pressure to approve applications quickly is a constant, resulting in drugs making it to the market with thin initial evidence. A "standard review" generally takes about 10 months, while a priority review, which abbreviates the time to approval, though not the process of approval, takes

six months.[6] Congressional Research Service, R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness,* May 8, 2018, at 7, 9, available at https://fas.org/sgp/crs/misc/R41983.pdf. *See also* 21 U.S. Code § 355(c). In 2016, the median review time was 7.8 months. John K. Jenkins, CDER New Drug Review: 2016 Update, at 20 (Dec. 14, 2016), https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM533192.pdf.

Recent substantial leaps in the speed of FDA review process periods has not stemmed industry complaints, often echoed by public officials, that the amount of data and the length and complexity of clinical trials that are a prerequisite to an NDA still excessively delay the entry of new drugs to market.[7] In late 2016, with industry support, Congress enacted and the president signed Public Law No. 114-255, 130 Stat. 1033 (Dec. 2016), the 21st Century Cures Act, which states that its purpose is to

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[6] The FDA employs several different expedited development and review pathways for drugs deemed to address serious or life-threatening conditions, referred to as "first-in-class" drugs: priority review, accelerated approval, fast track approval, and breakthrough therapy designation. *See, generally,* Erin E. Kepplinger, *FDA's Expedited Approval Mechanisms for New Drug Products,* 34 Biotechnol. Law Rpt. 15 (Feb. 1, 2015), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4326266/.

[7] *See* Executive Office of the President, President's Council of Advisors on Science and Technology, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation" (Sept. 2012), at 14.

"accelerate the discovery, development, and delivery of 21st century cures" by, *inter alia*, reducing the evidence needed to obtain FDA approval of new drugs. The expedited processes for premarket approval enacted in the 21st Century Cures Act puts a further premium on obtaining complete and accurate post-market information and the rapid incorporation of emerging information and appropriate new warnings.

C. Expedited Pathways to Approval Require the FDA to Approve Drugs With Less Safety Evidence than Standard Approvals.

The FDA has available to it four different expedited development and review pathways for investigational drugs: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review. FDA, Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, available at https://www.fda.gov/ForPatients/Approvals/Fast/default.htm.

To understand the impact that these pathways and processes have in facilitating the completion of testing and clinical studies in lesser time and with fewer subjects, it is useful to review the information the FDA uses to approve new drugs through the standard process. The FDA receives premarket information from clinical trials that are conducted by the drug manufacturers. While clinical trials represent an important aspect of drug development by providing efficacy assessments, their ability to assess a complete safety profile is inherently limited.

Institute of Med. of the National Academy of Science, *The Future of Drug Safety* (Alina Baciu, *et al*., eds., 2006), at 38. To demonstrate efficacy, studies generally range between a few hundred to 3000 subjects with a duration of a few weeks to a few years. These studies cannot fully account for: 1) the effects of long-term cumulative dose or latent side effects; 2) rare side effects or those most pronounced in sub-populations; or 3) potential side effects not accounted for in clinical trial designs. In addition, once a drug is used in routine clinical practice, it is often used in patients with multiple co-morbidities excluded from enrolling in trials or taking other medications not permitted for trial participants.

The FDA conducts no independent testing, but must rely upon information provided by the party most interested in bringing the drug to market – the drug manufacturer. That information often presents interpretative challenges. The manufacturer's first-hand knowledge of the data puts the FDA at a disadvantage compared to the company. *See* FDA Science Board Report, *FDA Science and Mission at Risk*, at 31 (2007) <http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%C20and%20Technology.pdf>.

Post-approval evaluation of drug risks has not cured the serious problems that were not identified in the pre-approval process. The FDA has acknowledged that expediting drug application approvals can pose risks for patients. GAO, No. 16-192, *FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement,* at 9 (Dec.

2015), available at https://www.gao.gov/assets/680/674183.pdf. Still, an ever-increasing number of drugs are reviewed under one of these expedited programs. *See* pp. 26-36 *supra.* Although intended to apply only to drugs "offering the greatest promise of therapeutic advance to patients with no other reasonable therapeutic choices," they have become the regular process for a growing number of NDAs. Aaron S. Kesselheim *et al.*, *Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014: Cohort Study*, 351 Brit. Med. J. h4633, at *2 (Aug. 17, 2015), available at https://www.bmj.com/content/bmj/351/bmj.h4633.full.pdf.

Approximately one-third of approved drugs since 1987 qualified and used one of the expedited approval programs, with the percentage jumping to 65 percent in 2014. Margot Sanger-Katz, "Speedy Drug Approvals Have Become the Rule, Not the Exception," N.Y. Times, May 1, 2015, https://www.nytimes.com/2015/05/02/upshot/speedy-drug-approvals-have-become-the-rule-not-the-exception.html. *See also* Jonathan J. Darrow *et al.*, *Drug Development and FDA Approval, 1938–2013,* 370 N.E.J.M. 2465 (Jun. 26, 2014).

It makes sense that testing in fewer patients, using "surrogate" markers of success (such as cholesterol level) instead of clinical endpoints (such as reduced mortality), and shortening review periods make it more difficult to cull indicators of harm in the data collections contained in an NDA. The reduced length of clinical trials and reviews, as well

as reliance on surrogate endpoints rather than clinical endpoints, correlate with increases in safety events discerned after market approval that have required the approved drugs to be withdrawn or feature a boxed warning.[8] *See* Nicholas S. Downing *et al.*, *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 J. Am. Med. Ass'n 1854 (2017), available at https://jamanetwork.com/journals/jama/fullarticle/2625319; Daniel Carpenter, *et al.*, *Drug-Review Deadlines and Safety Problems*, 358 New Engl. J. Med. 1354 (2008), available at https://www.nejm.org/doi/full/10.1056/NEJMsa070634 1; 2008;358:1354-61; Mary K. Olson, *The Risk We Bear: the Effects of Review Speed and Industry User Fees on New Drug Safety*, 175 J. Health Econ. 175 (2008). One recent matched cohort study of drugs approved over the last two decades found that compared with non-expedited pathway drugs, expedited pathway drugs had a 48% higher rate of post-approval safety-related labeling changes to boxed warnings and contraindications, the two most clinically important categories of safety warnings. Sana R. Mostaghim *et al.*, *Safety Related Label Changes for New Drugs after Approval in the US through Expedited Regulatory Pathways: Retrospective Cohort Study*, 358 Brit. Med. J. j3837

[8] A black-box warning "appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks." FDA, A Guide to Safety Terms 2 (Nov. 2012), available at https://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM107976.pdf.

(2017), available at https://www.bmj.com/content/358/bmj.j3837.

In sum, developments in the regulatory system in recent years make the tort system still more important as an impetus to transparency and as a strong incentive to encourage companies to disclose adverse events fully to the FDA as rapidly as possible. The higher incidence of safety issues strongly suggests that expedited review forces the FDA to approve NDAs before more preliminary data is available and requires every available tool to expose unknown risks once the drug is in the marketplace. Tort litigation addresses a gap and provides an essential tool in this process.

II. KNOWLEDGE OF RISKS POSED BY NEW PHARMACEUTICALS DEVELOPS EACH YEAR, BUT THE FDA LACKS THE CAPACITY TO REGULATE AND RESPOND EFFECTIVELY.

A. The FDA Has Limited Resources.

The FDA has suffered chronic underfunding, despites its mission to ensure the safety of drugs, medical devices, and food supplies. Institute of Medicine, Challenges for the FDA: The Future of Drug Safety: Workshop Summary 15 (2007). Its budget has increased largely by greater reliance on user fees charged under the Prescription Drug User Fee Act of 1992 (PDUFA), Pub. L. No. 102-571, 106 Stat. 4491. PDUFA originally limited user-fee revenue to apply to review of NDA time to approval,[9]

[9] The influx of money through PDUFA is credited with effecting a 52 percent reduction in the time to approval for NDAs during

though more recent versions have permitted some use for post-market safety activities. Still, the "spirit of the limitation remains the same," reflecting the motivation for PDUFA from the beginning: reducing NDA time to approval. Patrick O'Leary, *Funding the FDA: Assessing the User Fee Provisions of the FDA Safety and Innovation Act of 2012*, 50 Harv. J. on Legis. 239, 242-43 (2013). With ever-increasing dependence on user fees,[10] PDUFA has had the "unintended but pernicious consequence of shrinking the relative funding available for non-review activities such as enforcement" and post-approval drug safety oversight by the FDA. *Id*.

Little has changed since Kesselheim and Avorn concluded that "clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products." Aaron S. Kesselheim & Jerry Avorn, *The*

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the statute's first five years. Cassie Frank *et al*., *Era of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 Health Aff. 1453, 1453 (Aug. 2014).

[10] User fees constituted thirty-five percent of the FDA's total FY 2012 budget, and every subsequent budget proposal has asked the FDA to increase that dependence. O'Leary, 50 Harv. J. on Legis. at 249-50. For example, the FY2018 budget proposed a $1.3 billion increase in user fees to fund the FDA. Robert Atlas and Timothy J Murphy, *Opinion: Five key takeaways from Trump's budget proposal,* Managed Healthcare Executive (Jun. 18, 2017), available at http://www.managedhealthcareexecutive.com/healthcare-reform/opinion-five-key-takeaways-trumps-budget-proposal.

Role of Litigation in Defining Drug Risks, 297 J. Am. Med. Ass'n 308, 311 (2007).

Even if information produced by postmarket clinical trials were more perfect, the task of reviewing those results and synthesizing it with other medical knowledge is daunting. As one group of researchers observed, "the task keeps increasing in size and complexity." Hilda Bastian *et al.*, *Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?*, PLoS Med 7(9): e1000326 (2010), available at https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000326.

Because the regulatory scheme relies so heavily on manufacturers to undertake the post-marketing review and formulate changes to the label, in part, due to the resource imbalance between the FDA and the applicant for approval, it is entirely natural for the FDA to reject an inadequate and misdirected warning and suggest the manufacturer come back with a more appropriate one, rather than develop one on the FDA's own. After all, it is the manufacturer that conducted the research, and the FDA only had second-hand knowledge of its meaning. Still, as the tort system has shown by exposing internal documents obtained through discovery, manufacturers do not always share the misgivings and findings of their researchers with the FDA, and that litigation is the only way to obtain research hidden from the agency and the public.

B. The FDA Has Limited Access to Relevant Data.

The entire process of NDA approval and postmarket monitoring depends on the drug's manufacturers to conduct the clinical trials, monitor adverse events, and propose all labeling changes. *Wyeth*, 555 U.S. at 571. That dependency does not change once the FDA approves a drug for the market. In 2007, Congress enacted the Food and Drug Administration Amendments Act (FDAAA), Pub. L. No. 110-85, 121 Stat. 823, which gave the FDA authority to order pharmaceutical companies to conduct drug safety studies after a drug has received approval and is on the market. 21 U.S.C. § 355(o)(3). However, the enforcement mechanism is cumbersome to implement and results in relatively small monetary penalties; in fact, in the decade since FDAAA was enacted, despite ongoing reports of delayed or non-initiated postmarket study commitments, the FDA has not imposed such fines. Holly Lynch, It's Time to Levy Penalties for Failing to Report Clinical Trial Results, STAT, https://www.statnews.com/2018/01/17/time-levy-penalties-failing-report-clinical-trial-results/.

However, even the prospect that post-approval trials might be conducted does not fully ensure that all possible safety-related information will be acquired via this process. In particular, clinical trials may not be able to uncover risks that are rare, revealed over significant periods of time, or adversely affect specific segments of the population not enrolled in the trial. A recent study found that NDA holders frequently fail to meet their post-marketing

commitments and requirements. Steven Woloshin *et al.*, *The Fate of FDA Postapproval Studies*, 377 N. Engl. J. Med. 1114 (Sept. 21, 2017), available at https://www.nejm.org/doi/full/10.1056/NEJMp1705800?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed. Because post-marketing studies are not ensuring a flow of information on harms to the FDA, the discovery obtained through tort litigation is a necessary additional source of that information.

When the mandated studies do take place, they often result in labeling changes. In FY2014, the FDA required 61 safety actions, including 59 label changes, in light of information developed in a required postmarketing review out of the 108 reviews completed that year. Office of the Inspector General, Department of Health and Human Services, No. 01-14-00390, FDA Is Issuing More Postmarketing Requirements, But Challenges with Oversight Persist 14 (Jul. 2016). There were 32 instances of noncompliance with post-marketing requirements by manufacturers. *Id*. at 15.

FDA-ordered post-market reviews reflect a negotiated timetable with the manufacturer and can take up to seven years before the study or clinical trial is even started. *Id*. at 13. In 2015, the Government Accounting Office (GAO) found that the information the FDA does collect on post-market safety issues and studies were incomplete, outdated, inaccurate, and maintained "in a manner that made routine, systematic analysis difficult," despite an acute need for "complete, timely, and accurate information." GAO, FDA Expedites Many

Applications, at 29. The HHS Inspector General's report found that those problems persisted. *FDA Is Issuing More Postmarketing Requirements*, at 16-18.

Still, the FDA traditionally relies "on postmarket surveillance programs that passively aggregate adverse events: the FDA Adverse Event Reporting System for drugs and the Manufacturer and User Facility Device Experience Database for medical devices." Joseph Ross and Aaron S. Kesselheim, *FDA Policy and Cardiovascular Medicine*, 132 Circulation 1136, 1141 (2015), available at https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.114.010295. These databases compile adverse event reports submitted voluntarily by healthcare professionals, patients, and industry representatives to the FDA, but, as informal submissions, suffer from "incomplete, inaccurate, untimely, unverified, or biased data." *Id*. By their nature, these reports provide little basis for determining "the incidence or prevalence of an event … because of underreporting of events and lack of information about frequency of drug or device use." *Id*. The researchers concluded that "postmarket surveillance remains a challenge with methodological and resource limitations." *Id*. at 1143.

One attempt to engage in affirmative postmarket review is the Sentinel Initiative, "which mines insurance data and medical records to identify possible risks." Sheila Kaplan, *Failure to Warn: An Early Warning System for Drug Risks Falls Flat*, STAT News (Jun. 6, 2017), https://www.statnews.com/2017/06/06/sentinel-fda-drug-risks/. However, after being in place for a

decade, "its records have been used to revise only two drugs' warning labels." *Id*. The problem that this system faces is that it seeks the information largely from insurance company billing records that rarely study people over age 65, utilize inconsistent different diagnostic codes for the same conditions, and never records deaths from medications. *Id*. The Sentinel Initiative is just another example of a program instituted to address the FDA's lack of data that has not filled the gap and highlights once again the need for the supplemental information that is the product of tort litigation.

III. NEW DRUG SAFETY INFORMATION DEVELOPS AFTER APPROVAL AND AFTER THE DRUG IS ON THE MARKET.

The heavy emphasis that Congress and the FDA has placed on speeding the premarketing approval process has caused the FDA increasingly to "approve[] new drugs and biologics on the basis of shorter, smaller, and fewer trials," Joshua D. Wallach *et al*., *Postmarket Studies Required by the US Food and Drug Administration for New Drugs and Biologics Approved between 2009 and 2012: Cross Sectional Analysis*, 361 Brit. Med. J. k2031 (Apr. 16, 2018), available at https://www.bmj.com/content/361/bmj.k2031.
Virtually all applications are approved, and usually based on few studies of brief duration involving a modest number of subjects that are far healthier than the population targeted by the new drug. *See* David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Effort to Preempt Failure-*

to-Warn Claims, 96 Geo. L.J. 461, (2008) ("[P]re-approval testing generally is incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect subpopulations not included or adequately represented in the studies (*e.g.*, the elderly, ethnic minorities and pregnant women).").

Yet, as the FDA itself acknowledges, "the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime." FDA, Step 5: FDA Post-Marketing Drug Safety Monitoring (Jan. 4, 2018), https://perma.cc/QU75-KDAC. The increased reliance on expedited pathways to FDA approval, where authorization to market the drug supported by less rigorous evidence occurs, underscores the critical role that continuous evaluation after approval plays. *See* Joshua D. Wallach *et al.*, *The US Food and Drug Administration's expedited approval programs: Evidentiary standards, regulatory trade-offs, and potential improvements*, 15 Clinical Trials 219 (Jun. 5, 2018). In a review of recent academic literature examining the expedited pathways to approval, researchers confirmed that drugs are being approved by the FDA on the basis of fewer and smaller studies, where the data contained in the NDA may lack important benchmarks that assure scientific rigor, such as use of comparator groups and random allocation, and focus on weak predictive extrapolations from the studies and trials, called surrogate markers of disease, rather than clinical outcomes. *Id.* Despite the dearth of more trustworthy testing and clinical results, the newly approved drugs "are often quickly incorporated into clinical practice, and evidence generated in the postmarket period

may not necessarily address the evidentiary limitations at the time of market entry." *Id.* Perhaps just as troubling, not all expedited pathways mandate additional postmarket studies, and drugs receiving expedited approval are associated with a greater likelihood that the FDA will need to take a safety action following entry into the market. *Id.*[11]

In fact, complete withdrawals[12] from the market because the risk-benefit analysis tilts in a different direction than the premarket data indicated are not infrequent. *See* Drug Products Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness, 21 C.F.R. § §216.24, available at https://www.ecfr.gov/cgi-bin/text-idx?SID=9146635b2375a18de8912ddde721f7cb&mc=true&node=se21.4.216_124&rgn=div8.

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[11] In response to this article, the director of the FDA's Center for Drug Evaluation and Research, which is the part of the FDA that undertakes drug approvals, conceded that more is learned about a drug postmarket than at the approval stage, but emphasized the value of getting drugs to market early. Janet Woodcock, *Expediting Drug Development for Serious Illness: Trade-Offs between Patient Access and Certainty*, 15 Clinical Trials 230 (Jun. 5, 2018), available at https://journals.sagepub.com/doi/abs/10.1177/1740774518770656. A former FDA Commissioner also commented on the article, largely agreeing with the research but emphasizing that early access to new drugs and new ways of thinking about testing were needed. Robert M. Califf, *Expedited and Facilitated Drug Evaluations and Evidence of Benefit and Risk: The Cup is Half-Full*, 15 Clinical Trials 235 (Jun. 5, 2018), available at https://journals.sagepub.com/doi/abs/10.1177/1740774518771347.

[12] A withdrawal represents a decision the drug is unsafe for its intended use. 21 C.F.R. § 314.150(a)(2).

The editors of *Clinical Trials* put the problem succinctly:

> the less evidence required, the greater the risk that an ineffective or even harmful agent will be marketed, with the resulting downstream negative impact on the public health. A problematic concern is that as evidentiary standards for drug approval are lowered, the need for carefully designed and credible post-marketing studies becomes increasingly important. However, … rigorous post-marketing research is inherently challenging and it cannot fully compensate for the kind of evidence that can only be assembled in the pre-marketing setting.

Colin B. Begg and Susan S. Ellenberg, *Expedited Approval Programs at the Food and Drug Administration*, 15 Clinical Trials 217 (Jun. 5, 2018), available at https://journals.sagepub.com/doi/full/10.1177/1740774518770653.

A recent study of pharmaceuticals and biologics approved for use by the FDA from 2001 through 2010 found that 32 percent were the subject of a "postmarket safety event," including market withdrawal or, more frequently, black box warnings and FDA safety communications to health professionals. Nicholas S. Downing, *Postmarket Safety Events among Novel Therapeutics Approved by the US Food and Drug Administration between 2001 and 2010*, 317 J. Am. Med. Ass'n 1854, 1862 (May 9,

2017), available at https://J. Am. Med. Ass'n network.com/journals/JAMA/fullarticle/2625319. The study noted that safety events were more frequent at a statistically significant rate among those drugs and biologics that had received accelerated review or were approved near the regulatory approval deadline. *Id*. *Cf*. Frank, 33 Health Aff. at 1458. (finding that new drugs have a "one-in-three chance of acquiring a new black-box warning or being withdrawn for safety reasons within twenty-five years of approval"). Sometimes a black-box warning is rapidly followed by the drug's withdrawal, such as when Efalizumab, a drug used to treat psoriasis, was withdrawn in 2009, a month after the black-box warning was added, because of the risk of progressive multifocal leukoencephalopathy, the same risk highlighted in the boxed warning. Downing, 317 J. Am. Med. Ass'n at 1858.

FDA scientists have conducted their own studies of the impact of the premarket approval pathways. In one, they similarly concluded that drugs approved through priority review had a higher risk of safety withdrawals or black-box warnings. *Andreas Schick et al*., *Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals*, 40 Drug Safety 497 (Mar. 24, 2017), available at https://link.springer.com/article/10.1007%2Fs40264-017-0526-1. They also found that "post-marketing events are not discernible during a pre-marketing review and therefore might not be avoidable using current review data." *Id*. at 503.

Still, these studies may have substantially underestimated the frequency of these concerns because, as the Downing study points out, the researchers did not consider safety events that generated changes to labeling or to dosage. Downing, 317 J. Am. Med. Ass'n at 1862.

A group of FDA scientists examined the issue of changes to labels missing from these other studies. From a comprehensive list of postmarket safety outcomes, they found at least one safety-related update was added to 70.1% labels of the drugs studied, with the labeling change occurring as early as 160 days after approval. Ellen Pinnow *et al*., *Postmarket Safety Outcomes for New Molecular Entity (NME) Drugs Approved by the Food and Drug Administration Between 2002 and 2014,* 104 Clinical Pharmacology & Therapeutics 390 (Dec. 20, 2017), available at https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.944. The need for a labeling change were "significantly shorter" for drugs approved through expedited pathways. *Id*. The researchers emphasized "the importance of a robust safety surveillance system throughout a drug's lifecycle and for practitioners and patients to remain updated on drug safety profiles." *Id*. at 400. Tort litigation plays a critical role, as explained *infra*, in that postmarket surveillance system.

The FDA's limitations as a monitor of pharmaceutical risk is illustrated by the frequency with which labeling changes, warning letters, and/or drug withdrawals occur. One recent study examined 222 new drugs and biologics approved by the FDA

from 2001 through 2010. Downing, *Postmarket Safety* at 1858. The study identified 123 postmarket safety events involving 71 of the new drugs and biologics. *Id*. As a result of these events, three were withdrawn from the market, 61 boxed warnings were imposed, and 59 safety communications were sent. *Id*. The median time from approval to the first safety event for that product was 4.2 years. *Id*. at 1860. Products that were withdrawn from the market stayed in circulation before withdrawal for periods of 3.4, 4.7, and 5.4 years. *Id*. The median time between approval and a boxed warning was 4.0 years, while safety communications lagged even more with a median between approval and communication of 4.9 years. *Id*.

Drugs receiving expedited review have required especially high numbers of safety-related label changes. A study published in 2017 showed that "[c]ompared with standard pathway drugs, expedited pathway drugs had a 48% higher rate of changes to boxed warnings and contraindications, the two most clinically important categories of safety warnings." Mostaghim, 358 Brit. Med. J. j3837.

IV. PHYSICIANS REQUIRE FULL AND ACCURATE INFORMATION ABOUT DRUG SAFETY TO TREAT THEIR PATIENTS SAFELY.

The Hippocratic oath mandates that physicians "prescribe regimens for the good of [their] patients according to [their] ability and judgment and never do harm to anyone" or knowingly "prescribe a deadly drug." Lisa R. Hasday, *The Hippocratic Oath as Literary Text: A Dialogue Between Law and Medicine,*

2 Yale J. Health Pol'y, L. & Ethics 299, 299-300 (2002).

To fulfill that obligation and to assure the safety of their patients, health care professionals require the best and most complete information about the drug they prescribe. The revelation of known manufacturer concerns provides critical guidance to physicians about which prescription is right for a particular patient. When the manufacturer provides the FDA with a purposely limited warning that the FDA rejects, failure-to-warn litigation can bring to light important drug safety information that has not been conveyed to medical personnel or their patients.

FDA has recognized that "it is essential to the safe use of a drug for the physician to know all adverse reactions that are likely to occur with it." Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,443 (Jun. 26, 1979). The FDA "believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients." *Id.* at 37,447.

For that reason, the FDA requires prescription drug labeling to include a

> concise summary of the most clinically significant information … including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug,

> and measures that can be taken to prevent or mitigate harm.

21 C.F.R. § 201.57(a)(10). The information required further includes the "most frequently occurring adverse reactions." *Id*. at § 201.57(a)(11).

In today's environment, where patients perform their own Internet research on potential drugs that may address their self-perceived problems and receive direct-to-consumer advertising from drug companies touting their latest approved drug, doctors need the most complete and well-developed information to explain benefits and risks to patients who can be insistent that their limited and often skewed information is correct and whose entreaties may be hard for physicians to resist. *See Thompson v. Western States Med. Center,* 535 U.S. 357, 383-84 (2002) (Breyer, J., dissenting). Any approach that contracts the potential sources of good information works against physicians' duties.

V. THE CIVIL JUSTICE SYSTEM SERVES AS AN IMPORTANT DOUBLE PROTECTION THAT THE FDCA ANTICIPATED WOULD SUPPLEMENT AND ENHANCE PATIENT SAFETY.

Even though drug manufacturers are obliged to report adverse events involving patients treated with a drug, *see, e.g.*, 21 C.F.R. §§ 310.305; 312.32(d)(3), 314.80, these reports may not reflect understandings of the company's doctors and scientists, who have a heightened appreciation for issues with the drug and the risks it poses. The absence of this information in the reports highlights the value that failure-to-warn

litigation serves in developing safety information known to the manufacturer but kept under wraps in reports to the FDA. Kessler and Vladeck, 96 Geo. L.J. at 491-95 (2008) (and authorities cited therein).

The existence of state tort lawsuits provides an incentive for drug manufacturers to disclose their knowledge of product risks to the FDA more fully, improving the agency's ability to assure that an adequate warning is adopted. Further, state failure-to-warn suits encourage drug manufacturers to work with the FDA to ensure that labels accurately reflect the risks associated with a given treatment. When they do not discharge that obligation, the discovery made possible through litigation can unearth internal concerns expressed by the manufacturers doctors and scientists that have not been disclosed to the FDA. *See* Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 J. Am. Med. Ass'n 308 (2007), available at https://jamanetwork.com/journals/jama/article-abstract/205083. *See also* Alex Berenson, *For Merck, the Vioxx Paper Trail Won't Go Away*, N.Y. Times, Aug. 21, 2005, at 3, available at https://www.nytimes.com/2005/08/21/business/for-merck-vioxx-paper-trail-wont-go-away.html (reporting that documents placed in evidence proved that Merck's scientists were concerned about Vioxx's cardiovascular risks as early as 1997, two years before the drug went on sale); Teresa Curtin and Ellen Relkin, *Preamble Preemption and the Challenged Role of Failure to Warn and Defective Design Pharmaceutical Cases in Revealing Scientific Fraud, Marketing Mischief, and Conflicts of Interest*, 35 Hofstra L. Rev. 1773, 1791 (2007) ("after each

development which suggested that Vioxx might pose a heightened risk of heart attacks and strokes, Merck sent special bulletins or special messages to its sales force, "directing them to use highly questionable information to assuage any physician concerns.") (citation omitted).

Traditionally, many manufacturers have downplayed known emerging safety concerns. *Id.* ("Merck sales representatives [were] trained to view doctors' concerns about Vioxx's heart risks as 'obstacles' to be avoided or dismissed.").[13] *See also* Bruce M. Psaty and Richard A. Kronmal, *Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment*, 299 J. Am. Med. Ass'n 1813, 1814-15 (2008); Bruce M. Psaty *et al.*, *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis*, 292 J. Am. Med. Ass'n 2622, 2626-30 (2004). Civil tort trials can help reveal the unexpected effects of drugs after approval by the FDA by providing individuals with local recourse. As the FDA has limited information and capability to evaluate all possible risks of drugs after approval, state tort lawsuits play an extremely important role in ensuring that drugs on the market are safe and properly labeled. Litigation brought by individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in regulatory

[13] For a detailed discussion of facts learned from discovery in the Vioxx litigation and Merck's disregard for the FDA's safety concerns, *see McDarby v. Merck & Co.*, 401 N.J. Super. 10, 949 A.2d 223 (App. Div. 2008).

systems. Kesselheim and Avorn, 297 J. Am. Med. Ass'n at 308.

Product liability lawsuits and the FDA have peacefully coexisted for eighty years for one simple reason: they have complementary, rather than conflicting, goals. The tort system complements the federal regulatory structure by providing a mechanism for compensating victims of hazardous drugs. It also provides the FDA with key information unearthed in litigation that the agency can use to better protect the public from unsafe and inadequately labeled drugs. At the same time, the tort system and the FDA are similarly constrained. Whereas the FDA, as a regulatory body, weighs the risks against the benefits of a drug, in "failure-to-warn" litigation most state courts require a similar balancing between the cost of care owed to a patient versus the prospective harm. As former FDA chief counsel Margaret Porter wrote, "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection." Margaret Porter, *The Lohr Decision: FDA Perspective and Position,* 52 Food & Drug L.J. 7, 9 (1997).

Through discovery, litigation has regularly uncovered information about drug toxicity that would otherwise not have been known. Moreover, by levying damages for certain kinds of harm, tort law can provide powerful disincentives to risky behaviors, as well as aid the FDA in its mission. In these days of diminishing incentives to perform robust clinical trials as explained above, the products liability

system becomes a vital element in promoting compliance with the FDA's safety goals.

Even the threat of civil liability is a vital bargaining tool for the FDA in pressuring companies to amend labels to warn of newly understood risks. If pharmaceutical companies were granted almost complete immunity through federal preemption, they would have minimal incentive to report or warn of the adverse health effects of their drugs, constantly finding excuses to delay reporting or completion of required postmarketing reviews. *See* Kevin Fain *et al*., *The Food and Drug Administration Amendments Act and Postmarketing Commitments,* 310 J. Am. Med. Ass'n 202 (Jul. 10, 2013) (finding more than 40% of studies that were supposed to be proceeding had not yet been started in 2011, the number of studies with delays doubled to approximately 1 in 8, and the proportion of all studies that have been fulfilled remains low).

In fact, given that pharmaceutical companies have been known to equate increased warnings with a loss of sales, they would have an incentive to delay warnings as long as possible. It is chilling to imagine how such companies might conduct themselves if the threat of tort liability for dangerous drugs were eliminated entirely by virtue of federal preemption.

Finally, the civil justice system has the ability to improve the lives of injured patients and their families in ways that the FDA cannot. It can provide protection in cases where the FDA is late in acting. Meritorious lawsuits can transfer the obligation to pay for the losses caused by tragic adverse events from the healthcare system to those best equipped to

pay for the injury. As bluntly stated by FDA counsel Porter, the tort system remedies the "harsh implications" of the FDA's inability to provide "recourse for consumers injured by defective" drugs. Porter, 52 Food & Drug L.J. at 9.

Rofecoxib, better known as Vioxx, is an example of litigation that brought to light previously buried data. Its manufacturer, Merck & Co., Petitioners here, claimed it was a safer than traditional nonsteroidal anti-inflammatory drugs (NSAIDs), promoting it to the point that it generated $2 billion in sales annually shortly after its introduction. Joseph S. Ross *et al.*, *Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data: Lessons for Postmarket Pharmaceutical Safety Surveillance*, 169 Archives Internal Med. 1976, at *1 (2009), available at https://pdfs.semanticscholar.org/2784/8d1bb790a603cf9b2ca5740cc4f1c9bcf2e8.pdf. However, five years after its introduction, Merck voluntarily withdrew the drug from the market after studies showed significant cardiovascular risk. *Id.* Still, what hastened its withdrawal was the revelation in discovery that Merck's own researchers had expressed that precise concern before Vioxx hit the market. *Id.*, citing E.M. Scolnick, E-mail communication to Deborah Shapiro, Alise Reicin, and Alan Nies re: vigor [Bates No. MRK-ABH0016219, *Cona v. Merck & Co Inc*], Mar. 9 2000, http://dida.library.ucsf.edu/pdf/oxx00c10.

Other high-profile cases include:

- Baycol (cerivastatin): "manufacturer allegedly suppressed knowledge that patients were

developing a potentially life-threatening muscle disease, and that the risk of such condition increased with higher dosages at the time the company was negotiating with the FDA for approval of the drug at higher dosages." Curtin and Relkin, 35 Hofstra L. Rev. at 1783 & n. 55 (and accompanying text);

- Bextra (valdecoxib): Pfizer engaged in deceptive marketing by failing to warn increased cardiovascular risks and potentially life-threatening skin reactions, while falsely claiming Bextra provided superior pain relief and safety than traditional NSAIDs. *In re Bextra and Celebrex Mktg. Sales Practices and Prod. Liab. Litig.*, No. CV-05-1699, 2006 WL 2472484, at *2 (N.D. Cal. Aug. 24, 2006);
- Ortho Evra: manufacturer accused of misrepresenting that birth control contraceptive patch was as safe as oral contraceptives even though it knew or should have known that it could cause blood clots. Martha Mendoza, "Warning Issued for Birth-Control Patch," Wash. Post, November 11, 2005, available at http://www.washingtonpost.com/wp-dyn/content/article/2005/11/11/AR2005111100242.html (discussing documents made available through litigation);
- Paxil (paroxetine): manufacturer allegedly suppressed studies indicating increased suicidal behavior, while releasing the favorable study. Press Release, Office of the New York State Attorney General, Major Pharmaceutical

Firm Concealed Drug Information: GlaxoSmithKline Misled Doctors About the Safety of Drug Used to Treat Depression in Children (Jun. 2, 2004), available at http://www.oag.state.ny.us/press/2004/jun/jun2b_04.html; *see also* Jon N. Jureidini *et al.*, *Clinical Trials and Drug Promotion: Selective Reporting of Study 329,* 20 Int'l J. of Risk & Safety in Medicine 73 (2008) (detailing how documents obtained in litigation contradicted GlaxoSmithKline's claim that Study 329 showed that "paroxetine is generally well tolerated and effective for major depression in adolescents.") [14].

- Zyprexa (olanzapine): manufacturer hid adverse side effects from use of anti-psychotic drug. *In re Zyprexa Prod. Liab. Litig.*, 489 F. Supp. 2d 230 (E.D.N.Y. 2007).

It is indisputable that the civil justice system plays a critical role in exposing otherwise unknown or unrevealed adverse effects in approved drugs.

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[14] Paxil is the drug at issue in *Dolin v. GlaxoSmithKline LLC*, 901 F. 3d 803 (7th Cir. 2018), which both parties discuss. In considering what the Seventh Circuit did in that case, it is important to remember that appropriate warnings that apply across the board to a class of pharmaceuticals still may not be sufficient when discussing a particular drug within that class. *See Dolin v. GlaxoSmithKline, LLC*, 269 F. Supp.3d 851, 864 (N.D. Ill. 2017); *Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948, 954 (E.D. Wis. 2009) ("In denying the proposed language, the agency did not prohibit all enhanced warnings. Instead, the FDA merely required removal of Paxil-specific language from a particular portion of Paxil's label in favor of uniform class-wide labeling for all SSRI's.")

Through discovery, litigation has regularly uncovered information about drug toxicity that would otherwise not have been known outside the companies that manufactured the drug.

By levying damages for certain kinds of harm, tort law can provide powerful disincentives to risky behaviors, as well as aid the FDA in its mission. Even the threat of civil liability is a vital bargaining tool for the FDA in pressuring companies to amend labels to warn of newly understood risks. If pharmaceutical companies were granted almost complete immunity by virtue of federal preemption, they would have minimal incentive to report or warn of the adverse health effects of their drugs – or to propose warnings as appropriate as the research suggests. In fact, given that pharmaceutical companies have been known to equate increased warnings with a loss of sales, they would have an incentive to delay warnings as long as possible or to claim that the proposal of inadequate warning should foreclose a more adequate one.

Finally, it should not go unremarked that the civil justice system has the ability to improve the lives of injured patients and their families in ways that the FDA cannot. It can provide protection in cases where the FDA is late in acting. It can provide critically important compensation to those whose lives are devastated by undisclosed drug risks.

The academic research demonstrates the need to permit tort litigation to fill gaps and expose hidden

information about prescription drugs on the market. Limiting the reach of *Wyeth* would operate against that important public health imperative. Enforcing it, however, assures that a manufacturer does not have an incentive to withhold information or submit a patently inadequate warning with the expectation that rejection will earn a free pass against tort liability. It should not be enough to hint at a more appropriate warning secure in the knowledge that the FDA will usually neither approve the insufficient one nor develop its own. No safe harbor from liability should be recognized if the proposed, but rejected warning fails to alert physicians and patients of real and known dangers. The bottom line is that tort litigation plays a crucial role in the postmarket surveillance of drug risks and one that should not be curtailed by impact of the lessons of *Wyeth*.

CONCLUSION

For the foregoing reasons, amici curiae respectfully request that the decision of the Third Circuit be affirmed.

Respectfully submitted,

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